RADICAL REACTIONS OF CARBOHYDRATES I: RADICAL REACTIONS OF CARBOHYDRATES

Roger W. Binkley and Edith R. Binkley

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CHAPTER OVERVIEW

1: Advantages & Disadvantages of Radical Reactions

When deciding whether or not to conduct a radical reaction, certain information is crucial. It is important to know as completely as possible how intermediate radicals will form and, once formed, how these radicals will react with various reagents and solvents present in the reaction mixture. This information not only points to the expected product but also answers questions such as: What side reactions could take place? How might these reactions be avoided or minimized? What is the outcome of reactions that have been reported for similar compounds? A fitting way to begin framing the answers to these questions is by looking at the advantages and disadvantages of radical reactions.

II. Advantages of Radical Reactions

III. Disadvantages of Radical Reactions

IV. Looking Ahead

II. Advantages of Radical Reactions

Some advantages of radical reactions can be traced to the mild conditions under which they are conducted; others to the stability of common protecting groups during reaction. Ease in performing group and atom replacement is still another benefit, but the greatest value radical reactions bring to carbohydrate synthesis is in forming new, carbon–carbon bonds; in other words, even though radical reactions are capable of causing a variety of structural changes, their most valuable role is their most basic one, namely, building more complicated structures from less complicated ones.

III. Disadvantages of Radical Reactions

In addition to the advantages associated with radical reactions, there also are disadvantages. Deciding whether to use a radical reaction depends, in part, on knowing what these disadvantages are. Problems with radical reactions are described in the next four sections.

IV. Looking Ahead

The advantages of radical reactions discussed in this chapter provide an introduction to the possibilities these reactions bring to carbohydrate chemistry. The chapters immediately ahead are devoted to a systematic presentation of the various types of carbohydrate derivatives that are able to produce radicals and the reactions that these radicals undergo. Later chapters contain information about reactions that take place when radicals are generated by electron transfer from transition-metal complexes to various carbohydrate derivatives.

CHAPTER OVERVIEW

2: Halogenated Compounds

Halogen-atom abstraction to give a carbon-centered radical is the first step in many radical reactions. Among the more common of these are simple reduction, radical addition, and radical cyclization.

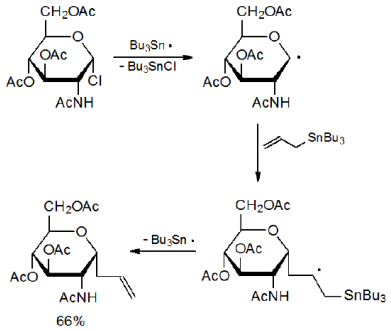
Topic hierarchy

I. Introduction
II. Radical Formation by Dehalogenation
III. Radical Reactions
IV. Halogenation
V. Summary

I. Introduction

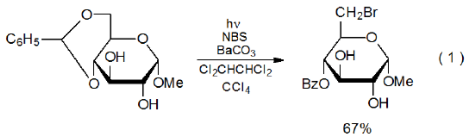
Halogen-atom abstraction to give a carbon-centered radical is the first step in many radical reactions. Among the more common of these are simple reduction, radical addition, and radical cyclization. A typical example is give in Scheme 1, where chlorine-atom abstraction produces a pyranos-1-yl radical that then adds to the carbon–carbon double bond in allyltri-*n*-butyltin.[1] Group migration, ring-opening, elimination, hydrogen-atom abstraction, and radical combination are less common reactions that also often begin with halogen-atom abstraction that forms a carbohydrate radical.

Scheme 1



Another way of viewing reactions that begin with halogen-atom abstraction is one taken from the perspective of the involvement of such reactions in carbohydrate synthesis. This view describes these reactions in terms of the changes in carbohydrate structure that they make possible; thus, halogen-atom abstraction is involved in synthesizing deoxygenated sugars and nucleosides, establishing glycosidic linkages, extending carbon-atom chains, forming new ring systems, introducing unsaturation, and modifying protecting group reactivity. This broad range of applications combines with generally good product yields to make halogen-atom abstraction the first step in many, useful synthetic reactions.

In addition to the variety of reactions that begin with loss of a halogen atom, there are others that reverse this process; that is, there are reactions that cause a halogen atom to be incorporated into a carbohydrate. The range of synthetically useful compounds prepared in this way is limited. Radical halogenation is not part of a general synthesis of carbohydrate halides, but it sometimes provides a route to compounds that are difficult to prepare in other ways. The specialized, but useful, nature of radical halogenation is illustrated by the conversion of a 4,6-*O*-benzylidene acetal into the corresponding bromodeoxy benzoate (eq 1).[2]



(1)

II. Radical Formation by Dehalogenation

Most mechanistic understanding of radical formation by dehalogenation comes from study of alkyl halides. It is reasonable to assume that the findings from these investigations also are applicable to reactions of halogenated carbohydrates but, at the same time, to recognize that such application does involve extrapolation of the data to more complex structures.

III. Radical Reactions

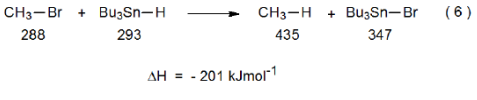
A. Simple Reduction

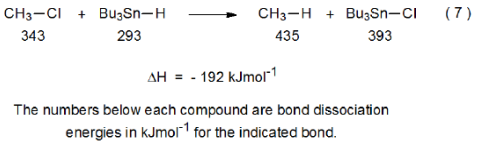
1. Typical Reaction Conditions

Simple reduction of a halogenated carbohydrate is a reaction in which the only change that occurs in the substrate is replacement of a halogen atom with a hydrogen atom. This change typically is brought about by heating a solution of a halogenated carbohydrate, tri-*n*-butyltin hydride, and a catalytic amount of 2,2'-azobis(isobutyronitrile) (AIBN) in benzene or toluene at 80-110 ^{o}C for a few hours.

2. Thermodynamic Driving Force for Reaction

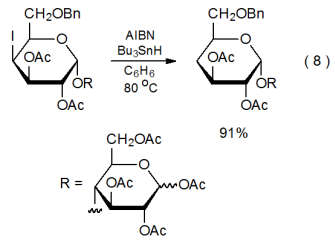
There is a powerful thermodynamic driving force for simple reduction of halogenated compounds with tri-*n*-butyltin hydride.[14] This driving force is apparent in the highly exothermic reaction of bromomethane with tri-*n*-butyltin hydride (eq 6).[14] The exothermic nature of this reaction derives from a carbon–bromine bond being replaced by a stronger carbon–hydrogen bond and a tin–hydrogen bond being exchanged for a stronger tin–bromine bond. The data in eq 7 show that simple reduction of chloromethane is also quite exothermic.[14]





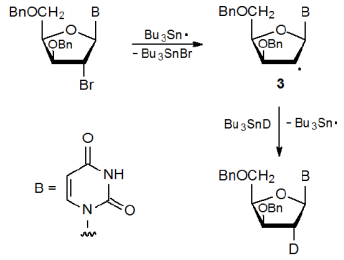
3. Synthesis of Deoxygenated Sugars and Nucleosides

Simple reduction is a common reaction for halogenated sugars and nucleosides. A typical example, one in which halogen replacement takes place at C-4 in a pyranoid ring, is shown in eq 8.[23] Other reactions, ones where the halogen atom is located at C-1,[24,25] C-2,[26,27] C-3,[28] C-4,[29,30] C-5,[31] or C-6[32,33] in a pyranoid ring, are common. There are fewer reports of simple reduction when the halogen atom is attached to a furanoid ring (C-1,[34,35] C-5,[36,37] or C-6[38]), but many nucleoside reactions are known where the halogen atom is bonded to C-2',[39,40] C-3',[41,42] or C-5' [43,44] in the substrate. (Each reference listed above refers to a simple-reduction reaction representative of those taking place at the indicated carbon atom.)



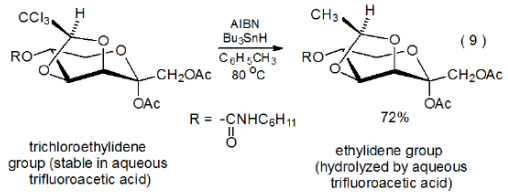
When a halogen atom is replaced by a deuterium atom, simple reduction can provide information about reaction stereoselectivity; thus, in the reaction shown in Scheme 7 the approach of Bu_3SnD to the nucleoside radical **3** is from the less hindered face of the furanoid ring.[45] Reaction at the 2'-position in other halogenated nucleosides also is stereoselective, but this selectivity, which is heavily influenced by the structure and positioning of ring substituents, sometimes is modest.[46–48]

Scheme 7



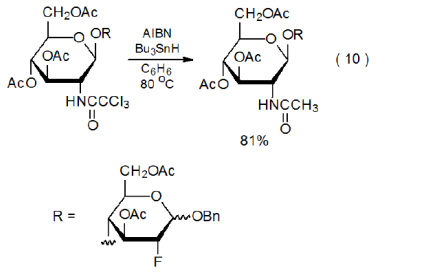
4. Protecting Group Modification

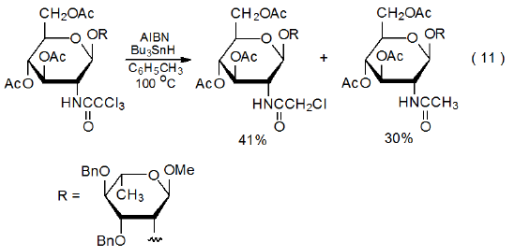
Simple reduction sometimes is used to modify protecting group reactivity.[49–57] In the reaction shown in eq 9, for example, replacement of the three chlorine atoms in the trichloroethylidene group with three hydrogen atoms makes hydrolytic removal of this group much easier.[49] In a related example, the trichloroacetamido group is converted to the more easily hydrolyzed acetamido group by three, successive simple reduction reactions (eq 10).[56] Reaction with tri-*n*-butyltin hydride as a means of replacing all the chlorine atoms in a protecting group with hydrogen atoms is not always successful because complete dechlorination sometimes is elusive (eq 11[58]).[58–60]



trichloroethylidene group (stable in aqueous trifluoroacetic acid)

ethylidene group (hydrolyzed by aqueous trifluoroacetic acid)

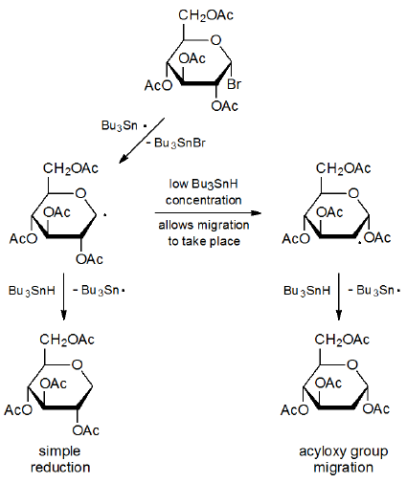




5. Acyloxy Group Migration

When an anomeric halide with a neighboring acyloxy group reacts with tri-*n*-butyltin hydride, acyloxy group migration leading to a 2-deoxy sugar competes with simple reduction (Scheme 8).[61] If 2-deoxy sugar synthesis (and not simple reduction) is the goal of the reaction,[61–64] conditions that maximize group migration need to be selected. Generally, this means maintaining the tri-*n*-butyltin hydride concentration at a low enough level to allow time for migration to occur.

Scheme 8



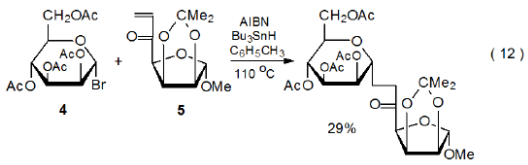
B. Addition

Halogenated compounds are common radical precursors for addition reactions involving carbohydrates, but other carbohydrate derivatives also function in this capacity; consequently, radical addition reactions are mentioned in most of the chapters in this book. They are discussed extensively not only in this chapter but also in Chapters 10, 12, 13, and 18. In Chapter 18 radical addition is considered from a different point of view, that is, with a focus on the compound to which addition is occurring rather than on the radical precursor.

Addition reactions can be divided into three groups based on what happens after formation of the adduct radical. The first group (addition-abstraction reactions) contains those reactions where the adduct radical abstracts a group or atom from a donor present in solution. Atom abstraction is more common that group abstraction and nearly always involves a hydrogen atom. The second type of reaction (addition-combination) is one in which the adduct radical combines with another radical or an organometallic reagent present in the reaction mixture. In the third reaction type (addition-elimination or addition-fragmentation) the adduct radical forms an unsaturated compound by a β-fragmentation process that eliminates a radical. Examples in which halogenated carbohydrates serve as radical precursors for each of these reaction types are given in the following three sections.

1. Addition-Abstraction Reactions

Formation of a carbon-centered radical by reaction of a glycosyl halide with a tin- or silicon-centered radical is the first step in many addition reactions. An addition-abstraction reaction takes place when a radical produced by halogen-atom abstraction adds to a multiple bond to generate an adduct radical that then abstracts a hydrogen atom. The hydrogen-atom transfer is nearly always a tin- or silicon hydride. An example of this type of reaction is given in eq 12, where a pyranos-1-yl radical generated from the D-mannopyranosyl bromide **4** adds to the α,β-unsaturated ketone **5**.[65] Pyranos-1-yl radicals generated from halogenated carbohydrates are known to add to α,β-unsaturated nitriles,[66,67] esters,[67,68] aldehydes,[67] ketones,[69,70] lactones,[71,72] and phosphonates.[73,74] In all of these reactions formation of the adduct radical is followed by hydrogen-atom abstraction. Pyranos-1-yl and other carbohydrate radicals formed from halogenated compounds also add to oximes[75–77] and electron-deficient enol ethers.[78,79] The reactions shown in equations 13 and 14 underscore a critical feature of radical addition reactions, namely, that unless a multiple bond is electron-deficient (eq 13), addition of a nucleophilic radical (which nearly all carbohydrate radicals are) will be too slow to compete effectively with simple reduction (eq 14).[80]



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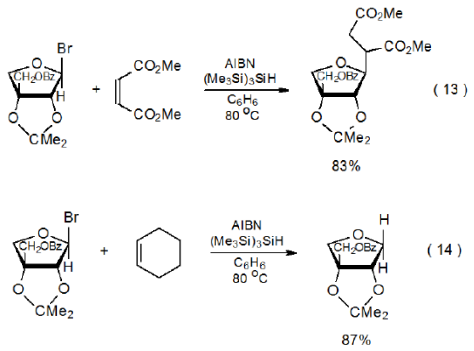
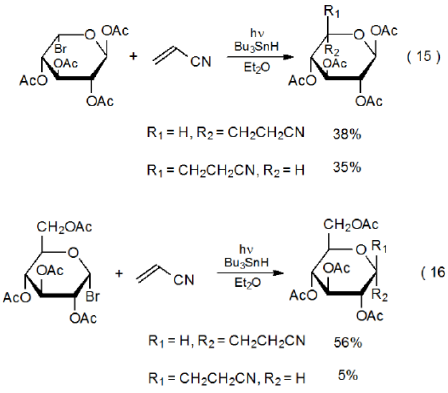


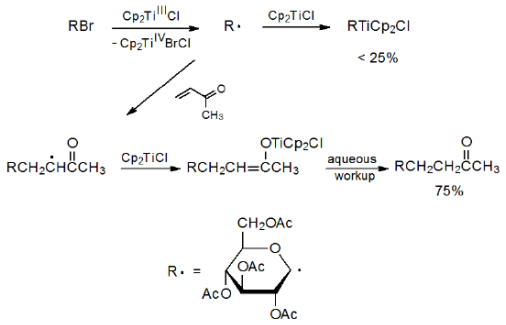
Addition-abstraction reactions that do not involve pyranos-1-yl radicals are much less common than those that do. An example of a non-pyranos-1-yl radical reaction is shown in eq 15.[81] The pyranos-5-yl radical formed in this reaction has reactivity similar to that of a pyranos-1-yl radical because both are nucleophilic species that are stabilized by a ring oxygen atom. This similarity in reactivity can be seen when comparing the reaction shown in eq 15[81] with that in eq 16.[82] Several addition-abstraction reactions of radicals centered on C-6[83–86] are known, but reaction of a radical located on an atom in or attached to a pyranoid ring (other than C-1or C-6) is rare.[87] There are reports of addition-abstraction reactions where the radical is centered on a carbon atom that is part of or attached to a furanoid ring.[88–90]



2. Addition-Combination Reactions

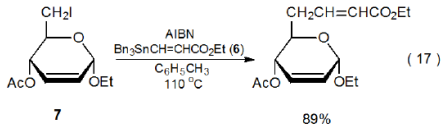
Although radical formation from a glycosyl halide normally involves halogen-atom abstraction by a tin or silicon centered radical, a radical also can be generated by electron transfer to the glycosyl halide from a metal ion, such as the samarium ion in SmI_2 or the titanium ion in Cp_2TiCl. An example of this type of reaction is shown in Scheme 9, where the pyranos-1-yl radical (R·) is formed by electron transfer from titanium to the glycosyl bromide (RBr).[91] In the reaction shown in Scheme 9, radical addition to an electron-deficient multiple bond is faster than combination of the radical with a second molecule of Cp_2TiCl. Once addition occurs, however, the situation changes. The reactivity of the adduct radical is so different from the far more nucleophilic pyranos-1-yl radical that the fastest reaction for the adduct radical is combination with a molecule of Cp_2TiCl. (Chapters 20-24 contain further discussion of addition-combination reactions brought about by electron-transfer from organometallic complexes to carbohydrate halides.)

Scheme 9



3. Addition-Elimination Reactions

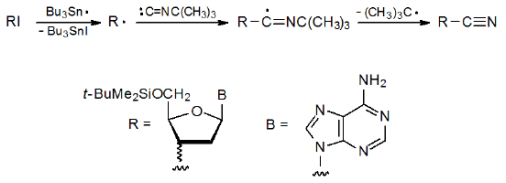
When a carbon-centered radical adds to allyltri-*n*-butyltin, it begins a sequence of reactions that replaces a halogen atom with an allyl group (Scheme 1).[1] This type of transformation (an addition-elimination reaction) often occurs when the halogen atom is attached to C-1[1,92–94] but also takes place when such an atom is bonded elsewhere in a carbohydrate framework.[95,96] For example, the reaction between the tri-*n*-butyltin acrylate **6** and the deoxyiodo sugar **7** involves a radical centered at C-6 (eq 17).[97]



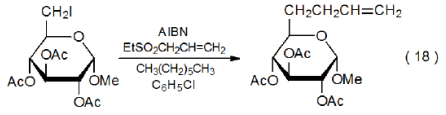
(17)

A reaction mechanistically similar to that shown in eq 17, but one with a quite different outcome, occurs when a halogen atom is abstracted by $Bu_3Sn\cdot$ in the presence of *t*-butyl isocyanide. When this happens, an addition-elimination reaction produces a nitrile (Scheme 10).[98]

Scheme 10



Most addition-elimination reactions transfer an allyl or substituted allyl group from a tin-containing compound to a carbon-centered radical; however, this transfer can be tin-free.[99,100] In the reaction shown in eq 18 the allyltin reactant is replaced by allyl ethyl sulfone.[99]



(18)

C. Cyclization

New ring formation is pervasive in the radical reactions of carbohydrates; consequently, radical cyclization, like radical addition, is mentioned in many of the chapters in this book. Significant discussion exists in this chapter because halogenated carbohydrates often are the precursors for radical-based formation of new ring systems. A large portion of Chapter 12 also is devoted to radical cyclization because *O*-thiocarbonyl compounds frequently are precursors for radicals involved in new ring formation. Chapter 19 is devoted entirely to cyclization reactions and is concerned less with radical formation and more with the internal radical addition that produces new rings.

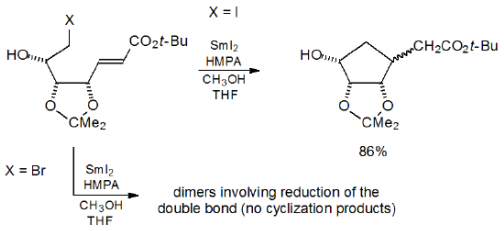
1. Substrate Reactivity

As with simple reduction reactions, the abstracting radical that begins radical cyclization nearly always is derived from a tin or silicon hydride. The well-established order of reactivity for halogenated compounds with silicon and tin hydrides (RI > RBr > RCl

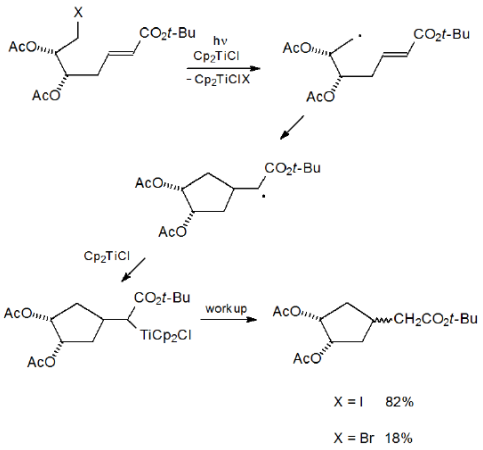
>> RF), mentioned in Section II.B, accounts for the usual selection of a carbohydrate iodide or bromide as the substrate in a cyclization reaction.

Halogen identity is especially critical to dehalogenation with either SmI_2 or Cp_2TiCl. In the cyclization reaction shown in Scheme 11 the iodide gives a good yield of the substituted cyclopentane, but the bromide is enough less reactive that it produces only bromine-containing dimers arising from reduction of the double bond by SmI_2.[101] Reaction of a similar compound with Cp_2TiCl results in an 82% yield of substituted cyclopentanes from the iodide but only an 18% yield from the corresponding bromide (Scheme 12).[102] More forcing reaction conditions might have improved product yield from the bromide because its attempted cyclization returned primarily unreacted starting material.

Scheme 11



Scheme 12

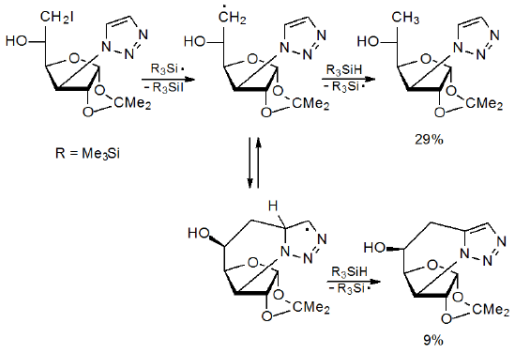


Successful cyclization of halogenated carbohydrates by reaction with SmI_2 or Cp_2TiCl depends upon reaction conditions and additives. The presence of hexamethylphosphoramide (HMPA) is so important to the reactivity of SmI_2 that the cyclic product shown in Scheme 11 does not form unless HMPA is present in the reaction mixture.[101] In a similar fashion, UV radiation is critical to the reaction shown in Scheme 12. If it is omitted, little reaction takes place.[102]

2. Competition between Cyclization and Hydrogen-Atom Abstraction

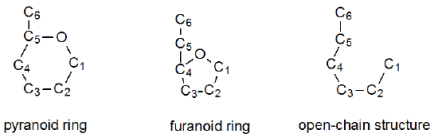
Whenever a cyclization reaction is conducted in the presence of a tin or silicon hydride, hydrogen-atom abstraction by the initially formed radical, leading to simple reduction, competes with cyclization (Scheme 13).[38] Other reagents that are not hydrogen-atom transfers but are capable of generating radicals from halogenated carbohydrates (e.g., $Bu_3SnSnBu_3$,[103] SmI_2,[101,104,105] and Cp_2TiCl[102]) have the advantage that simple reduction is suppressed. Even though simple reduction is not a problem when using SmI_2 and Cp_2TiCl, each of these compounds can prevent cyclization by combining with a carbon-centered radical before ring formation takes place; therefore, rapid ring closure remains an important criterion for successful reaction.

Scheme 13



3. Organization of Cyclization Reactions

Successful radical cyclization requires a multiple bond and radical center that are suitably positioned with respect to each other. The radical center in such a reaction can be either on an atom that is part of the carbohydrate framework (Figure 2) or on a substituent group. The same possibilities exist for the multiple bond. For purposes of discussion it is useful to divide cyclization reactions into the four basic types shown in Figure 3. This Figure also contains a short-hand terminology that has been proposed to identify each reaction type.[105] Chapter 19 contains extensive tables of cyclization reactions in which radicals are formed from halogenated and nonhalogenated carbohydrates.



The framework in a typical hexose has one of the three structural types shown above. A framework radical is one centered on a numbered carbon atom, and a framework multiple bond is one involving at least one of these atoms. The basic carbohydrate framework is sometimes extended by the bonding of additional carbon atoms to C-1or C-6 or both.

Figure 2. Possible carbohydrate frameworks

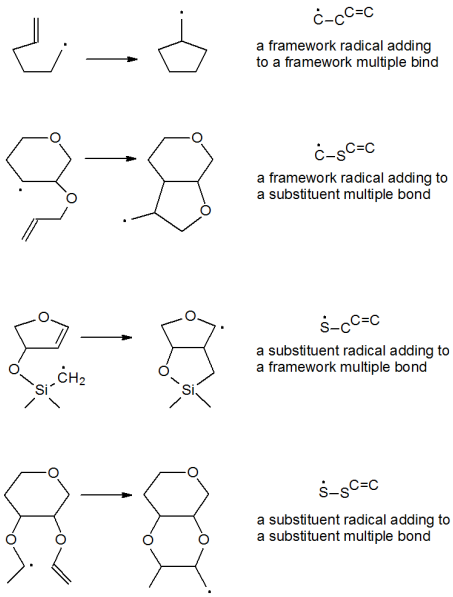
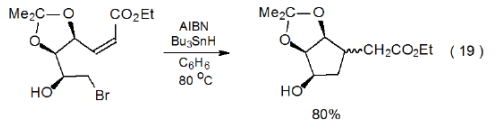


Figure 3. Possible types of cyclization reaction for carbohydrate radicals

a. Addition of a Framework Radical to a Framework Multiple Bond

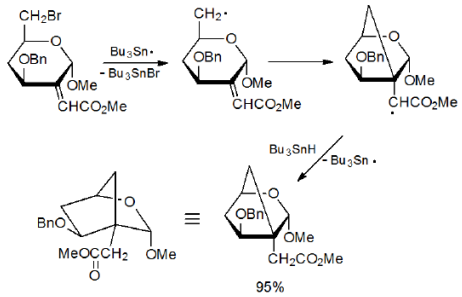
The possibilities for a framework radical adding internally to a framework multiple bond are limited by the size of the rings that are easily produced; thus, only five- and six-membered rings generally form rapidly enough to compete with other radical reactions. Since radical cyclization produces five-membered rings more quickly than six-membered ones, the typical cyclization reaction produces a pair of heavily substituted, cyclopentane derivatives (eq 19[106]).[106–111] When five-membered ring formation is not possible but producing a six-membered ring is, cyclization gives a substituted, cyclohexane derivative (eq 20).[112] Addition of a framework radical to a framework multiple bond also can produce a bicyclic compound (Scheme 14).[113]



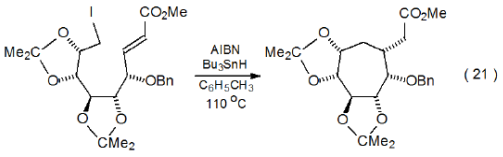
(19)

(20)

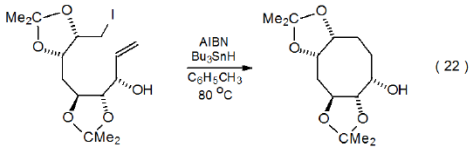
Scheme 14



Although forming either a five- or six-membered ring is the typical result of radical cyclization, larger rings are possible if the carbohydrate framework is held so that the radical center easily can approach the multiple bond. Striking examples of such a situation are found in the reactions shown in equations 21 and 22, where the *O*-isopropylidene groups cause the iodides **8** and **9** to adopt conformations that favor formation of seven- and eight-membered rings, respectively.[114]

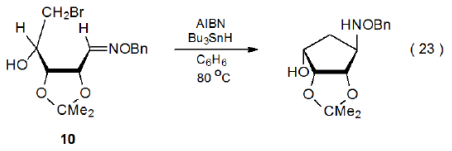


(21)

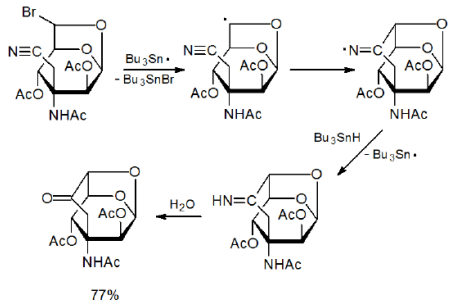


(22)

One way to increase the reactivity of a multiple bond in a radical cyclization reaction is to replace one of the carbon atoms with an electronegative heteroatom.[115–121] The remaining carbon atom then will have electron density drawn from it and, as a result, have enhanced reactivity toward nucleophilic radicals. The oxime **10** contains a double bond activated in this way (eq 23).[115] Having reactive centers able easily to come within bonding distance translates into cyclic products being formed in reactions involving other carbon–nitrogen[116–119] and even carbon–oxygen[120,121] multiple bonds. In the reaction shown in Scheme 15, for example, ring formation occurs because the radical center easily comes into contact with the cyano group.[118]

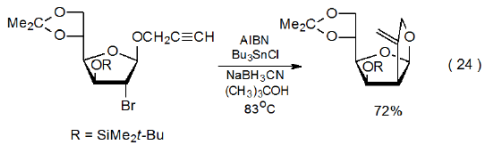


Scheme 15

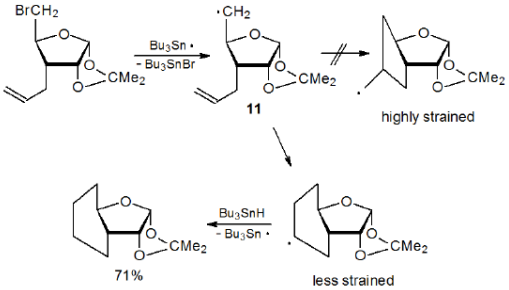


b. Addition of a Framework Radical to a Substituent Multiple Bond

An example of a reaction in which a framework radical adds to a substituent multiple bond to form a five-membered ring is shown in eq 24.[122] If five-membered-ring formation introduces too much strain into a system, reaction to give a larger ring becomes a possibility; thus, the radical centered at C-5 in **11** adds to the substituent double bond to form a six-membered ring (Scheme 16) and, in so doing, avoids producing highly strained, trans-fused, five-membered rings.[123]



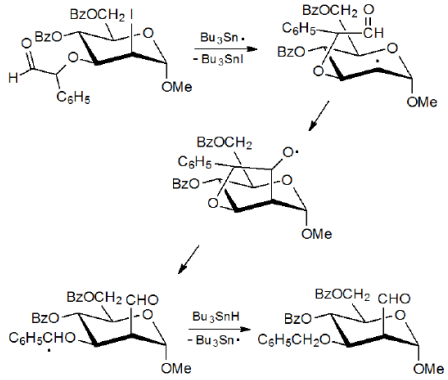
Scheme 16



Although bimolecular addition of a carbohydrate radical to a multiple bond is fast enough to be observed only when the multiple bond is electron-deficient, radical cyclization is not limited in this way. Having a radical center, such as the one at C-5 in **11** (Scheme 16), in close proximity to a double bond makes cyclization competitive with other radical reactions (e.g., simple reduction) even though the multiple bond is not electron-deficient.

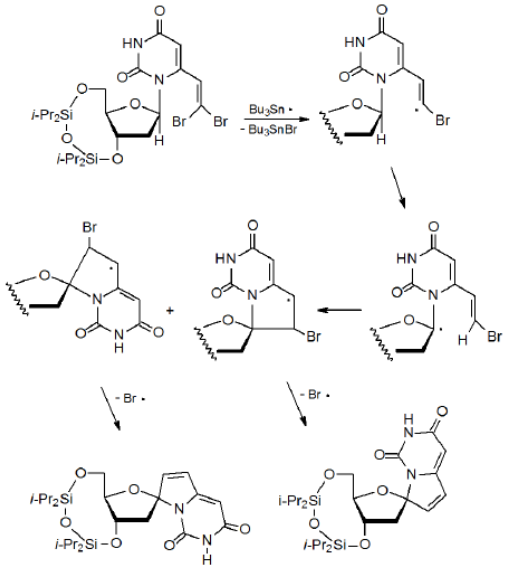
Radical cyclization followed by ring opening that breaks the newly formed bond is a degenerate addition-elimination reaction that is rarely useful or even detectable. Sometimes, however, ring opening breaks a different bond from that produced during cyclization.[124,125] The result of such a reaction is an addition-elimination process, such as that shown in Scheme17, where the effect of the reaction is migration of a part of a substituent group.[124]

Scheme 17



A unique type of cyclization between a framework radical and a substituent multiple bond takes place in nucleosides that have properly placed dibromovinyl groups.[103,126–131] Bromine-atom abstraction by $Bu_3Sn·$ produces a vinyl radical that begins a sequential reaction leading to two spiro compounds (Scheme 18).[103] Using $Bu_3SnSnBu_3$ in this reaction (rather than Bu_3SnH) improves the yield of the cyclization product because competing simple reduction involving a tin hydride is not an option.[103]

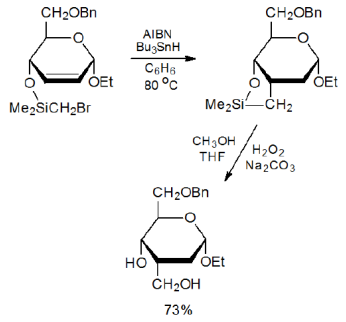
Scheme 18



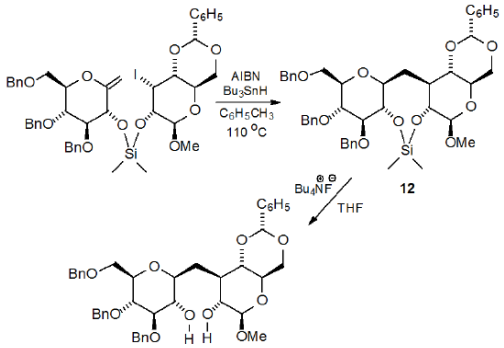
c. Addition of a Substituent Radical to a Framework Multiple Bond

Cyclization involving halogenated carbohydrates often occurs when the halogen atom is part of a substituent group and the multiple bond is located in the carbohydrate framework. The substrate in many of these reactions is a silyl ether with a bromine atom incorporated into the silicon-containing group.[132–139] An example is shown in Scheme 19, which describes a reaction that stereoselectively creates a new C–C bond at C-3 in the product.[132] Nonradical reaction of the resulting product transforms it into a diol (Scheme 19) that can be readily converted into other compounds. An extension of this type of reaction to a pair of saccharide units connected by a silaketal tether leads to formation of a protected *C*-disaccharide (**12**) from which the tether is easily removed (Scheme 20).[140]

Scheme 19

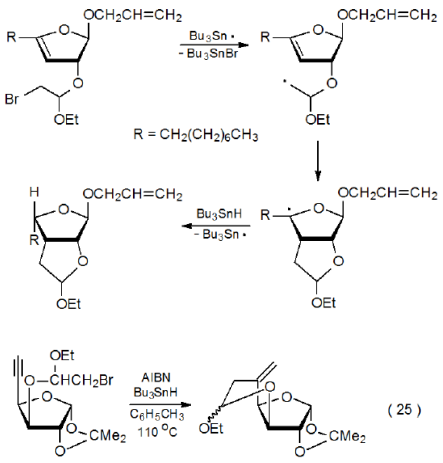


Scheme 20



Cyclization of an unsaturated carbohydrate in which an acetal substituent contains a halogen atom is similar to cyclization of brominated silyl ethers such as that pictured in Scheme 19. High stereoselectivity is the norm in these reactions.[141–147] In the process shown in Scheme 21, for example, the stereochemistry at C-3 is controlled by the kinetically and thermodynamically favored formation of a cis-fused ring system.[141] [There is a second chiral center (C-4) created during this reaction. The stereochemistry at this center is determined by the least-hindered approach of tri-*n*-butyltin hydride to the reacting radical.] The reaction shown in eq 25 provides an example of new ring formation when a radical formed from a halogen-containing, acetal substituent adds internally to a triple bond.[142]

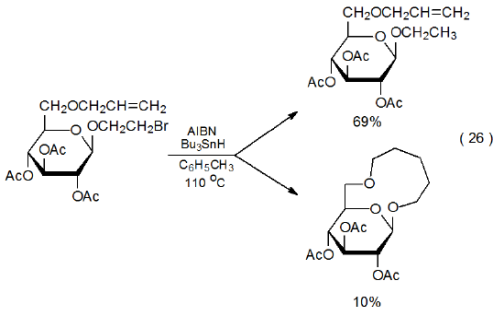
Scheme 21



d. Addition of a Substituent Radical to a Substituent Multiple Bond

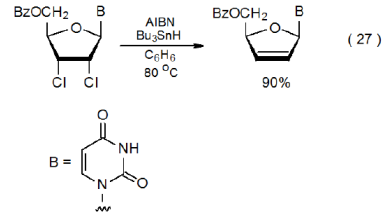
Sometimes in a radical cyclization reaction neither the carbon atom bearing the radical center nor the carbon atoms of the multiple bond are part of the carbohydrate framework.[148,149] When this occurs, the carbohydrate portion of the molecule has only an indirect influence on the reaction; that is, it can affect reaction stereoselectivity by acting as a chiral auxiliary, or its cyclic structure can

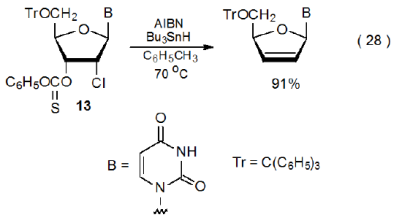
bring reactive centers into bonding distance. It is the latter role that assists eleven-membered ring formation in the reaction shown in eq 26.[148]



D. Elimination

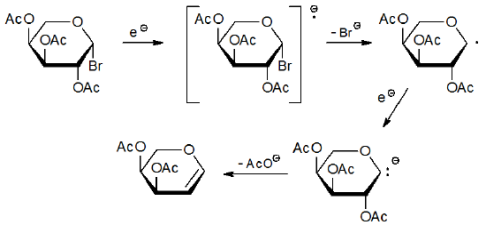
Free-radical elimination takes place when a vicinal dihalide reacts with tri-*n*-butyltin hydride (eq 27).[150] A similar reaction occurs if one of the vicinal substituents is a halogen atom and the other contains an *O*-thiocarbonyl group.[151,152] In the reaction shown in eq 28[151] there is little doubt that the initial interaction between $Bu_3Sn\cdot$ and compound **13** in most instances is with the substituent at C-3' because the rate constant for reaction of $Bu_3Sn\cdot$ with a compound containing an *O*-thiocarbonyl group is much larger than that for reaction with a chlorinated compound.

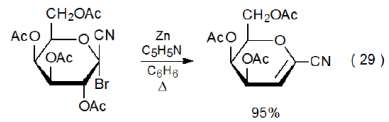




Electrochemical reduction of glycosyl halides (and their sulfur-containing analogs[154a]) begins with electron transfer to the halide to produce a radical anion that reacts further to give the corresponding glycal (Scheme 22[153]). Reaction of glycosyl bromides with zinc dust also leads to glycal formation by electron-transfer to a glycosyl halide (eq 29).[154b] The mechanism for this reaction may parallel that shown in Scheme 22, but the possibility also exists that an organozinc intermediate forms following the initial electron transfer.

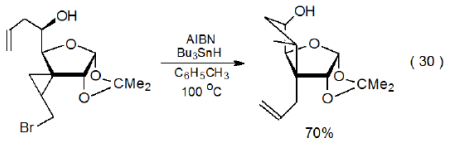
Scheme 22





E. Ring-Opening

If halogen-atom abstraction produces a cyclopropylcarbinyl radical, cyclopropane ring opening takes place. The radical remaining after ring opening then can undergo hydrogen-atom abstraction,[155] addition,[156] or, as shown in eq 30, cyclization.[157]

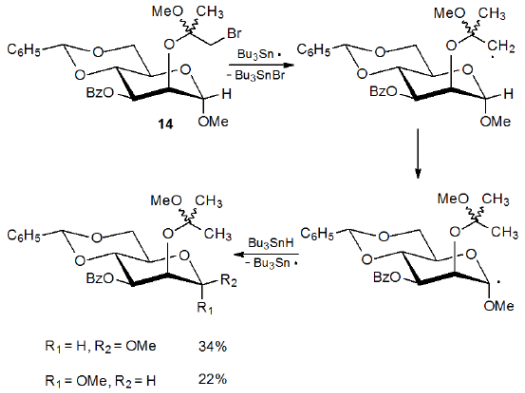


(30)

F. Internal Hydrogen-Atom Abstraction

Reaction of a halogenated carbohydrate to form a carbon-centered radical rarely results in this radical abstracting a hydrogen atom from a carbon–hydrogen bond in another molecule because such abstraction is, in most instances, too slow to compete with other radical reactions. If, however, the abstraction is internal and the radical is quite reactive (primary, vinyl or aryl), hydrogen-atom abstraction can take place.[158–160] Dehalogenation of the bromide **14** begins such a reaction by producing a primary radical that abstracts a hydrogen atom from C-1, a process that leads to epimerization at this carbon atom (Scheme 23).[158] Internal hydrogen-atom abstraction by a vinyl radical takes place in the reaction pictured in Scheme 18.[103]

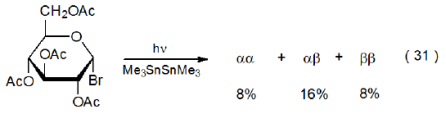
Scheme 23



G. Radical Combination

1. Dimerization

Radical combination is not a common synthetic reaction for carbohydrates, but it does take place when conditions are adjusted so that reactions such as hydrogen-atom abstraction are to slow to compete.[161–163] Having the source of the chain-carrying radical be $Me_3SnSnMe_3$ (as opposed to a tin hydride) reduces the rate of hydrogen-atom abstraction by the carbohydrate radical to the point that the three dimers shown in eq 31 are formed. {Similar dimer formation takes place during reaction of glycosyl phenyl sulfones [Chapter 3, Section VII.B.1.c] and glycosyl phenyl selenides [Chapter 4, Section II.B.6]} Electrochemical reactions of glycosyl halides also produce radical dimers.[163]

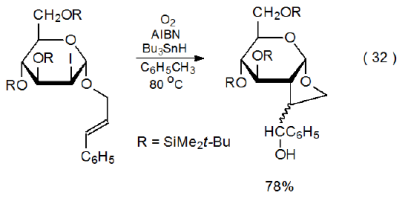


(31)

2. Reaction with Molecular Oxygen

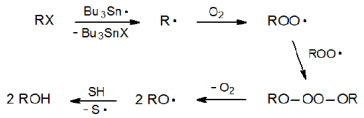
Reaction of halogenated carbohydrates with tri-*n*-butyltin hydride in the presence of oxygen replaces the halogen atom with a hydroxyl group.[164–168] Since combination of a carbon-centered radical with molecular oxygen is either diffusion-controlled or nearly so ($k \cong 2 \times 10^9\ M^{-1}s^{-1}$),[169] any other reaction of the radical taking place in the presence of oxygen must be rapid enough to happen before O_2 reaches the radical center. An example of a cyclization reaction that is fast enough to meet this criterion is shown

in eq 32.[164] Since the oxygen concentration in the reaction mixture is approximately 1 x 10^{-3} M, the rate constant for cyclization needs to be at least 1 x 10^{7} s^{-1} in order for an acceptable yield of a cyclic product to be obtained.[166b] A proposed mechanism for replacement of a halogen atom with a hydroxyl group is given in Scheme 24.[170]

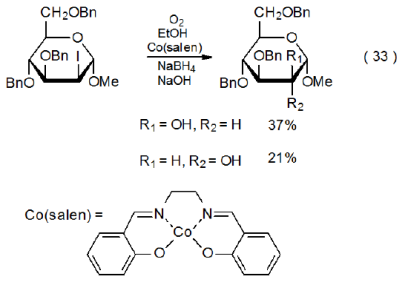


(32)

Scheme 24



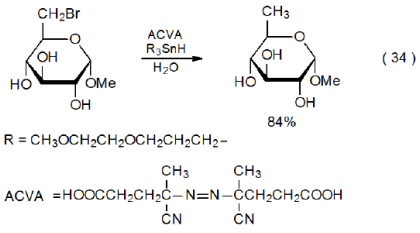
Other reagents and reaction conditions also cause replacement of halogen atoms with hydroxyl groups. These include Et_3B–O_2 initiated reaction of a deoxyiodo sugar with molecular oxygen[171,172] and adding O_2 to a reaction mixture in which AIBN is both initiator and reactant.[166] Another set of conditions leading to replacement of a halogen atom with a hydroxyl group consists of reacting a deoxyiodo sugar with $NaBH_4$ and O_2 in the presence of a catalytic amount of Co(salen) (eq 33[173]).[162,173–175] A comparative study found Co(salen)-catalyzed oxidation reactions to be experimentally more convenient than those with a tin hydride.[162]

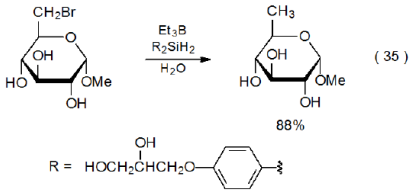


(33)

H. Water-Soluble Halides

Most halogenated carbohydrates used in synthesis are rendered soluble in organic solvents by the introduction of various hydroxyl protecting groups, but sometimes it is useful to be able to conduct dehalogenation reactions in aqueous solution on unprotected or partially protected carbohydrates. Such a situation requires a water-soluble replacement for the tin and silicon hydrides typically used. Water-soluble hydrogen-atom transfers can be formed by replacing the alkyl substituents normally attached to tin or silicon with more polar ones. This replacement produces hydrides that are sufficiently soluble in water to allow simple reduction to take place in aqueous solution (eq 34[176] and eq 35[177]).





There are potential advantages to conducting reactions in water, advantages that extend beyond substrate solubility.[176,177] One of these is that reactions conducted in aqueous solution may exhibit new reactivity because, rather than taking place in an essentially nonpolar liquid, these reactions occur in a polar, heavily hydrogen-bonded solvent. Since water generally does not participate in radical reactions, it is effectively an inert solvent. Also, using water as the reaction medium can reduce or even eliminate the need for recycling or disposal of organic solvents.

I. Hypohalites

Hypohalites are intermediates in the formation of alkoxy radicals. Reactions of hypohalites and the alkoxy radicals they produce are discussed in Chapter 6.

J. Organotin Hydrides

The majority of reactions of halogenated carbohydrates use an organotin hydride (nearly always Bu_3SnH) as a hydrogen-atom transfer and as a source of a chain-carrying-radical; however, there are serious problems associated with the toxicity of tin-containing compounds and the difficulty in removing their residues from reaction products. A variety of solutions to these problems have been proposed. Since most of these solutions apply not only to reactions of halogenated carbohydrates but also to those of a broad range of carbohydrate derivatives, the solutions will not be discussed here (and then repeated in later chapters); rather, they are gathered together in Appendix 1, which is found at the end of this book.

IV. Halogenation

Regioselectively replacing a particular hydrogen atom in a carbohydrate with a halogen atom depends upon a radical abstracting one hydrogen atom from among the many present in a typical molecule. When this type of selectivity occurs, it sometimes is linked to radical philicity; that is, a hydrogen atom that is more electron rich than others in a molecule can be abstracted preferentially by a highly electrophilic radical. This regioselectivity caused by radical philicity only occurs when the transition state is early in a reaction. When the transition state is late, selective reaction also can take place, but in this case selectivity exists because abstraction of a particular hydrogen atom produces a carbon-centered radical that is much more stable than radicals formed by abstraction of other hydrogen atoms. Since there are relatively few carbohydrates where highly selective hydrogen-atom abstraction occurs and since hydrogen-atom abstraction typically is the first step in halogenation, regioselective, free-radical halogenation reactions are limited in number.

V. Summary

Halogen-atom abstraction by a tin-centered radical is a common reaction in carbohydrate chemistry. Ample evidence supporting radical intermediates in this type of reaction comes from chemical reactivity and from direct radical observation by ESR spectroscopy. Iodides are the most reactive of the halogenated carbohydrates. Bromides are slightly less so, but the reactivity of chlorides is considerably reduced. Fluorides are essentially unreactive. In dehalogenation reactions the transition-state structure is thought to involve partial tin–halogen and carbon–halogen bonds.

Simple reduction (replacement of a halogen atom with a hydrogen atom) occurs under mild reaction conditions. The halogen atom being abstracted can be attached to any carbon atom in the carbohydrate framework. Although the primary role of simple reduction is in the synthesis of deoxy sugars and deoxy nucleosides, this reaction also can be used to modify the reactivity of halogenated protecting groups. Replacement of halogen atoms with hydrogen atoms can convert a group that is difficult to hydrolyze into one that does so more easily.

Simple reduction of anomeric halides must compete with group migration when there is an acyloxy group at C-2. This migration, which is useful in the synthesis of 2-deoxy sugars, is most likely to occur when the concentration of the hydrogen-atom transfer (e.g., tri-*n*-butyltin hydride) is held at a very low level.

Halogen-atom abstraction often is the first step in the addition of a carbohydrate radical to a compound containing a multiple bond. Such addition will occur in an intramolecular fashion if the multiple bond is electron-deficient because under the proper conditions a nucleophilic carbohydrate radical adds to an electron-deficient multiple bond more rapidly than it abstracts a hydrogen atom.- When the radical center and the multiple bond are in the same molecule and easily come within bonding distance, cyclization takes place so readily that it will occur even if the multiple bond is not electron-deficient. A characteristic of cyclization reactions is that formation of the new carbon–carbon bond often occurs in a highly stereoselective fashion.

Halogenated carbohydrates participate in a variety of less common reactions. These include double bond formation, internal hydrogen-atom abstraction, addition to molecular oxygen, cyclopropane ring opening, and radical anion formation.

Free-radical bromination produces several types of brominated carbohydrates. Bromination of benzylidene acetals leading to formation of bromodeoxy benzoates is a standard reaction in carbohydrate synthesis. Modifications of this reaction also are known; thus, the cation produced following benzylidene acetal bromination can be intercepted by water to give a hydroxy benzoate. Carbohydrates protected as benzyl ethers react with bromine to produce unstable bromides that, in turn, react with water to give benzaldehyde and the deprotected carbohydrate. Reaction with bromine of carbohydrates that do not contain benzyl or benzylidene protection regioselectively replaces a hydrogen atom on one of the carbon atoms attached to the ring oxygen atom.

CHAPTER OVERVIEW

3: Compounds with Carbon–Sulfur Single Bonds

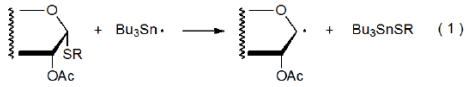
A carbohydrate derivative that contains a sulfur atom bonded to two carbon atoms is capable of forming carbon-centered radicals. A common pathway for radical formation in compounds of this type is homolytic cleavage of a carbon–sulfur bond brought about by group abstraction.

Topic hierarchy

I. Introduction
II. Reaction Mechanisms
III. Alkylthio and Arylthio Substituted Carbohydrates and Related Compounds
IV. Dithioacetals
V. Thiocarbonates and Dithiocarbonates
VI. O-Thiocarbonyl Compounds
VII. Sulfones
VIII. Thiols and Thiyl Radicals
IX. Summary

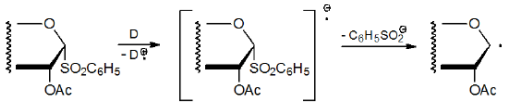
I. Introduction

A carbohydrate derivative that contains a sulfur atom bonded to two carbon atoms is capable of forming carbon-centered radicals. A common pathway for radical formation in compounds of this type is homolytic cleavage of a carbon–sulfur bond brought about by group abstraction (eq 1). When the sulfur atom in a C–S bond is part of an electronegative group, as is the case in a glycosyl phenyl sulfone, electron transfer of the type shown in Scheme 1 represents another pathway to carbon-centered radical formation. A beginning point for discussing these reactions is examining their possible mechanisms.



R = an alkyl or aryl group

Scheme 1



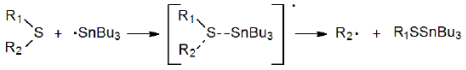
D = an electron donor

II. Reaction Mechanisms

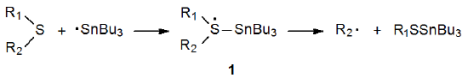
A. Group Abstraction

Two mechanisms are considered to be reasonable possibilities for the carbon–sulfur bond cleavage described by the reaction shown in eq 1.[1] The first is the bimolecular, homolytic, substitution (S_H2) reaction pictured in Scheme 2, and the second is a stepwise process that involves formation of an intermediate (**1**) with a hypervalent sulfur atom (Scheme 3). The choice between these two hinges on the existence of **1**.

Scheme 2



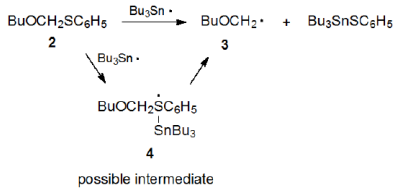
Scheme 3



1

There is little experimental evidence upon which to base a decision about formation of a compound with a hypervalent sulfur atom during carbon–sulfur bond cleavage, but reaction of the thioacetal **2** with the tri-*n*-butyltin radical provides some suggestive information (Scheme 4).[2] Although this reaction produces $BuOCH_2$· (**3**), the effect of temperature on the ESR signal for this radical is unexpected because the intensity of the signal increases as the temperature in the ESR cavity rises. (Signals due to radicals arising from reaction of bromides with Bu_3Sn· decrease with rising temperature due to leveling of the Boltzmann distribution of spin states.[2]) A possible explanation for this behavior is that a slow, temperature-dependent reaction between the thioacetal **2** and Bu_3Sn· produces the hypervalent, sulfur-centered radical **4** (not observable by ESR), an intermediate that then fragments rapidly to give the ESR observable radical **3** (Scheme 4).[2]

Scheme 4

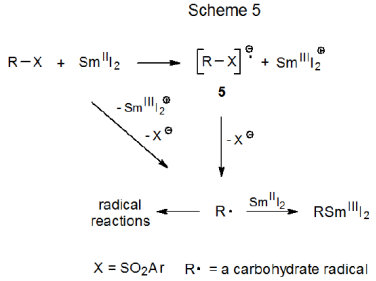


Molecular orbital calculations also have been used to study the possibility of formation of intermediates with hypervalent sulfur atoms. When these calculations focus on the reactions of sulfides, they do no support the existence of such intermediates.[1,3–6]

B. Electron-Transfer

Electron transfer to a sulfur-containing carbohydrate naturally depends upon such a compound having a group that readily accepts electrons. Sulfones meet this requirement and, thus, are prime candidates for electron-transfer reaction.[7] Two proposed mechanisms showing how such transfer could lead to cleavage of a carbon–sulfur bond are shown in Scheme 5. In one of these a sulfone reacts with an electron donor (e.g., SmI_2) to produce a radical anion (**5**) that then fragments to give an anion and a carbon-centered radical. In the other, dissociative electron transfer forms an anion and a carbon-centered radical directly from reaction of a sulfone with SmI_2.

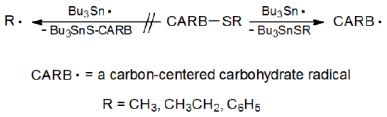
Scheme 5



III. Alkylthio and Arylthio Substituted Carbohydrates and Related Compounds

The identity of the carbon–sulfur single bond broken during reaction of a carbohydrate that has two such bonds depends upon the stability of the carbon-centered radical being formed. If the sulfur atom is part of a methylthio,[8–11] ethylthio,[12–15] or arylthio[15–24] group, radical stability favors producing a carbohydrate radical rather than a methyl, ethyl, phenyl, or *p*-tolyl radical (Scheme 6).

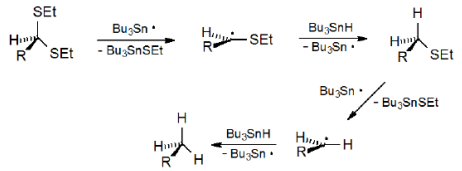
Scheme 6



IV. Dithioacetals

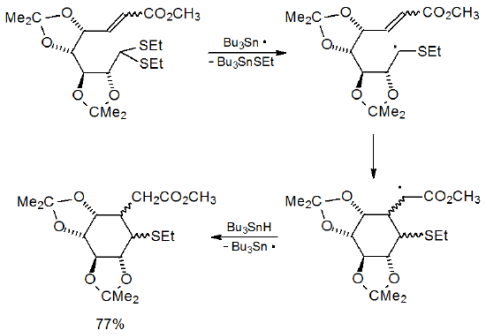
Dithioacetals react with tri-*n*-butyltin hydride to replace first one, and then the second, alkylthio group with a hydrogen atom (Scheme 10).[30] Because the first group is replaced more rapidly than the second, good yields of compounds with a single sulfur atom are obtained under the proper reaction conditions.[31–35] The greater reactivity of the first ethylthio group in these compounds is due to formation of an intermediate, carbon-centered radical that is stabilized by the sulfur atom in the remaining ethylthio group.

Scheme 10



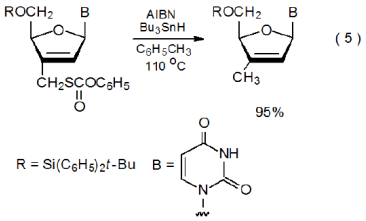
An unsaturated dithioacetal in which the double bond is properly positioned undergoes intramolecular radical addition.[31–34] Reaction typically involves capture of the first-formed, carbon-centered radical by the multiple bond; thus, in the reaction shown in Scheme 11, the major product has a new ring system with an ethylthio substituent.[31] Here again the greater reactivity of the first ethylthio group allows reaction to occur with no detectable loss of the second.

Scheme 11



V. Thiocarbonates and Dithiocarbonates

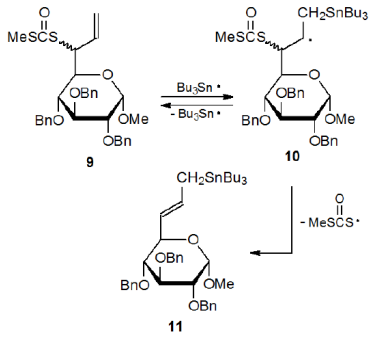
Thiocarbonates and dithiocarbonates are compounds in which at least one sulfur atom is bonded to the carbon atom of a carbonyl group. The reactivity of these compounds is similar to that of the sulfur-containing compounds already discussed in that reaction begins with carbon–sulfur bond cleavage producing the more stable of the possible carbon-centered radicals; thus, in the reaction shown in eq 5, product identity is consistent with forming an intermediate allylic radical from reaction of a thiocarbonate.[36]



(5)

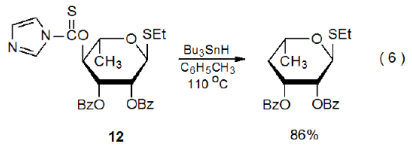
Addition of $Bu_3Sn\cdot$ to the dithiocarbonate **9** is the first step in an addition-elimination reaction that produces the tin-containing compound **11** (Scheme 12).[37] The stability of $CH_3SC(=O)S\cdot$ is critical to this type of reaction because it, rather than $Bu_3Sn\cdot$, is expelled when a radical such as **10** forms a tin-containing product.[37,38] Since $Bu_3Sn\cdot$ addition to a double bond often is reversible, **10** sometimes may break a carbon–tin bond causing an undetectable regeneration of $Bu_3Sn\cdot$ and the substrate **9**.

Scheme 12

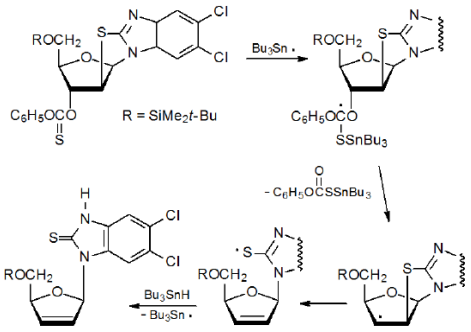


VI. O-Thiocarbonyl Compounds

Compounds with carbon–sulfur single bonds are substantially less reactive with tin- and silicon-centered radicals than are compounds with C–S double bonds. Among carbohydrates these double bonds are almost always part of *O*-thiocarbonyl groups. (The reactions of *O*-thiocarbonyl carbohydrate derivatives are discussed in Chapter 12.) The reaction shown in eq 6 illustrates the greater reactivity of a C–S double bond when compared to a C–S single bond because only the *O*-thiocarbonyl group in the 1-thioglycoside **12** reacts even though an ethylthio group is present in the molecule.[39] Greater reactivity of a carbon–sulfur double bond also can be seen in the reaction shown in Scheme 13, where $Bu_3Sn\cdot$ reacts only with the *O*-thiocarbonyl group.[26] A quantitative measure of the reactivity of C–S single and double bonds comes from comparing absolute rate constants for their reactions; thus, rate constants for reaction of $(Me_3Si)_3Si\cdot$ with $C_{10}H_{21}SC_6H_5$ and $C_6H_{11}OC(=S)SMe$ are less than 5 x 10^6 and 1.1 x 10^9 $M^{-1}s^{-1}$, respectively, at 21 °C.[40] The reactions in Schemes 12 and 13 also illustrate the ease of fragmentation of a carbon–sulfur single bond when a radical is centered on an adjacent carbon atom.



Scheme 13

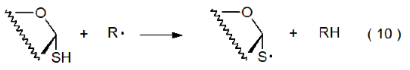


VII. Sulfones

Radicals are involved in both the synthesis and the reactions of carbohydrate sulfones. Sulfones produce carbon-centered radicals by group abstraction, dissociative electron-transfer, and photochemical bond homolysis. Sulfone synthesis takes place when a sulfonyl radical adds to an unsaturated carbohydrate.

VIII. Thiols and Thiyl Radicals

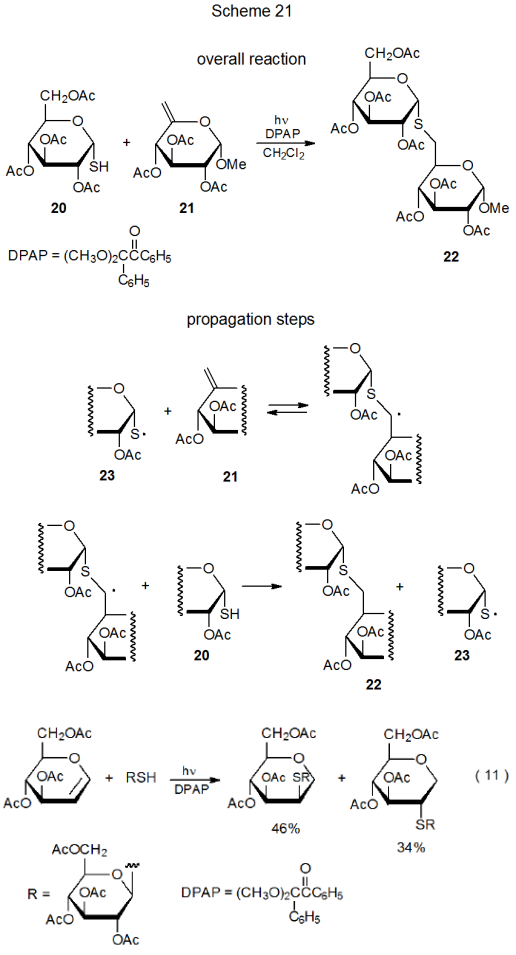
In compounds with an H–S bond, hydrogen-atom abstraction to produce a sulfur-centered radical (eq 10) is a significant (sometimes the exclusive) reaction pathway. Such reactivity exists because thiols are among the most effective hydrogen-atom transfers in organic chemistry. Rate constants for hydrogen-atom abstraction by primary, secondary, and tertiary, carbon-centered radicals from thiophenol range from 0.8 x 10^8 to 1.5 x 10^8 $M^{-1}s^{-1}$ at 25 °C.[70]



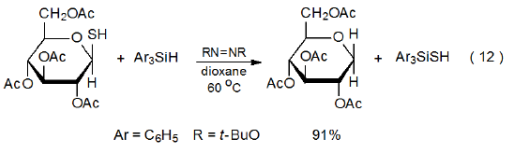
R· = a carbon-centered radical

A characteristic reaction of a thiyl radical is addition to a carbon–carbon multiple bond.[71–85] In the reaction shown in Scheme 21, for example, addition of the thiyl radical **23** to the unsaturated carbohydrate **21** leads to formation of the *S*-disaccharide **22**.[77] This reaction is not only regiospecific but hydrogen-atom abstraction from **20** is so much faster than reaction with the molecular oxygen dissolved in the reaction mixture that an inert atmosphere is not required for successful *S*-disaccharide formation. Similar radical addition takes place between the thiol **20** and various D-glycals, including the D-glucal **24** (eq 11).[78]

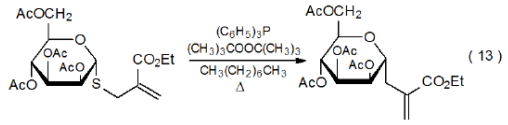
Scheme 21



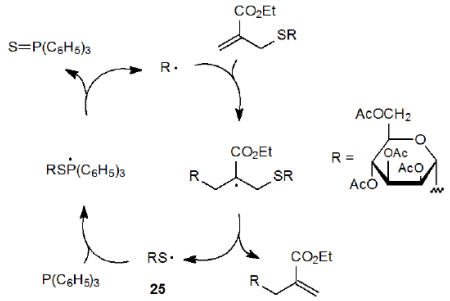
Even though the most common radical reaction of a compound with an H–S bond is hydrogen-atom abstraction, under some conditions the HS group is replaced by a hydrogen atom (eq 12).[86]



Although a carbohydrate containing a sulfur-centered radical typically is generated by hydrogen-atom abstraction from a thiol, the reaction shown in eq 13 forms a thiyl radical by the addition-elimination sequence pictured in Scheme 22.[87] Critical to chain propagation in this reaction is the removal of the sulfur atom from **25** by reaction with triphenylphosphine.



Scheme 22



IX. Summary

Tin-centered radicals react with carbohydrates that contain methylthio, ethylthio, or phenylthio groups to produce carbon-centered radicals. Two mechanisms have been proposed for such a reaction. The first is a concerted S_H2 process, and the second is a stepwise reaction that forms an intermediate with a hypervalent sulfur atom. Molecular orbital calculations favor the concerted process.

Compounds with alkylthio or arylthio groups break the C–S bond that produces the more stable, carbon-centered radical. This means that when fragmentation takes place in a carbohydrate containing a methylthio, ethylthio, or phenylthio substituent, a carbohydrate radical forms rather than an alkyl or aryl radical. Reactions that begin with carbon–sulfur bond cleavage often lead to either simple reduction or radical cyclization. Similar reactions occur when the sulfur atom is part of a dithioacetal, thiocarbonate, or dithiocarbonate.

When the carbon–sulfur bonds in a carbohydrate are part of a sulfone and when an electron-donor (usually SmI_2) is present, bond cleavage occurs via an electron-transfer reaction. The resulting radical combines rapidly with a second molecule of SmI_2 to produce an organosamarium intermediate that undergoes reactions typical of an organometallic compound (e.g., proton abstraction, β elimination, or addition to an aldehyde or ketone). Radical cyclization is one of the few reactions fast enough to occur before this combination takes place.

If a compound has a hydrogen–sulfur bond, the major reaction pathway usually is hydrogen-atom abstraction to form a sulfur-centered radical. This radical adds readily to a carbon–carbon double bond.

CHAPTER OVERVIEW

4: Selenides & Tellurides

Carbohydrates containing selenium–carbon bonds react with tin and silicon hydrides to generate carbon-centered radicals. Phenyl selenides are the most common type of selenium-containing carbohydrate used in radical formation. As radical precursors, phenyl selenides rival the reactivity of bromides and iodides. (Absolute rate constants for reaction of simple organic iodides,[1] phenyl selenides,[2] and bromides[2,3] with $(CH_3Si)_3Si\cdot$ are 4.0 x 10^9, 9.6 x 10^7, and 2.0 x 10^7 $M^{-1}s^{-1}$, respectively.)

Selenophenyl glycosides have a distinct advantage over the corresponding iodides and bromides when it comes to radical formation because anomeric phenyl selenides are thermally more stable than the corresponding anomeric halides. Anomeric iodides are, in fact, too unstable to have a significant role in generating pyranos-1-yl or furanos-1-yl radicals. Anomeric bromides are acceptable radical precursors in many instances, but when they are too unstable, phenyl selenides become attractive alternatives. Phenyl selenide advantage is apparent in the generation of furanos-1-yl radicals where glycosyl bromides typically are unable to survive the heating at reflux in benzene or toluene that normally is used in such reactions. Selenophenyl glycosides are stable enough under these conditions to avoid nonradical, thermal decomposition and, therefore, they are able to form the desired radicals.[4,5]

Organotellurium compounds represent another source of carbohydrate radicals. Although selenides are used much more frequently as starting materials for radical formation, tellurides undergo many of the same types of reaction. A problem with many tellurium-containing compounds is that they decompose so readily that they can be difficult to purify and store.

Topic hierarchy

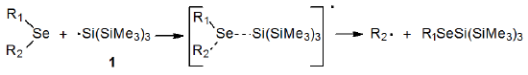
II. Selenides
III. Tellurides
IV. Summary

II. Selenides

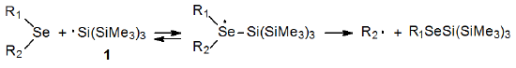
A. Reaction Mechanism

The S_H2 mechanism pictured in Scheme 1 and the stepwise process shown in Scheme 2 both are considered possibilities for explaining the reaction between a phenyl selenide and a tin- or silicon-centered radical.[6] The tris(trimethylsilyl)silyl radical (**1**) is used in illustrating these two mechanisms because it plays a significant role in the choice between them.[2] A way for making this choice begins with the observation that the absolute rate constant for reaction of **1** with cyclohexyl phenyl selenide to give cyclohexane (k_{Se}) is 9.6 x 10^7 $M^{-1}s^{-1}$ and the rate constant for reaction of 1-bromooctane to give octane (k_{Br}) is 2.0 x 10^7 $M^{-1}s^{-1}$. If every cyclohexyl and 1-octyl radical is formed irreversibly and abstracts a hydrogen atom from $(CH_3Si)_3SiH$ (Scheme 3), then the ratio k_{Se}/k_{Br} should be equal to the ratio of cyclohexane to octane formed when an equal-molar mixture of the selenide and bromide react with a limited amount of **1**. When an experiment to test this possibility is conducted, the ratio of cyclohexane to octane in the product mixture is 0.08, a value far less than the 4.8 ratio predicted from the absolute rate constants (Scheme 3).[2] This result is inconsistent with a process in which both the bromide and selenide react according to the S_H2 mechanism shown in Scheme 3. The 0.08 ratio is consistent with the bromide reacting as pictured in Scheme 3 but the selenide producing an intermediate that can return to the starting materials (Scheme 4). A likely intermediate in such a reaction is one with a hypervalent selenium atom.[2] The results from this comparative experiment, therefore, favor the stepwise mechanism for selenide reaction shown in Scheme 2 over the concerted process pictured in Scheme 1.

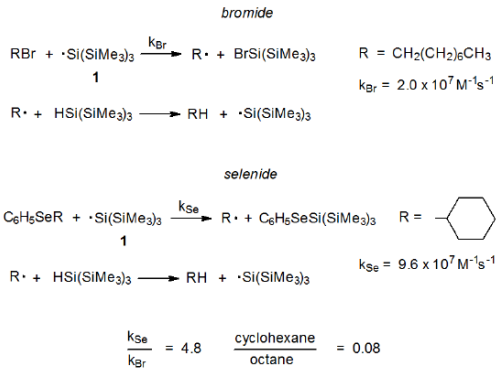
Scheme 1



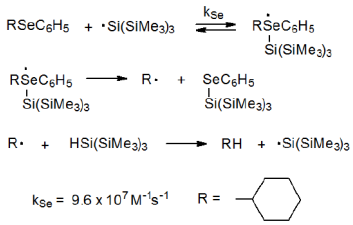
Scheme 2



Scheme 3



Scheme 4

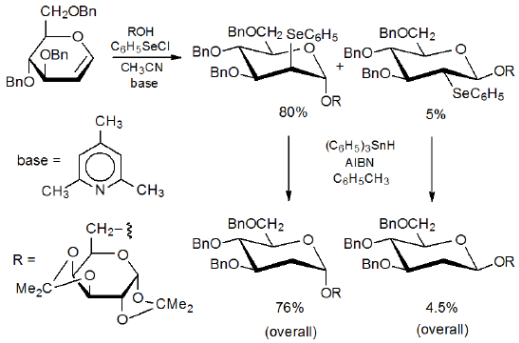


B. Reactions

1. Reduction

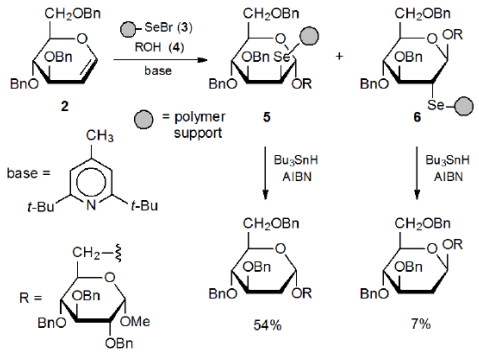
Carbohydrates that have a selenophenyl group attached to a pyranoid ring react with tri-*n*-butyltin hydride, triphenyltin hydride, or tris(trimethylsilyl)silane to replace the selenium-containing group with a hydrogen atom.[7–19] Such a reaction is the final step in the disaccharide synthesis shown in Scheme 5.[7] Although reduction involving selenophenyl group replacement is usually at C-2 in monosaccharides or at C-2' in disaccharides and nucleosides, reaction in monosaccharides also has been observed at C-1[17,18] and at C-6.[20]

Scheme 5

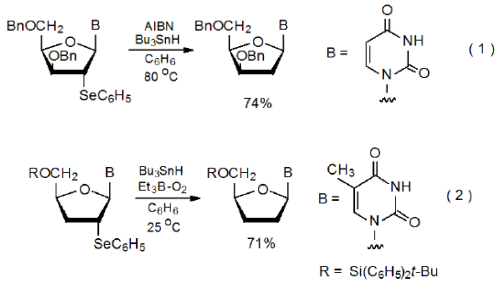


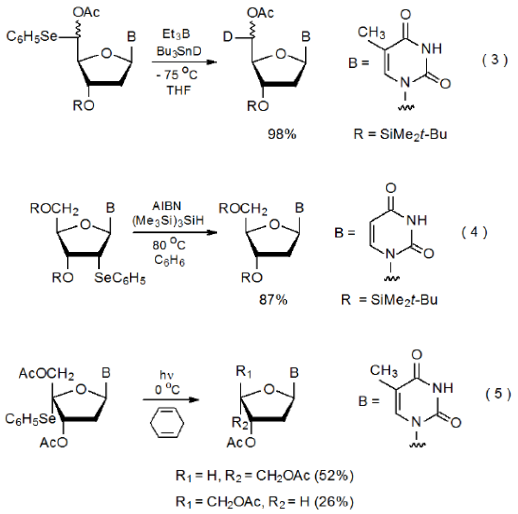
The polymer **3**,[21,22] with selenium attached to the aromatic rings in polystyrene, reacts with the glycal **2** in the presence of the partially protected sugar **4** to produce the carbohydrate-containing polymers **5** and **6** (Scheme 6).[21] (The polymer-bound reagent **3** has the advantage that it is odorless, safer, and more convenient to handle than C_6H_5SeCl, which is toxic and foul smelling.[21]) Reaction of **5** and **6** with tri-*n*-butyltin hydride releases the carbohydrates from the polymers and, at the same time, completes the reduction process.

Scheme 6



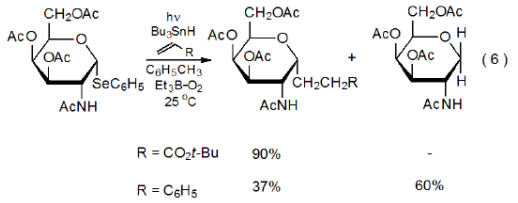
Replacing a selenophenyl group in a five-membered ring by a hydrogen atom is a common reaction for nucleosides and nucleoside analogs.[23–32] This replacement can be conducted either at 80-110 °C with AIBN initiation (eq 1),[23] or at room temperature with $Et_3B–O_2$ as the initiator (eq 2).[26] [Selenophenyl group replacement, when initiated by $Et_3B–O_2$, can occur at temperatures as low as -75 °C (eq 3).[31]] Tri-*n*-butyltin hydride is the normal hydrogen-atom transfer in such reactions, but tris(trimethylsilyl)silane (eq 4)[28] and 1,4-cyclohexadiene (eq 5)[30] also are effective in this role. Yields from reaction of Bu_3SnH with carbohydrates containing selenophenyl groups remain high when the oxygen atom in a furanoid ring is replaced by a sulfur atom.[33–35]





2. Addition

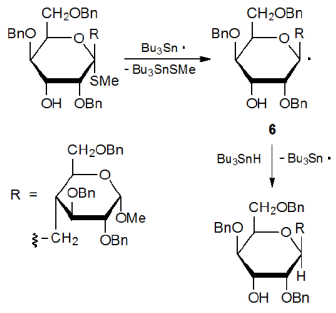
Carbohydrate radicals generated from phenyl selenides undergo characteristic addition reactions with compounds containing multiple bonds.[19,36–39] These radicals add not only to decidedly electron-deficient double bonds, such as that found in *t*-butyl acrylate, but also to less electron-deficient double bonds, such as that present in styrene.[19,37,38] Product yields from addition to styrene are lower, however, because hydrogen-atom abstraction from tri-*n*-butyltin hydride to give the reduction product competes effectively with addition to a less electron-deficient multiple bond (eq 6). Conditions are critical to the success of these addition reactions because only hydrogen-atom abstraction is observed unless $Et_3B–O_2$ is the initiator and the reaction is run at room temperature.[38] As is typical for reactions of this type (i.e., ones that form intermediate pyranos-1-yl radicals), the stereoselectivity of addition is controlled by the kinetic anomeric effect [Section III.B of Chapter 11 in Volume I].



3. Cyclization

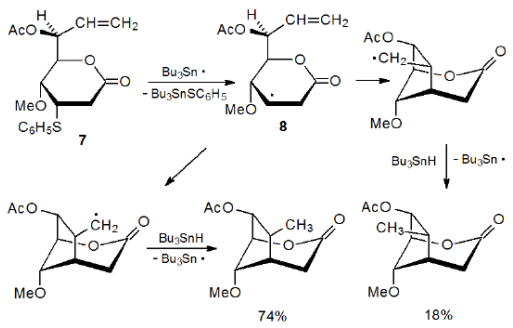
The reaction shown in Scheme 7[40] illustrates the established preference of unsaturated radicals for forming five-membered rings even when six-membered ones are possible.[40–43] This reaction (Scheme 7) also reveals a complication in radical cyclization caused by internal hydrogen-atom abstraction, a process that leads in this instance to epimerization at C-5. Only carbon-centered radicals that are very reactive, such as the primary radical **7**, are able to abstract a hydrogen atom from a carbon–hydrogen bond fast enough to be of consequence. Epimerization at C-5 in this reaction can be reduced or even eliminated by increasing the tri-*n*-butyltin hydride concentration to the point that internal hydrogen-atom abstraction by **7** no longer competes successfully with abstraction from Bu_3SnH (Scheme 7).[40]

Scheme 7

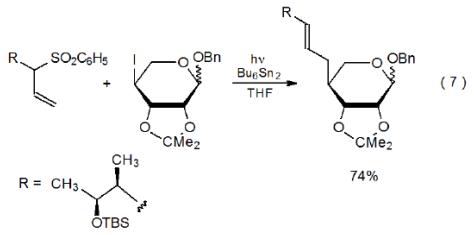


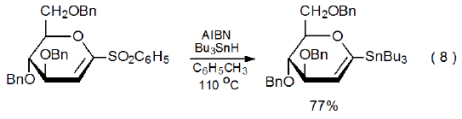
Cyclization of unsaturated carbohydrates in which a selenophenyl group is attached to a pyranoid ring is marked by a surprising variety of new ring systems that can be produced. In addition to the expected five-[40–44] and six-membered[45] rings, formation of seven-membered,[46] eight-membered,[47,48] and even nine-membered[49–54] rings also takes place. Larger rings usually are generated when a radical center and a multiple bond are linked through a silicon–oxygen connector.[46–52] Reactions of this type often produce carbohydrates in which two saccharide units are linked by a methylene bridge (Scheme 8.)[48] Although bridges containing silicon and oxygen atoms are common, reactions also occur between monosaccharides connected by other combinations of atoms.[53,54]

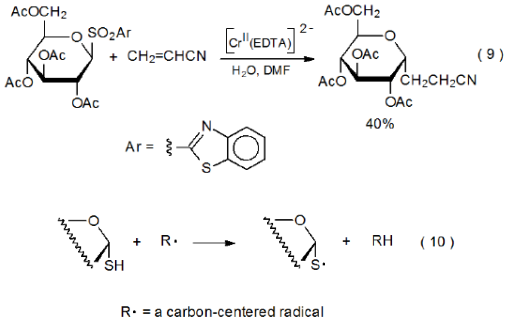
Scheme 8



In cyclization reactions a selenophenyl group attached to a furanoid ring behaves in a manner similar to one attached to a pyranoid ring; that is, reaction produces a radical that adds to a connected multiple bond. The connecting group sometimes contains a nitrogen atom (eq 7)[55] or an oxygen atom[56–58] (eq 8[56]) or the collection of atoms that make up an ester linkage,[59,60] but as is the case for compounds with pyranoid rings, a radical centered in a furanoid ring frequently has the unsaturated group tethered to the five-membered ring through a silicon–oxygen bridge[61–69] (eq 9[61]). Reported radical cyclization of this type, such as that shown in eq 10,[62] often involves reaction of a nucleoside.

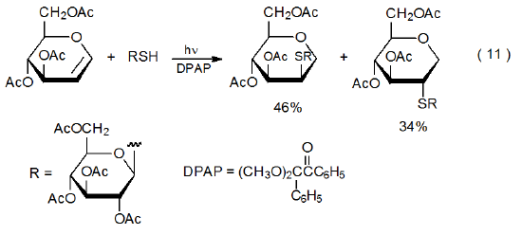




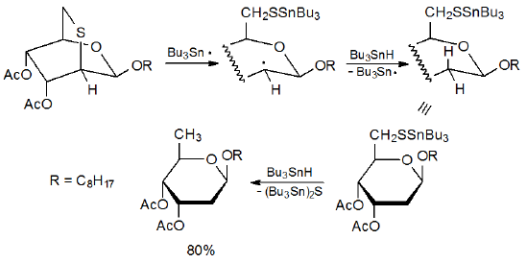


R· = a carbon-centered radical

Although in most carbohydrates a selenophenyl group undergoing reaction is bonded to a ring carbon atom, cyclization[70,71] (and addition[72]) reactions also can start with a ring-open structure. An example is given in eq 11.[70] Cyclization of the ring-open selenide **8** begins with electron transfer from samarium(II) iodide. The intermediate samarium ketyl formed during this reaction displaces a benzyl group from selenium to give a ring system that contains a selenium atom (Scheme 9).[73] This is an unusual method for ring formation because it takes place by group displacement rather than addition to a multiple bond.

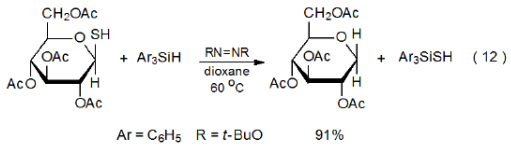


Scheme 9



4. Group Migration

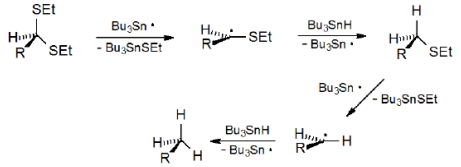
Group migration is a characteristic reaction of a pyranos-1-yl radical that has an acyloxy group attached to C-2. Since phenyl selenides are one type of precursor for these radicals, it is reasonable to expect selenides to be substrates for such a migration.[5,74,75] The reaction shown in eq 12 justifies this expectation.[5] (Acyloxy-group-migration reactions are discussed in Section V. of Chapter 8.)



5. Radical-Cation Formation

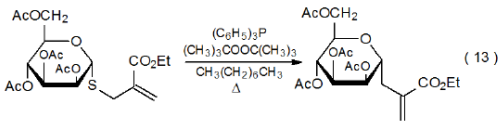
In the reaction shown in Scheme 10 abstraction of the selenophenyl group from **9** by $Bu_3Sn·$ gives the pyranos-1-yl radical **10**, which then fragments to produce the radical cation **11**.[76] This radical cation then undergoes a combination of cyclization, proton loss, and hydrogen-atom abstraction to give the final product. Investigating radical-cation formation from nucleotides containing selenophenyl groups is used to study the mechanism of DNA strand scission.[77,78]

Scheme 10



6. Radical Combination

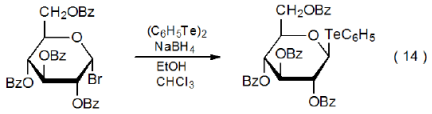
Replacement of a selenophenyl group with a hydrogen atom typically depends on the ability of a reagent such as tri-*n*-butyltin hydride both to provide a chain-carrying radical ($Bu_3Sn·$) and to serve as a hydrogen-atom transfer. If this reagent is replaced by one that lacks hydrogen-donating ability but retains the capacity to generate a chain-carrying radical, selenophenyl group loss still will occur, but hydrogen-atom abstraction cannot be depended upon to complete the reaction. If unsaturated reactants are present, radical addition is possible, but if such compounds are absent, radical combination can take place (eq 13).[4] {[Combination of the type shown in eq 13 also happens when pyranos-1-yl radicals are formed from glycosyl bromides [Chapter 2, Section III.G.1] and glycosyl phenyl sulfones [Chapter 3, Section VII.B.1.c.]}



(13)

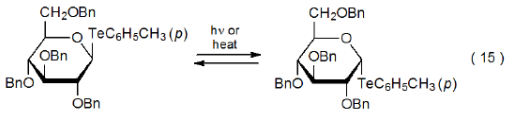
III. Tellurides

The organotellurium compounds that are used as radical precursors in carbohydrate chemistry usually are synthesized by a nucleophilic displacement reaction such as that pictured in eq 14.[79]



(14)

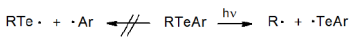
The majority of compounds prepared in this way are anomeric tellurides. Furanosyl tellurides are relatively unstable and tend to decompose within a few days,[80–82] but although their pyranosyl counterparts can exist unchanged in the solid state for months,[79] heating or exposing pyranosyl tellurides to UV light causes epimerization (eq 15).[83]



(15)

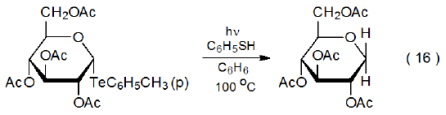
Two procedures, both of which involve photolysis, cause radical reaction of carbohydrate tellurides. The first of these is photochemical homolysis of a carbon–tellurium bond, a reaction that generates the more stable of the two possible, carbon-centered radicals (Scheme 11).

Scheme 11



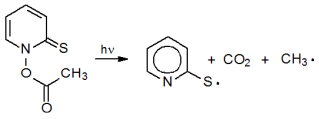
R· = carbohydrate radical

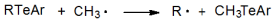
An example of reaction brought about in this way is found eq 16.[83] The second procedure for radical formation from a carbohydrate telluride calls for photochemical decomposition of *N*-acetoxy-2-thiopyridone to produce a methyl radical that then reacts with the telluride (Scheme 12).



(16)

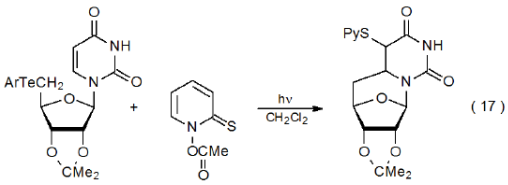
Scheme 12



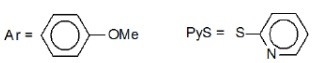


R· = carbohydrate radical

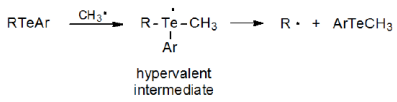
Equation 17 describes a cyclization reaction initiated in this way.[84] Reactions of carbohydrate radicals formed from tellurides include cyclization,[84,85] addition,[86–89] reduction,[83] and group migration.[83] It is reasonable to assume that reaction of a carbohydrate telluride with a methyl radical involves, as molecular orbital calculations indicate, formation of an intermediate with a hypervalent tellurium atom (Scheme 13).[90]



(17)



Scheme 13



IV. Summary

Reactions of carbohydrate selenides with tin-centered and silicon-centered radicals produce carbon-centered, carbohydrate radicals. These radicals can undergo hydrogen-atom abstraction, intra- and intermolecular addition, group migration, radical-cation formation, and radical combination. Reduction and radical cyclization are the two most common of these reactions. Reduction is involved in the synthesis of 2-deoxy sugars and 2'-deoxy disaccharides and nucleosides. Cyclization, which is characterized by the formation of compounds with a variety of ring sizes, is the central reaction in a general procedure for converting monosaccharides into *C*-disaccharides. In this procedure glycosyl phenyl selenides are chosen to generate pyranos-1-yl and furanos-1-yl radicals because a carbohydrate with a selenophenyl group at C-1 is thermally more stable than other substituents usually used for radical generation at this position. Carbohydrate tellurides are relatively unstable compounds that form carbohydrate radicals upon absorption of light or reaction with methyl radicals.

CHAPTER OVERVIEW

5: Acetals & Ethers

I. Introduction

Acetals are pervasive in carbohydrate chemistry. They link together saccharide units in oligo- and polysaccharides, provide the bonding in glycosides that joins carbohydrate and aglycon portions of a molecule, and furnish protection for hydroxyl groups during synthetic transformations. Because acetals have these vital protective and connective roles, their stability in the presence of free radicals is critical in enabling radical reactions selectively to modify other parts of a carbohydrate structure. Even though most acetals are stable in the presence of the carbon-centered radicals typically encountered in carbohydrate chemistry, there are reactions between heteroatom-centered radicals and acetals that are useful in carbohydrate transformation.

Ethers also serve as hydroxyl protecting groups during carbohydrate synthesis because, like acetals, they are unreactive in the presence of most carbon-centered radicals. When reaction of an ether or acetal does occur, it typically is hydrogen-atom abstraction from a carbon atom that has an attached oxygen atom.

Topic hierarchy

II. Bromination of Acetals and Ethers
III. Thiol-Catalyzed Reactions of Acetals: Polarity-Reversal Catalysis
IV. Ring Opening of Specially Designed Acetals
V. Internal Hydrogen-atom abstraction in Acetals and Ethers
VI. Radical Cyclization: The Role of Ethers and Acetals
VII. Silyl Ether Rearrangement
VIII. Summary

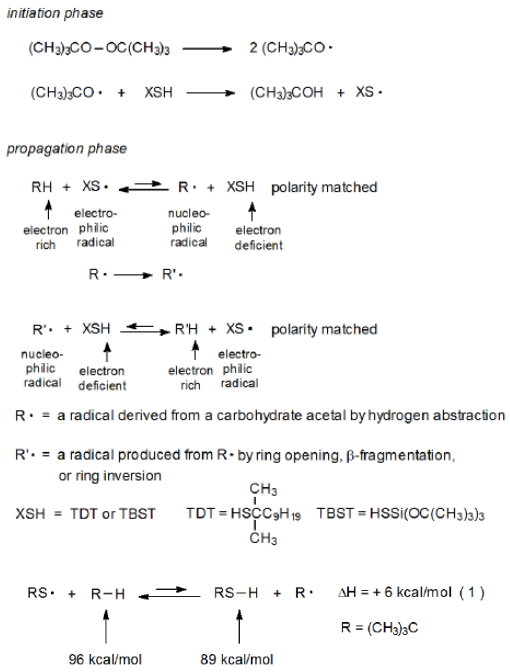
II. Bromination of Acetals and Ethers

Free-radical bromination of acetals and ethers is discussed in Section IV of Chapter 2.

III. Thiol-Catalyzed Reactions of Acetals: Polarity-Reversal Catalysis

Thiols act as catalysts for hydrogen-atom abstraction from acetals.[1–10] The initiation phase in these reactions generates a thiyl radical that then abstracts a hydrogen atom from the acetal in the first propagation step (Scheme 1). This first step is reversible and a pseudo equilibrium is established that favors the reactants (RH and XS·). (The position of this equilibrium is based on the enthalpy calculated from the bond-dissociation energies given in eq 1.[11]) The overall process is driven by the second propagation step, a reaction that irreversibly converts one carbon-centered radical (R·) into another (R'·). The final step is rapid hydrogen-atom abstraction from the thiol by the newly formed, carbon-centered radical R'.

Scheme 1



Hydrogen-atom abstraction from a molecule of substrate should have a lower transition-state energy when the abstracting radical is sulfur-centered (Scheme 1) rather than carbon-centered (Scheme 2). In reactions of this type the transition state can be described as a hybrid of valence-bond structures **1**-**4** (Figure 1).[10] If the abstracting radical is carbon-centered, structures **1** and **2** are the major contributors to the hybrid; the charge-separated structures **3** and **4** are of little consequence. If, however, abstraction is done by a thiyl radical, not only are structures **1** and **2** important, but contribution from the charge-separated structure **3** also is significant.[10] (In the case where a thiyl radical abstracts a hydrogen atom from an acetal, the valence-bond structures **1**-**4** can be represented in the more descriptive manner shown in Figure 2.) Significant contribution from **3** means that the energy required to reach the transition state for abstraction of a hydrogen atom is less than that needed when a carbon-centered radical abstracts the same hydrogen atom. Faster hydrogen-atom abstraction in propagation step 1 (Scheme 1) means that as R· is converted into R'· in step 2, the R· needed to continue the propagation sequence will be replenished more rapidly.

Scheme 2

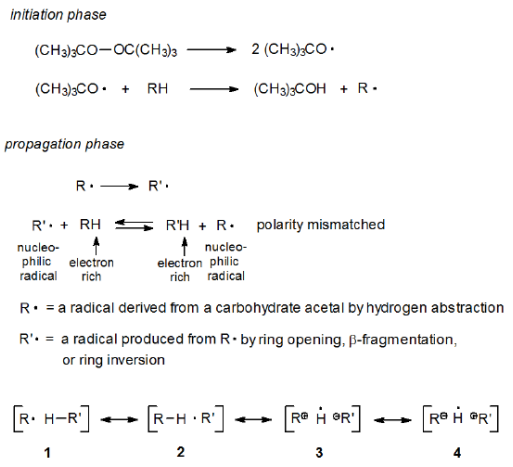


Figure 1. Valence-bond structures describing the transition-state for hydrogen abstraction

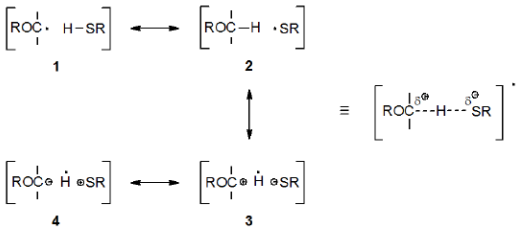


Figure 2. Representations for the transition state in hydrogen-atom transfer between carbon and sulfur atoms

A structure such as **3** is a transition-state-stabilizing contributor in any hydrogen-abstraction reaction where a change in radical philicity takes place. Such a change occurs in propagation steps 1 and 3 in the thiol-catalyzed mechanism pictured in Scheme 1, but it does not take place at all in the uncatalyzed mechanism shown in Scheme 2. When a change in radical philicity occurs during a reaction, either due to abstraction of an electron-rich hydrogen atom by an electrophilic radical or abstraction of an electron-deficient hydrogen atom by a nucleophilic radical (propagation steps 1 and 3, respectively, in Scheme 1), the reaction is described as polarity-matched.[4,10] If one radical must be converted into another by hydrogen-atom abstraction without benefit from a change in radical philicity (step 2 in Scheme 2), the reaction is described as being polarity-mismatched. The transition state for a polarity-matched reaction will be stabilized by contribution from the charge-separated, valence-bond structure **3** (Figures 1 and 2), but a polarity-mismatched reaction will not experience similar, transition-state stabilization. A polarity-matched reaction, therefore, will have transition-state stabilization that is denied to a polarity-mismatched reaction.

Although the combination of steps 1 and 3 in Scheme 1 achieves the same result as step 2 in Scheme 2 (see Figure 3), the polarity-matched steps in Scheme 1 can be fast enough that in combination they are more rapid, sometimes much more rapid, than the single, polarity-mismatched step in Scheme 2. When this occurs, the added thiol is said to catalyze the entire reaction by polarity-reversal catalysis.[10] The next three sections describe reactions that either are made possible by or have improved yields due to polarity-reversal catalysis.

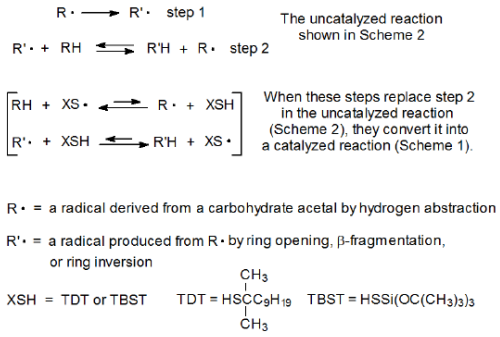
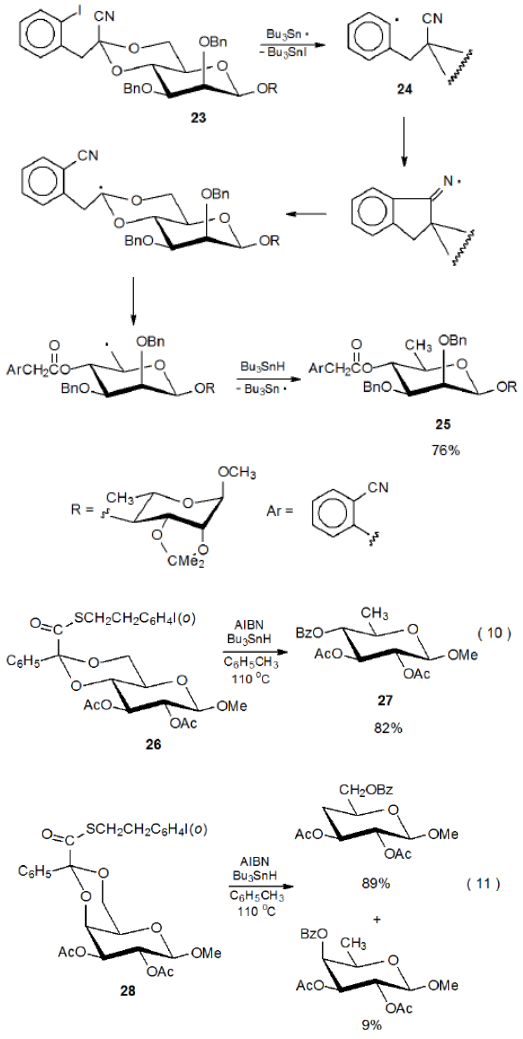


Figure 3. Catalyzed and uncatalyzed hydrogen-atom transfer

IV. Ring Opening of Specially Designed Acetals

Search for compounds with more versatile reactivity than that provided by a 4,6-*O*-benzylidene group has stimulated development of some specially designed structures.[14–18] The acetal **23**, which fits into this "specially designed" category, reacts with $Bu_3Sn\cdot$ to form the aryl radical **24**. The iodine-atom abstraction that generates **24** is the first step in a sequence of radical reactions that culminates in producing the protected glycoside **25** (Scheme 9).[14–16] An example of the synthetic usefulness of this reaction is found in the conversion of a tetrasaccharide containing four such protecting groups into one in which each group is transformed into an *O*-benzoyl group.[15] The glycoside **26** is another cyclic benzylidene acetal with an aromatic iodo substituent that undergoes a sequential radical reaction that leads to the corresponding deoxy benzoate **27** (eq 10).[17] The reactions pictured in Scheme 9 and eq 10 are two more examples (in addition to those shown in equations 2 and 3) where *trans*-fused rings open to produce primary rather than a secondary radicals. Ring opening of the 4,6-*O*-benzylidene acetal **28** to give a secondary radical (eq 11) further supports the proposal made for the acetal **11** (eq 4) that for a more flexible, *cis*-fused ring system the direction of ring opening is controlled by radical stability rather than ring strain at the transition state.

Scheme 9



V. Internal Hydrogen-atom abstraction in Acetals and Ethers

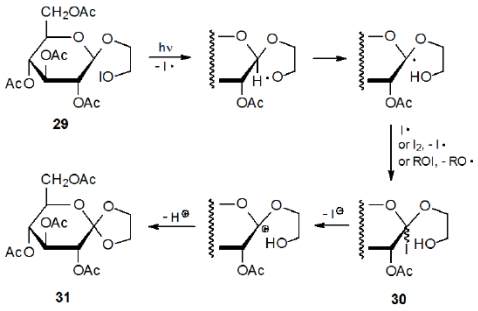
A. Abstraction by Alkoxy Radicals

Hydrogen-atom abstraction by alkoxy radicals from acetals and ethers is described in the next several sections. More information about the formation and reactions of alkoxy radicals is found in Chapter 6.

1. Abstraction From an Acetal

Intramolecular hydrogen-atom abstraction by an oxygen-centered radical from the central carbon atom in an acetal linkage is the "key" step in the orthoester formation pictured in Scheme 10.[19] The radical phase of this reaction begins with photochemically initiated fragmentation of the hypoiodite **29**. Internal hydrogen-atom abstraction followed by carbon–iodine bond formation completes the radical phase of the reaction. Formation of the orthoester **31** from the iodide **30** then occurs by an ionic process.

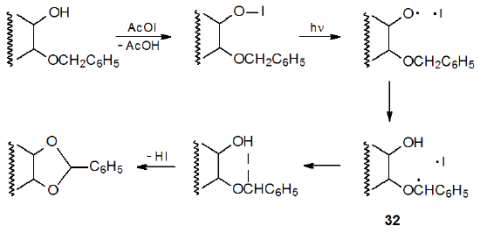
Scheme 10



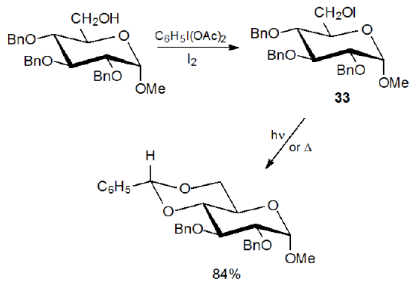
2. Abstraction From an Ether

Internal hydrogen-atom abstraction from a benzyloxy group produces a highly stabilized radical (**32**) that can be an intermediate in the formation of a benzylidene acetal (Scheme 11). This type of reaction takes place in good yield when the substrate contains adjacent *O*-benzyl and hydroxyl groups (Scheme 11).[20] The reaction in Scheme 12 illustrates the type of transformation possible. In this reaction the hypoiodite **33** is not just assumed to exist but is actually observed by ^{13}C NMR spectroscopy. Such direct observation of a hypoiodite is rare.

Scheme 11



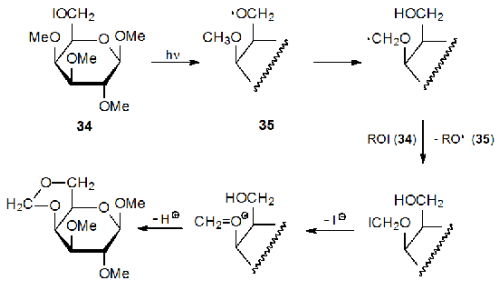
Scheme 12



It is not essential to have aromatic stabilization in the developing radical for internal hydrogen-atom abstraction to take place.[21–23] In the alkoxy radical **35** abstraction from a nearby methoxy group begins a process that ultimately unites the interacting groups as

an acetal (Scheme 13).[21] This reaction constitutes a regioselective transformation of a methoxy group that is in close proximity to an oxygen-centered radical.

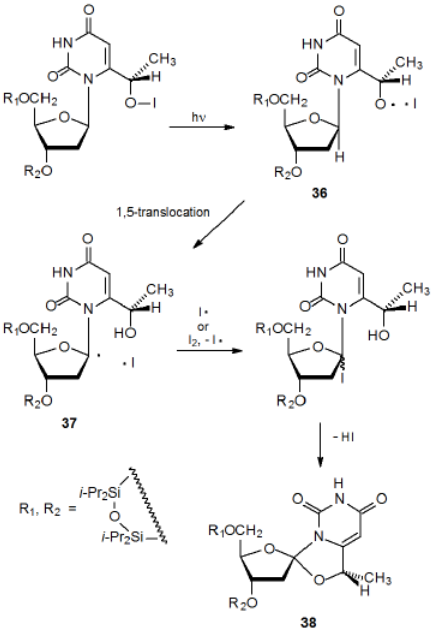
Scheme 13



3. Abstraction From an α-Aminoether

Internal hydrogen-atom abstraction by an alkoxy radical from an α-aminoether linkage can lead to the same type of ring formation observed in reactions of acetals and other ethers. For example, 1,6-hydrogen-atom abstraction converts the alkoxy radical **36** into the α-amino radical **37**. Combination of **37** with an iodine atom or reaction of **37** with I_2 then produces a reactive iodide that cyclizes to give the spiro nucleoside **38** (Scheme 14).[24,25]

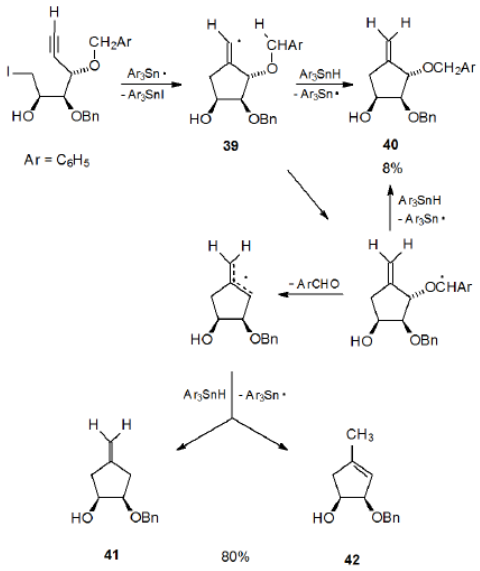
Scheme 14



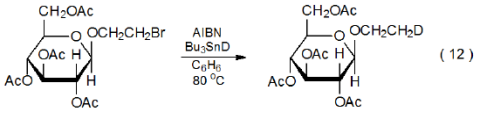
B. Abstraction by Carbon-Centered Radicals

Although internal hydrogen-atom abstraction usually involves an alkoxy radical, some carbon-centered radicals are capable of such reaction. One element associated with successful hydrogen-atom abstraction is that ring strain in the transition state be minimal. (Ring strain usually is minimized when hydrogen-atom abstraction involves a six-membered-ring transition state.[26] Such a reaction can be described as a 1,5-hydrogen-atom transfer or 1,5-HAT.) A second characteristic of successful abstraction is that stabilization of the developing radical contribute to lowering the transition-state barrier.[26] The need for radical stabilization means that primary[27] and vinylic[28,29] radicals are prime candidates for hydrogen-atom abstraction because their reactions typically lead to much more stable radicals; however, even a secondary radical will abstract a hydrogen atom internally if the developing radical is sufficiently stabilized.[30] In the reaction shown in Scheme 15, the vinylic radical **39** abstracts a hydrogen atom from the adjacent *O*-benzyl group in route to the major products **41** and **42** (80% combined yield). The product **40**, formed when **39** abstracts a hydrogen atom from $(C_6H_5)_3SnH$, is produced in only 8% yield, demonstrating that intermolecular reaction from this tin hydride has difficulty competing with internal hydrogen-atom abstraction.[29]

Scheme 15



It is often difficult to predict the extent of internal hydrogen-atom abstraction when a reactive, carbon-centered radical is formed in the presence of an effective hydrogen-atom transfer. For example, generating the radical **39** with $(C_6H_5)_3SnH$ present in solution still results primarily in internal reaction (Scheme 15);[29] in contrast, in the reaction shown in eq 12 deuterium incorporation demonstrates that even though a primary radical is formed, abstraction from Bu_3SnH is more rapid than internal 1,4- or 1,5-HAT.[31]

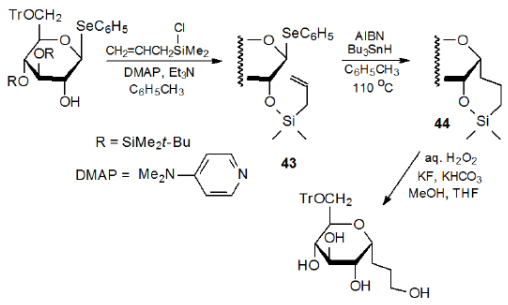


(12)

VI. Radical Cyclization: The Role of Ethers and Acetals

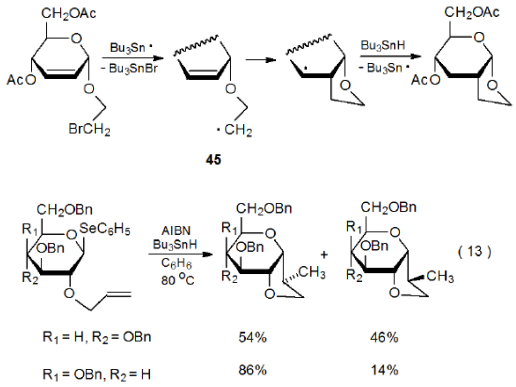
Radical cyclization depends upon having a radical center and multiple bond held in close enough proximity for internal addition to take place. In carbohydrates an ether linkage often is the means for connecting these two reactive centers. In the reaction shown in Scheme 16, for example, a carbohydrate (**43**) with a radical precursor at C-1 is connected by a silyl ether linkage at C-2 to a substituent containing a double bond.[32] Radical cyclization to give the silyl ether **44** creates a new carbon–carbon bond. Nonradical ring opening of **44** produces a silicon-free carbohydrate with an extended, carbon-atom chain.

Scheme 16



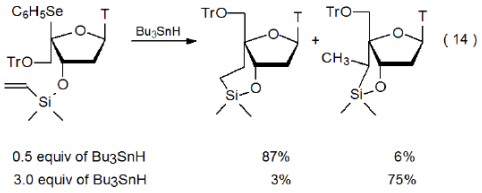
Acetals and nonsilyl ethers also act as tethers that connect reactive centers during radical cyclization. In the reaction shown in Scheme 17, for example, the acetal linkage holds the double bond and the radical center in **45** close enough for ring formation to occur.[33] In a similar manner an ether linkage connects the reactive centers during the cyclization reaction shown in eq 13.[34] Unlike silyl ethers, the rings formed when acetals and nonsilyl ethers act as tethers usually are not destined for immediate ring opening. (Section IV.C of Chapter 19 contains additional examples of ethers and acetals serving as tethers in radical cyclization reactions.)

Scheme 17

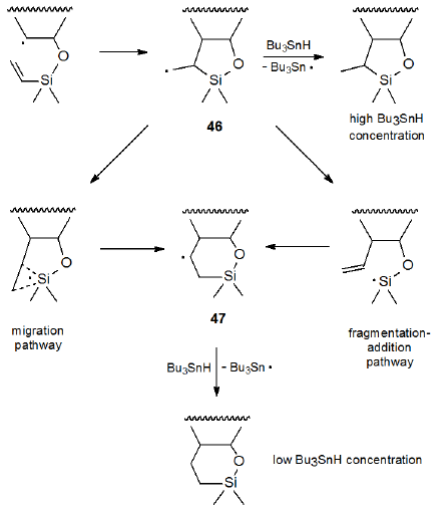


VII. Silyl Ether Rearrangement

Rearrangement takes place during radical cyclization involving some silyl ethers. The primary evidence for this rearrangement is the dependence of product ring size on the concentration of Bu_3SnH, the hydrogen-atom transfer in these reactions. When the reaction shown in eq 14 is conducted in dilute Bu_3SnH solution, the major product contains a six-membered ring,[35] but at high Bu_3SnH concentration reaction regioselectivity changes to give a product with a five-membered ring.[36,37] This concentration dependence can be explained by the more rapidly formed, but less stable, radical **46** having sufficient time and energy, when the concentration of Bu_3SnH is low, to be converted into the more stable radical **47**, either by a rearrangement that involves a cyclic transition state or by a fragmentation-addition sequence (Scheme 18).[37] At high Bu_3SnH concentration hydrogen-atom abstraction occurs before ring expansion can take place.



Scheme 18



VIII. Summary

The free-radical bromination of a benzylidene acetal is a standard procedure in carbohydrate chemistry for ring opening that results in the formation of bromodeoxy sugars. Ring opening in the absence of bromine occurs when 4,6-*O*-benzylidene acetals react with peroxides in the presence of a thiol catalyst. Hydrogen-atom abstraction by an electrophilic, thiyl radical is the first step in this reaction. This is also the first step in reactions of other acetals leading to epimerization and deoxygenation.

Ethers, like acetals, serve as protecting groups during carbohydrate synthesis, but this protection is not total because both ethers and acetals undergo hydrogen-atom abstraction in the presence of reactive, electrophilic radicals. These radicals can be sulfur-, oxygen-, or bromine-centered. When hydrogen-atom abstraction by an alkoxy radical is intramolecular, it typically is highly regioselective and can lead to formation of a new ring system.

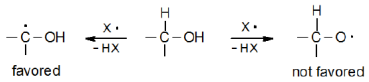
Acetals and ethers, including silyl ethers, have a connective role in radical cyclization reactions. The radical center and the multiple bond involved in a cyclization reaction are often joined together by an acetal or ether linkage.

CHAPTER OVERVIEW

6: Alkoxy Radicals

Radical formation by abstraction of a hydrogen atom potentially can convert a partially protected carbohydrate into either an oxygen-centered or carbon-centered radical (Scheme 1). In practice, however, such abstraction produces only carbon-centered radicals because their greater stability is reflected in the transition state leading to their formation. Because hydroxyl groups in unprotected or partially protected carbohydrates do not react with radicals typically present during transformation of carbohydrates (e.g., $Bu_3Sn\cdot$, $(Me_3Si)_3Si\cdot$, or various carbon-centered radicals), protecting these groups is not necessary to prevent them from becoming involved in radical reactions.

Scheme 1



Topic hierarchy

II. Alkoxy Radicals
III. Summary
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TitlePage
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6: Alkoxy Radicals

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II. Alkoxy Radicals

Although oxygen-centered radicals are not formed in significant number by direct hydrogen-atom abstraction from carbohydrates, these radicals can be produced indirectly in high yield from carbohydrate derivatives. Since such radicals are capable of internal reaction, intramolecular abstraction provides a pathway for oxygen-centered radicals to produce specific, carbon-centered radicals and, in so doing, to participate in synthetically useful reactions. (Alkoxy and alkoxyl are both terms used in describing oxygen-centered radicals derived from alcohols. The alkoxy designation will be used here.)

III. Summary

Alcohols are converted indirectly into alkoxy radicals through intermediate hypoiodites, nitrates, and phthalimides. A common reaction of alkoxy radicals is hydrogen-atom abstraction. This reaction becomes synthetically useful when the abstraction is internal because regioselective formation of a carbon-centered radical takes place. This selectivity depends on a combination of factors that include transition-state ring size, stability of the developing radical, and polarity matching between reacting atoms. Alkoxy radicals also can undergo carbon–carbon bond fragmentation that produces a carbonyl group and a carbon-centered radical. No matter which pathway is taken by the alkoxy radical (hydrogen-atom abstraction or β fragmentation), the resulting carbon-centered radical can undergo new ring formation, epimerization at a chiral center, ring opening, and other reactions characteristic of this radical intermediate.

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Epimerization
I. Organocobalt Compounds

CHAPTER OVERVIEW

7: Unprotected Carbohydrates

Radical reactions of unprotected carbohydrates begin with hydrogen-atom abstraction from a carbon–hydrogen bond in the carbohydrate structure. Such reaction requires a radical more reactive than the tin- or silicon-centered ones that are common in reactions of carbohydrate derivatives. A hydrogen atom usually is abstracted from an unprotected carbohydrate by a hydroxyl radical (HO·), but sometimes the sulfate radical anion ($SO_4^{\cdot-}$) is the abstracting agent. A beginning point for discussing radical reactions of unprotected carbohydrates is to examine how the abstracting radicals HO· and $SO_4^{\cdot-}$ are formed.

Topic hierarchy

II. Radicals That Abstract Hydrogen Atoms from Unprotected Carbohydrates

III. First Formed Radicals: Radicals Produced by Hydrogen-Atom Abstraction from Unprotected Carbohydrates

IV. Reactions of First-Formed Radicals

V. Reactions of Carbonyl-Conjugated Radicals

VI. Oxidative Degradation of Carbohydrates

VII. Reactions of Polysaccharides

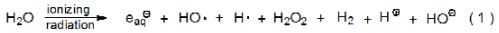
VIII. Summary

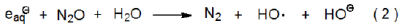
II. Radicals That Abstract Hydrogen Atoms from Unprotected Carbohydrates

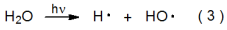
A. Hydroxyl Radicals

1. Ionizing Radiation and Ultraviolet Light

γ-Radiolysis of water produces hydroxyl radicals along with the compounds, ions, and other radicals shown in eq 1.[1–4] The yield of hydroxyl radicals in this reaction can be increased by adding N_2O to the reaction mixture because hydrated electrons react with N_2O to form hydroxyl radicals (eq 2).[2–4] In N_2O-containing solutions 85% of the radicals are HO· and 15% are H·.[4] Both HO· and H· abstract hydrogen atoms from carbon–hydrogen bonds.[4] Hydroxyl radicals (and hydrogen atoms) also can be produced by photolysis of water with ultraviolet light of wavelength less than 185 nm (eq 3).[1]

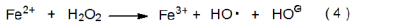


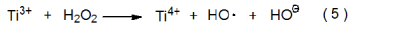


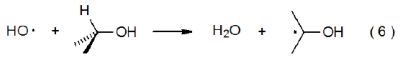


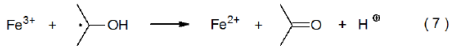
2. Reaction of H_2O_2 with Fe^{2+} and Ti^{3+}

Reaction of H_2O_2 with Fe^{2+} (eq 4) or Ti^{3+} (eq 5) produces hydroxyl radicals.[5–8] (These reagent combinations are sometimes described as radiomimetic, that is, imitating radiation.) Each hydroxyl radical produced is capable of abstracting a hydrogen atom from a carbon–hydrogen bond present in a molecule of substrate (eq 6). The Ti^{4+} generated by the reaction shown in eq 5 does not react further with the carbon-centered radical produced, but the Fe^{3+} formed in the reaction shown in eq 4 does;[8] Fe^{3+} oxidizes an α-hydroxy radical to a carbonyl group while itself being reduced to Fe^{2+}. Regeneration of Fe^{2+} from Fe^{3+} by the reaction shown in eq 7 means that when this reaction occurs, only a catalytic amount of Fe^{2+} may be necessary for complete decomposition of H_2O_2 (eq 4). (The combination of H_2O_2 and Fe^{2+} is known as Fenton's reagent,[9] and that of H_2O_2 and Te^{3+} as a Fenton-type reagent.[8])



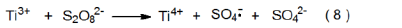


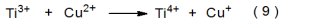


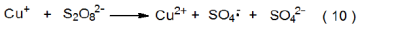


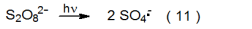
B. Sulfate Radical Anions

The sulfate radical anion ($SO_4^{\cdot -}$) forms when the peroxydisulfate dianion ($S_2O_8^{2-}$) reacts with Ti^{3+} (eq 8).[10] A low concentration of Cu^{2+} present in the reaction mixture enhances the rate of generation of $SO_4^{\cdot -}$ via the reactions shown in equations 9 and 10. The sulfate radical anion also forms from direct photolysis of $S_2O_8^{2-}$ (eq 11).[10]









III. First Formed Radicals: Radicals Produced by Hydrogen-Atom Abstraction from Unprotected Carbohydrates

A hydroxyl radical is sufficiently reactive to abstract a hydrogen atom from any of the carbon atoms in an unprotected carbohydrate.[3,6] The radicals produced by such a reaction often are referred to as “first-formed” radicals, a terminology that correctly implies further transformation is likely.[6] The ESR spectrum produced by the mixture of radicals generated from reaction of even a simple sugar with hydroxyl radicals is understandably complex; nevertheless, in the reaction of D-glucose (the most heavily studied of the simple sugars) signals for all six of the first-formed radicals can be detected.

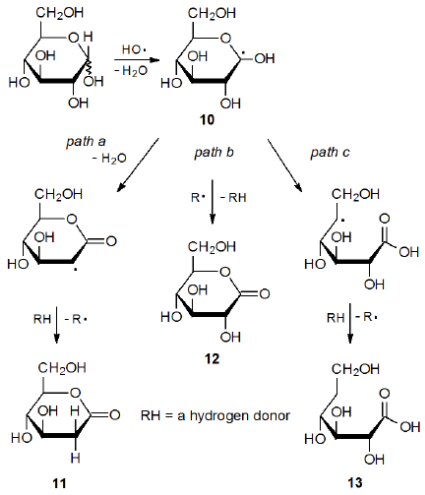
IV. Reactions of First-Formed Radicals

A. Reactions in Neutral Solution

In discussing the various products arising from reaction in neutral solution of first-formed radicals (typically reactions in which the hydroxyl radical is generated by γ-radiolysis), it is convenient to distinguish between products with a molecular weight less than or equal to that of the substrate and those with a higher molecular weight. Because first-formed radicals can undergo dimerization, disproportionation, elimination, and rearrangement, the number of possible reaction products is staggering; nevertheless, many of them have been identified.[1,2,24,25]

Product yields for reactions begun by γ-radiolysis of water can be expressed in terms of G-values; that is, the molecules or radicals formed per 100 eV of energy absorbed. A G-value also can be used as a measure of substrate reacted. In the reaction of D-glucose shown in Scheme 2 the G-value for consumption of starting material is 5.6.[2] The values for formation of products **11**-**13** are 0.95, 0.15, and <0.08, respectively. The G-values cited for D-glucose and compounds **11**-**13** were determined in the presence of N_2O to maximize the formation of the hydroxyl radical.

Scheme 2

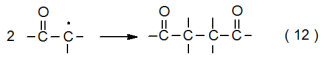


1. Low-Molecular-Weight Products

Although many low-molecular-weight products are formed in detectable amounts from reactions of simple sugars, the yields of most are quite low. Many of these compounds are produced by reactions of the first-formed radicals; for example, the major, low-molecular-weight product (**11**) from reaction of D-glucose is believed to arise by loss of the elements of water from the first-formed radical **10** (Scheme 2, path a).[2] Another reaction of **10** that forms a low-molecular-weight product is loss of a hydrogen atom to give D-glucono-1,5-lactone (**12**) (Scheme 2, path b), and a third reaction is opening of the pyranoid ring in **10** by fragmentation of the bond between C-5 and the ring oxygen atom to give, after hydrogen-atom abstraction, a carboxylic acid (**13**) (Scheme 2, path c).[2] All of the reactions of the radical **10** shown in Scheme 2 are driven, at least in part, by the stability gained from forming a C–O double bond.

2. High-Molecular-Weight Products

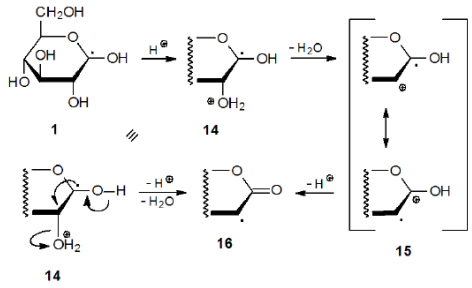
The products **11**-**13** (Scheme 2) and the other low molecular-weight products (more than twenty identified) account for less than half of the D-glucose consumed during γ-radiolysis because most products formed have high molecular weights. Little is known about either the structure of the high-molecular-weight materials or the mechanism of their formation. One proposal is that dimerization of radicals that have lost the elements of water may be the first step in formation of some high-molecular-weight products (eq 12).[2]



B. Acid-Catalyzed Reactions

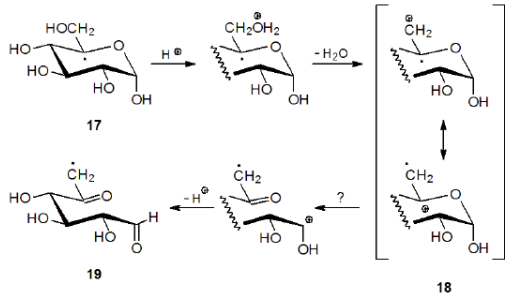
Under strongly acidic conditions (pH = 1) four of the first-formed radicals generated from D-glucose eliminate the elements of water to give in each case a carbonyl-conjugated radical.[6,26] A proposed mechanism for this reaction, shown in Scheme 3, involves protonation of the hydroxyl group adjacent to a radical center in the first-formed radical **1** to produce an intermediate (**14**) with an excellent leaving group that departs to form a radical cation (**15**). This radical cation then deprotonates to give the carbonyl-conjugated radical **16**. Another mechanistic possibility for forming **16** is a concerted reaction beginning with the protonated radical **14** (Scheme 3). Forming carbonyl-conjugated radicals by acid-catalyzed reaction also has been studied in noncarbohydrate systems.[5,27,28]

Scheme 3

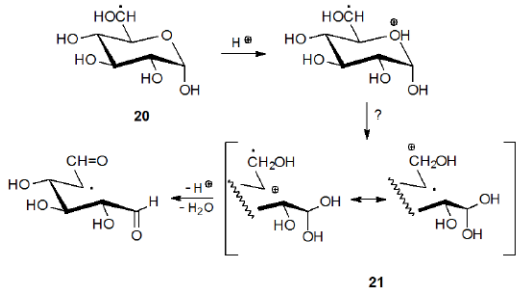


The acid-catalyzed reactions of three first-formed radicals produced from D-glucose deserve further comment. Two of these radicals, **17** (Scheme 4) and **20** (Scheme 5), do not undergo the carbonyl-group-forming reaction characteristic of the other first-formed radicals (Scheme 3).[6] Although **17** could start along this pathway by producing the radical cation **18**, deprotonation of **18** to give a carbon-centered radical with an adjacent carbonyl group cannot take place. Formation of a carbonyl-conjugated radical from **18** would require opening of the pyranoid ring (Scheme 4). Evidence against such reaction is that **17** is less reactive than other first-formed radicals, and when it does react, no carbonyl-conjugated radical can be detected. The first-formed radical **20** also must undergo ring opening if a carbonyl-conjugated radical is to be produced; in fact, ring opening in this case is necessary to form the radical-cation **21** (Scheme 5). The radical **20**, which is the least reactive of the first-formed radicals derived from D-glucose, also gives no indication of forming a carbonyl-conjugated radical.6

Scheme 4



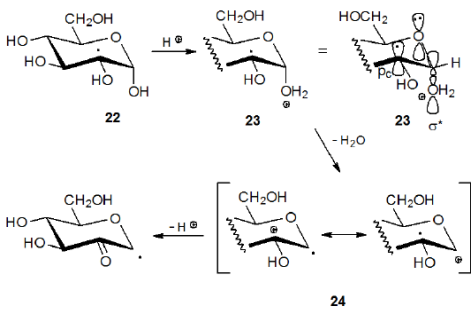
Scheme 5



The radical **22** is the third, first-formed radical produced from D-glucose that deserves further comment. This radical is noteworthy because it is the most reactive of the first-formed radicals. Protonation of **22** gives the intermediate **23** in which the leaving group

has an axial orientation and, therefore, the *p*-type orbitals on C-2 and the ring oxygen atom in **23** begin stabilizing the radical cation **24** as it starts to develop (Scheme 6).[6]

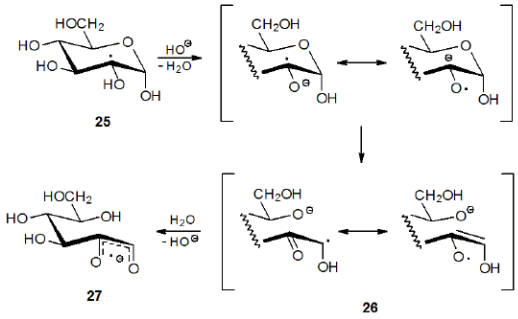
Scheme 6



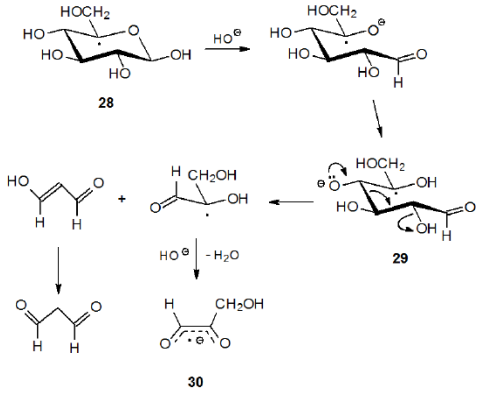
C. Base -Catalyzed Reaction

Proton abstraction from O-2 in the first-formed radical **25** begins a process that generates the ring-open radical anion **26** (Scheme 7). (Since an α-hydroxy radical is far more acidic than its parent alcohol,[2] the proton attached to O-2 should be removed much more readily than any other proton in **25**.) The radical anion **26** rapidly undergoes a proton transfer to produce the semidone **27**, one of two semidiones formed from base-catalyzed reaction of a first-formed, D-glucopyranosyl radical.[11,29] The second of these two (**30**) is proposed to arise from the radical **28** according to the mechanism outlined in Scheme 8.[11] (Semidiones **27** and **30** are readily detected because for each of them the negative charge slows the rates of dimerization and reduction and thus leads to more prominent ESR spectra.[11])

Scheme 7

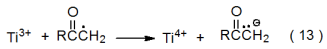


Scheme 8



V. Reactions of Carbonyl-Conjugated Radicals

In addition to dimerization (eq 12) carbonyl-conjugated radicals also can be reduced to anions in a pH-dependent reduction by Ti^{3+} (eq 13).[30] At pH 1 the reaction shown in eq 13 is negligible, but at pH 7 this reaction becomes an important pathway for removing carbonyl-conjugated radicals from a reaction mixture.[30]

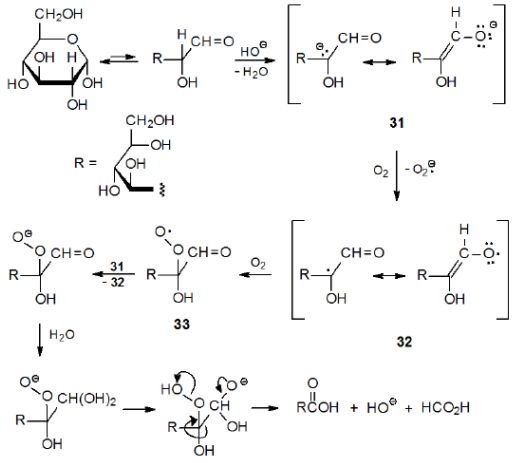


(13)

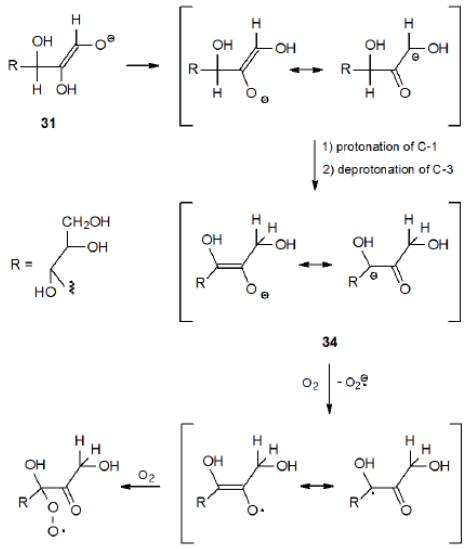
VI. Oxidative Degradation of Carbohydrates

The oxidative degradation of carbohydrates in the presence of base is another reaction that involves radical intermediates. Such reaction of D-glucose begins with ring opening and deprotonation to give the enediolate anion **31** (Scheme 9).[31,32] Oxidation of this anion with O_2 produces the resonance stabilized radical **32**, which then is converted to the peroxy radical **33** by addition of O_2. Subsequent reduction of **33** gives an anion that ultimately fragments the C_1–C_2 bond to give a five-carbon aldonic acid (Scheme 9). Fragmentation of other carbon–carbon bonds also takes place because base-catalyzed isomerization of the 1,2-enediolate anion **31** produces the 2,3-enediolate anion **34** (Scheme 10). Reaction of **34** with O_2 and fragmentation analogous to that shown in Scheme 9 cleaves the D-glucose structure into two-carbon-atom and four-carbon-atom carboxylic acids. Continued isomerization of this type (**31** to **34**) produces other enediolates that undergo similar fragmentation reactions.[32]

Scheme 9



Scheme 10



VII. Reactions of Polysaccharides

Study of radical reactions of polymeric carbohydrates is a challenging undertaking. The reactions that occur are documented by changes in physical properties that come from polymer degradation (e.g., reduced solution viscosity, differences in solubility, and gel formation). Changes in physical properties have been recorded in the reactions of the hydroxyl radical with cellulose,[8,32] hemicellulose,[32] starch,[16] and various dextrans.[33]

Studies of dextrans [polymers of 1→6 linked α-D-glucose with α-(1→3) linked side chains], for example, show essentially indiscriminate attack by hydroxyl radicals produced from reaction of Ti^{3+} with H_2O_2.[33] (The polymers studied had molecular weights ranging from 10,000 to 500,000 Da) These reactions cause depolymerizations (as evidenced by reduced solution viscosity) and an increase in the number of carbonyl and carboxyl groups in the polymer fragments. Upon lowering or raising the solution pH, the first-formed radicals appear to rearrange in a manner similar to the rearrangement of first-formed radicals derived from D-glucose.

VIII. Summary

The hydroxyl radical and the sulfate radical anion both abstract hydrogen atoms from unprotected carbohydrates. In each case first-formed, carbon-centered radicals are produced. The hydroxyl radical is so reactive that it shows little regioselectivity when reacting with D-glucose; that is, spectroscopic evidence indicates that hydrogen-atom abstraction occurs from each of the six carbon atoms in this molecule. The hydroxyl radical remains unselective in reaction with other simple sugars that contain only pyranoid rings, but it does regioselectively abstract H_5' from the furanoid ring in sucrose. The sulfate radical anion is a more selective abstracting agent. Hydrogen-atom abstraction occurs primarily from C-2, C-5, and C-6 in α-D-glucopyranose and at C-1, C-5, and C-6 in β-D-glucopyranose.

First-formed radicals derived from D-glucose undergo acid-catalyzed rearrangement under strongly acidic conditions to produce carbonyl-conjugated radicals. Under basic conditions first-formed radicals produce radical anions that form semidiones. When oxygen is present in the reaction mixture, first-formed radicals react to give peroxy radicals.

CHAPTER OVERVIEW

8: Carboxylic Acids & Esters

Carbohydrates containing typical *O*-acyl groups are unreactive under the reduction conditions (AIBN initiation, Bu_3SnH, 80-110 ^oC) normally used for radical reactions. This lack of reactivity changes when *O*-acyl groups become part of the more complex structures found in α-acyloxy ketones, methyl oxalyl esters, and *p*-cyanobenzoates. For such compounds radical reaction with Bu_3SnH under normal reaction conditions replaces the acyloxy group with a hydrogen atom.

There are conditions under which a less complex *O*-acyl group (e.g., an *O*-acetyl or *O*-benzoyl group) is replaced with a hydrogen atom. One set of conditions includes raising the reaction temperature dramatically, a change with potentially destructive consequences for the compounds involved. A more attractive approach depends upon photochemically promoted electron transfer to an esterified carbohydrate. Electron transfer (both photochemical and nonphotochemical) permeates the radical reactions of carboxylic acid esters; that is, many of these reactions either involve (or may involve) electron transfer.

Another way in which *O*-acyl groups participate in radical reactions is by group migration. When a radical centered at C-1 in a pyranoid or furanoid ring has an *O*-acyl group attached to C-2, this group will migrate to C-1 when the conditions are properly selected. Such migration provides an effective method for producing 2-deoxy sugars.

Although esters of carboxylic acids are rich sources for substrates in radical-forming reactions, the acids themselves also can produce radicals. Under the proper conditions carboxylic acids generate carboxyl radicals, intermediates that lose carbon dioxide to form carbon-centered radicals. Carboxyl radicals are generated by electrolysis of carboxylate anions and by the reaction of carboxylic acids with hypervalent iodine compounds.

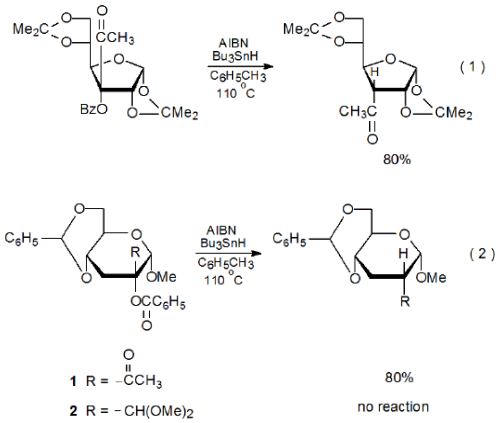
Topic hierarchy

II. Replacement of an Acyloxy Group with a Hydrogen Atom
III. Photochemical Electron Transfer to Carboxylic Acid Esters
IV. Nonphotochemcal Electron Transfer to Carboxylic Acid Esters
V. Acyloxy Group Migration
VI. Reactions of Carboxylic Acids
VII. Summary

II. Replacement of an Acyloxy Group with a Hydrogen Atom

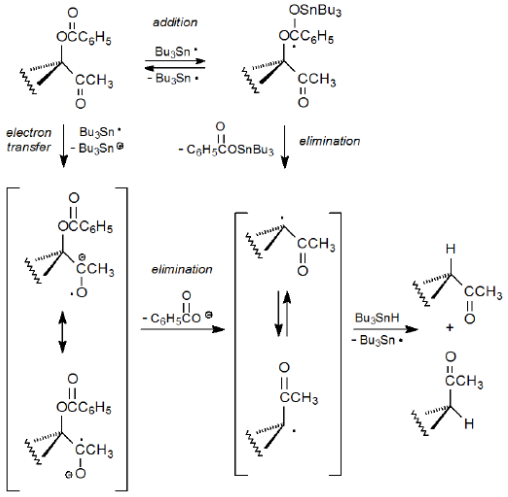
A. α-Acyloxy Ketones

α-Acyloxy ketones react with tri-*n*-butyltin hydride by replacing the acyloxy group with a hydrogen atom (eq 1).[1] The importance of the carbonyl group to this replacement process is evident in the two reactions shown in eq 2. In the first of these a benzoate (**1**) containing a keto group forms a deoxy sugar in good yield, but in the second a benzoate (**2**) lacking such a group is unreactive.[1] Even though reactions of α-acyloxy ketones lead to formation of deoxy sugars, the usefulness of such reactions is limited by the relatively small number of carbohydrates that either have the necessary substituents or easily can be converted into compounds that do.[1,2]



A proposed mechanism for group replacement in α-acyloxy ketones is pictured in Scheme 1. Both addition/elimination and electron-transfer/elimination sequences are presented as possibilities for acyloxy group loss. The addition-elimination possibility was proposed at the time of the discovery of this reaction,[1] but the electron-transfer option was recognized as a viable alternative later when loss of the benzoyloxy group from α-(benzoyloxy)acetophenone was shown to involve electron transfer from $Bu_3Sn\cdot$ to this α-acyloxy ketone.[3] There is no decisive evidence favoring either mechanism.

Scheme 1

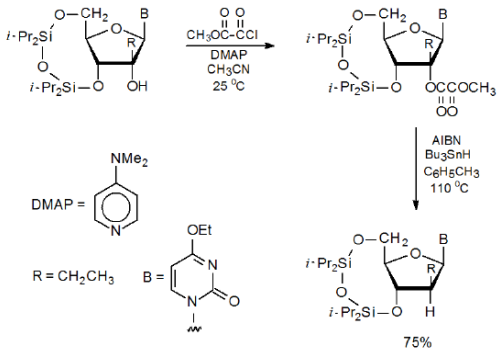


B. Methyl Oxalyl Esters

Methyl oxalyl esters can be prepared easily by esterification of partially protected carbohydrates with methyl oxalyl chloride (Scheme 2).[4] These esters react with tri-*n*-butyltin hydride to replace the methyl oxalyloxy group with a hydrogen atom.[4–19] Studies of noncarbohydrate esters show that those derived from secondary and tertiary alcohols are suitable starting materials in this deoxygenation process, but esters of primary alcohols are not because they regenerate the alcohols from which they were synthesized.[20] Most of the reactions of methyl oxalyl esters of carbohydrates are of compounds in which a tertiary hydroxyl group

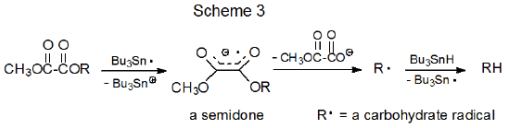
has been esterified. Many of these compounds are nucleosides.[4,7–16] One reason that most methyl oxalyl esters are formed from tertiary alcohols is that the *O*-thiocarbonyl compounds commonly used for deoxygenation in the Barton-McCombie reaction- (Section II in Chapter 12) sometimes have difficulty forming when an alcohol is tertiary.[6] Methyl oxalyl chloride typically esterifies tertiary alcohols without difficulty.[4,6–19]Another reason for selecting methyl oxalyl esters is that they are less likely to experience the thermal elimination (Chugaev reaction) that is common for tertiary *O*-thiocarbonyl compounds. In molecules with the proper structure cyclization can precede hydrogen-atom abstraction.[13]

Scheme 2



A proposed mechanism for reaction of methyl oxalyl esters with tri-*n*-butyltin hydride is shown in Scheme 3. According to this mechanism the tri-*n*-butyltin radical transfers an electron to the π system of the ester to produce a highly stabilized radical anion (a semidione).[20] (Supporting the idea that such a transfer takes place is the observation that $Bu_3Sn\cdot$ reacts with oxalate esters to produce intermediates with ESR spectra characteristic of radical anions.[21]) Fragmentation of such a radical anion then generates a carbon-centered radical that abstracts a hydrogen atom from Bu_3SnH (Scheme 3).

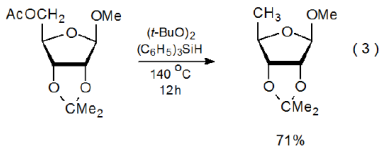
Scheme 3



There are two significant problems associated with the synthesis and reaction of methyl oxalyl esters. One of these is the difficulty in starting- material purification that arises because these esters hydrolyze readily, in particular, during chromatography on silica gel.[4,22] A second problem has to do with alcohol regeneration, a significant side reaction from treatment of some methyl oxalyl esters with tri-*n*-butyltin hydride.[5,20]

C. Acetates and Trifluoroacetates

Acetylated carbohydrates do not react with tri-*n*-butyltin hydride under normal conditions (80-110 °C, 2 h, AIBN initiation), but under different, more vigorous conditions (triphenylsilane, 140 °C, 12 h, two equivalents of benzoyl peroxide) these compounds produce the corresponding deoxy sugars (eq 3).[23] These more vigorous conditions cause similar reaction in *O*-trifluoroacetyl substituted carbohydrates.[24] The need for two equivalents of benzoyl peroxide in the reaction shown in eq 3 indicates that a nonchain process is taking place.

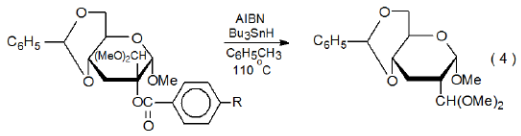


(3)

D. *p*-Cyanobenzoates

Replacement of the benzoyl group in compound **2** with a *p*-cyanobenzoyl group converts an unreactive compound (**2**) into a reactive one (**3**) (eq 4).[25] One explanation for this difference in reactivity is that because a cyano group is quite effective at stabilizing a radical anion, electron transfer to compound **3** is taking place where analogous transfer to the unsubstituted benzoate **2** does not occur. Since radical anions can form by electron transfer from the tri-*n*-butyltin radical to easily reduced organic com-

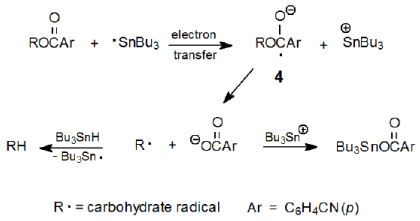
pounds,[21,26] the electron-transfer mechanism pictured in Scheme 4 represents a possible pathway for replacement of a *p*-cyanobenzoyloxy group with a hydrogen atom.



2 R = H — no reaction

3 R = CN — 82%

Scheme 4

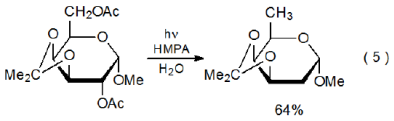


R• = carbohydrate radical Ar = $C_6H_4CN(p)$

III. Photochemical Electron Transfer to Carboxylic Acid Esters

A. Acetates and Pivalates

Photochemical electron transfer from excited hexamethylphosphoramide (HMPA) to an *O*-acyl group in a carbohydrate begins a series of events that result in replacing each *O*-acyl group with a hydrogen atom. An example of a typical reaction is shown in eq 5.[27] The temperature at which this reaction can be conducted (~25 °C) is synthetically far more attractive than the 140 °C needed for the corresponding thermal reaction of an acetylated carbohydrate (eq 3).[23] Photochemical electron transfer to acetates has been used for the synthesis of a number of deoxy sugars.[27–34] Esters of pivalic acid, which also can serve as substrates in this type of reaction,[28,35–41] sometimes give better yields than the corresponding acetates.[28,35,36]

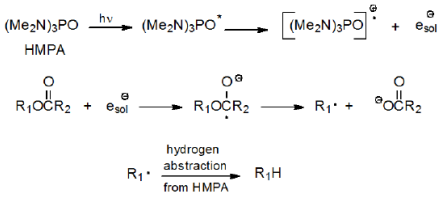


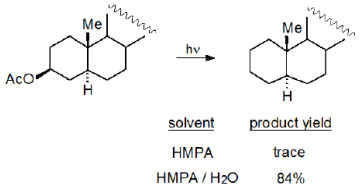
(5)

1. Reaction Mechanism

Photochemical electron transfer begins with absorption of light by HMPA to produce a highly reactive, electronically excited molecule that ejects an electron into the solution (Scheme 5).[42,43] The ejected electron is captured by the acylated carbohydrate to produce a radical anion that cleaves to give a carboxylate anion and a carbohydrate radical (R·).[43] Hydrogen-atom abstraction by the carbohydrate radical then completes the replacement process (Scheme 5). The water present in the reaction mixture extends the lifetime of the solvated electron and, in so doing, increases the probability that this electron will be captured by a molecule of ester.[43] (The importance of water to the success of this process is demonstrated by the yields of the reactions shown in eq 6.[44,45])

Scheme 5

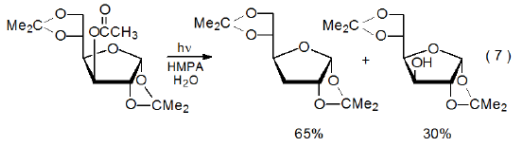




(6)

2. Alcohol Regeneration

Ester photolysis in aqueous HMPA sometimes regenerates the alcohol from which the ester was synthesized (eq 7).[34] In some instances, alcohol formation may be due to nonphotochemical ester hydrolysis. Nonphotochemical reaction provides a reasonable explanation for the easily hydrolyzed, anomeric acetate shown in eq 8 undergoing only hydrolysis (no deoxygenation) when photolyzed in aqueous HMPA.[34] Even though simple hydrolysis may be significant for some compounds, as described below, alcohol regeneration during photolysis of other, probably most, esters must occur in a different way.



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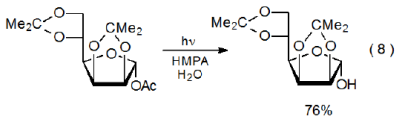
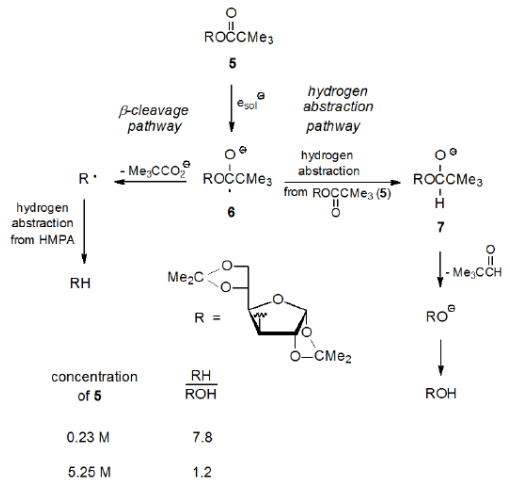


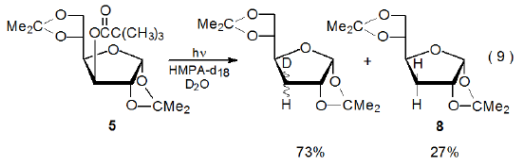
(8)

Alcohol formation during ester photolysis cannot be explained, in general, by simple hydrolysis because, as is shown by the reaction pictured in Scheme 6, the yield of the alcohol can depend on the concentration of the starting ester.[43] One explanation for this dependence begins with the ester **5** capturing a solvated electron to form the radical anion **6**. This radical anion then abstracts a hydrogen atom from a second molecule of **5** to produce the anion **7**, which then forms an alkoxide ion that protonates to give the observed alcohol.[43] Since, according to this explanation, raising ester concentration should increase the rate of hydrogen-atom abstraction to give **7** but not the rate of the competing β-cleavage that forms R·, greater ester concentration should increase the amount of alcohol (ROH) produced at the expense of the deoxygenated product (RH).

Scheme 6



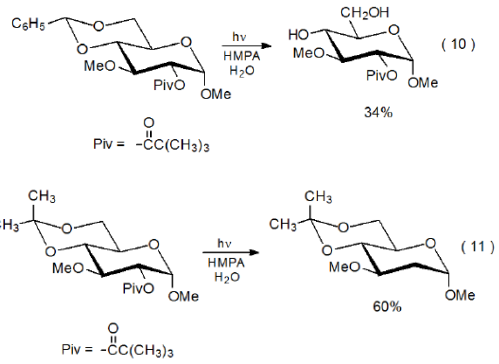
A critical question about the mechanism for alcohol formation presented in Scheme 6 concerns whether the radical anion **6** can abstract a hydrogen atom from the ester **5**. The evidence found in eq 9 supports the idea that **5** can function as a hydrogen-atom donor. Irradiation of **5** in HMPA-d_{18}/D_2O gives a 27% yield of **8**, a reduction product that contains no deuterium. Since the only source for the second hydrogen atom at C-3 in **8** is one of the carbohydrates in the reaction mixture and since the ester **5** is the only carbohydrate present at the beginning of the reaction, abstraction from **5**, at least in the early stages of reaction, seems unavoidable. If **5** can act as a hydrogen-atom donor in the formation of **8**, it becomes a strong candidate for the same role in the conversion of the radical anion **6** into the alkoxide ion **7** (Scheme 6).



(9)

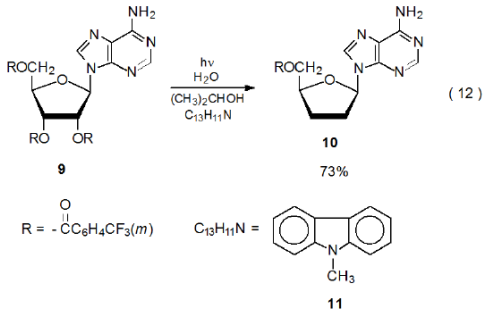
3. Competition From Light-Absorbing Chromophores

If an ester contains a strongly absorbing chromophore, HMPA excitation will be effectively precluded because most of the incident light will be absorbed by the ester. Failure to excite HMPA will forestall replacement of the acyloxy group with a hydrogen atom by preventing electron transfer. The light absorbing properties of the benzoyloxy group, for example, render benzoates much less desirable participants in these electron-transfer reactions because far less incident light reaches the HMPA. This means that an important factor in reaction of simple acetates and pivalates is that these compounds contain no strongly absorbing chromophore.[42] An example of an ester that fails to undergo replacement of the acyloxy group due to the presence of a light-absorbing substituent (i.e., the 4,6-*O*-benzylidene group) is shown in eq 10.[41] Even though the benzylidene group is removed during photolysis, the aromatic chromophore remains in the solution and continues to absorb the incident light. Changing 4,6-*O*-benzylidene to 4,6-*O*-isopropylidene protection allows reaction to proceed in the normal fashion (eq 11).[41]

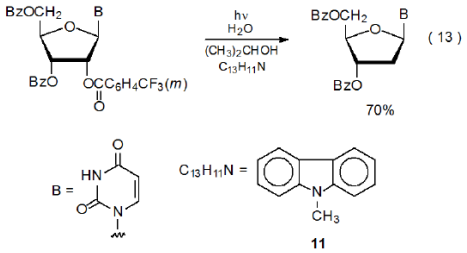


B. *m*-(Trifluoromethyl)benzoates

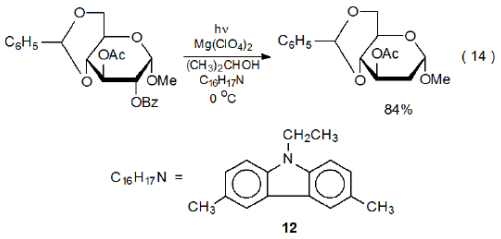
A *m*-(trifluoromethyl)benzoate will accept an electron from excited *N*-methylcarbazole (**11**) in a reaction that leads to replacement of the acyloxy group with a hydrogen atom; for example, photolysis of 2',3',5'-tri-*O*-[*m*-(trifluoromethyl)benzoyl]-adenosine (**9**) produces the 2',3'-dideoxyadenosine derivative **10** (eq 12).[46] (Most,[46–52] but not all,[48] compounds reported to undergo this type of reaction are nucleosides.) Reactions, such as the one shown in eq 12, are regioselective because the radical anion generated from a *m*-(trifluoromethyl)benzoyl group does not fragment to give a primary radical.



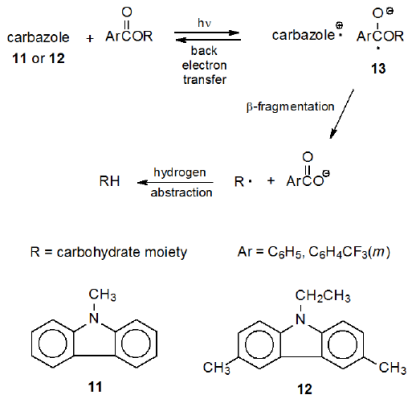
Photochemical electron transfer involving *m*-(trifluoromethyl)benzoates and *N*-methylcarbazole (**11**) has several advantages over electron transfer between HMPA and acetates or pivalates. One of these is that *N*-methylcarbazole has greater molar absorptivity than HMPA, a fact that renders the carbohydrate reactant less likely to stop the reaction by absorbing the incident light.[52] From a safety point of view, eliminating HMPA from the reaction mixture avoids handling a highly toxic, cancer-suspect agent. Because the *m*-(trifluoromethyl)benzoyl group is an effective electron acceptor (better than an acetyl or pivaloyl group) few substituents in the carbohydrate will compete with this group for an electron donated by excited *N*-methylcarbazole (**11**); consequently, reactions of *m*-(trifluoromethyl)benzoates usually are highly chemoselective. An example of this selectivity is shown in eq 13, where the benzoyl group remains bonded to C-3' while the *m*-(trifluoromethyl)benzoyl group at C-2' is replaced by a hydrogen atom.[49]



When reaction is conducted in the presence of $Mg(ClO_4)_2$, it is possible to replace even an unsubstituted benzoyloxy group with a hydrogen atom (eq 14[50]).[50–52] Magnesium perchlorate affects this reaction by hindering back electron transfer, a process that competes with the fragmentation of the radical anion **13** (Scheme 7). Another factor that affects the reaction of a benzoyloxy group is the choice of the electron donor; thus, replacing *N*-methylcarbazole (**11**) with 3,6-dimethyl-9-ethylcarbazole (**12**) causes deoxygenation to take place more rapidly.[50] Compound **12** is superior to **11** because it forms a more stable radical cation upon electron transfer.[50,53,54]



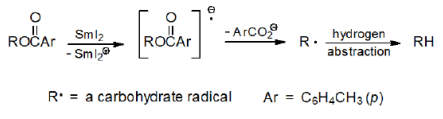
Scheme 7



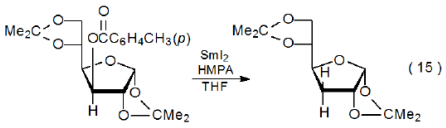
IV. Nonphotochemcal Electron Transfer to Carboxylic Acid Esters

Electron transfer to carboxylic acid esters also can occur via nonphotochemical reaction. Transfer of an electron from SmI_2 to a carbohydrate *p*-methylbenzoate produces a radical anion that fragments to give a carbon-centered, carbohydrate radical and a *p*-methylbenzoate anion (Scheme 8).[54,55] The carbohydrate radical abstracts a hydrogen atom from a donor present in the solution to form a deoxy sugar. An example of such a reaction is shown in eq 15.

Scheme 8



R· = a carbohydrate radical Ar = $C_6H_4CH_3$ (*p*)



(15)

60%

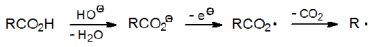
V. Acyloxy Group Migration

Group migration in radical reactions follows one of two basic pathways. For aldehydo, cyano, and aryl groups, migration takes place by a sequence of elementary reactions consisting of cyclization and β-fragmentation steps. (An example of this type of reaction is shown in Scheme 8 of Chapter 10). Group migration in esters is governed by a different mechanism, one that has been the subject of considerable investigation. To follow the progress in understanding this reaction, it is useful to view the advances in mechanistic discovery in a chronological order.

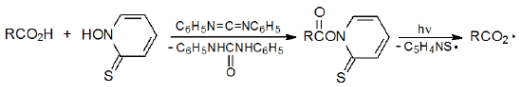
VI. Reactions of Carboxylic Acids

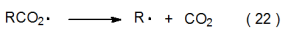
Carboxylic acids cannot be converted directly into carboxyl radicals, but they can form these radicals indirectly. One method for indirect formation calls for converting the acid into its anion, which then is subjected to electrolysis (Scheme 22).[95] Other indirect methods require formation of carboxylic acid derivatives, such as esters of *N*-hydroxypyridine-2-thione, compounds that produce carboxyl radicals by photochemically initiated reaction (Scheme 23).[96] Carboxyl radicals expel carbon dioxide to produce carbon-centered radicals (eq 22).

Scheme 22



Scheme 23





VII. Summary

Carbohydrates with simple acyloxy groups are unreactive under conditions normally used in reduction reactions. Reduction does occur, however, if the reaction temperature is raised to 140 ^{o}C and the reaction time is greatly extended. Esters with special structural features undergo reduction at lower temperatures; thus, both α-acyloxy ketones and methyl oxalyl esters react with tri-*n*-butyltin hydride at or below 110 ^{o}C.

Photochemical electron transfer provides a way for acyloxy groups to be replaced by hydrogen atoms under mild reaction conditions (at room temperature in neutral solution). Electron transfer occurs when either excited HMPA or *N*-methylcarbazole donates an electron to an ester to form a radical anion. Fragmentation of the radical anion generates a carbon-centered radical that then abstracts a hydrogen atom to produce a deoxygenated compound. Regeneration of the partially protected carbohydrate from which the ester was synthesized sometimes competes with deoxygenation.

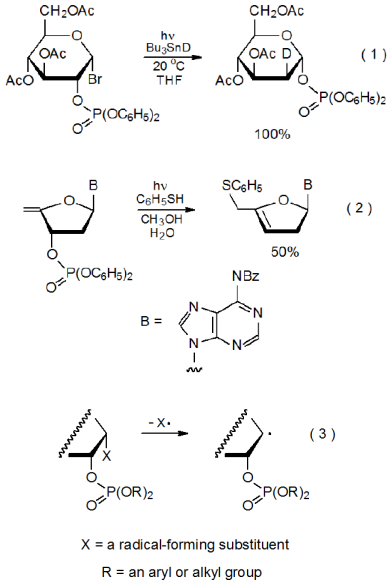
Acyloxy group migration to a radical center on an adjacent carbon atom is a reaction that is useful in the synthesis of 2-deoxy sugars. Early proposals for the mechanism of this reaction turned out not to be correct. The considerable investigation that has taken place since then has shown that this reaction is likely to involve the formation of an intimate ion pair consisting of a carboxylate anion and a radical cation. Recombination of this pair produces a new radical, one that has undergone group migration.

Carboxylic acids produce carboxyl radicals by reaction with hypervalent iodine reagents or electrolysis of carboxylate anions. These radicals expel carbon dioxide to form carbon-centered radicals. Electrochemical reaction results in radical coupling, or if the radical is further oxidized, carbocation formation. Reaction of carboxylic acids with hypervalent iodine reagents often is conducted in the presence of heteroaromatic compounds, where radical addition to the aromatic ring takes place.

CHAPTER OVERVIEW

9: Phosphoric Acid Esters

Two types of radical reaction of phosphoric acid esters are important in carbohydrate chemistry. One of these is migration of a phosphatoxy group from C-2 to C-1 in a pyranoid or furanoid ring (eq 1),[1] and the other is elimination of this group from C-3' in nucleotide derivatives (eq 2).[2] Even though these reactions are different in their outcome and very specific in terms of the type of structure undergoing reaction, they are mechanistically similar. An indication of this similarity is that each reaction begins by forming a radical in which a phosphatoxy group is β-related to the radical center (eq 3).



Topic hierarchy

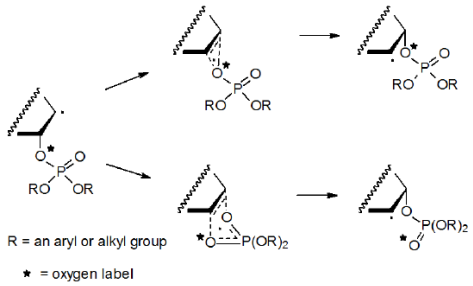
II. Phosphatoxy Group Migration
III. Radical Cation Formation from Nucleotides
IV. Migration Reactions in Other β-Ester Radicals
V. Summary

II. Phosphatoxy Group Migration

A. Reaction Mechanism

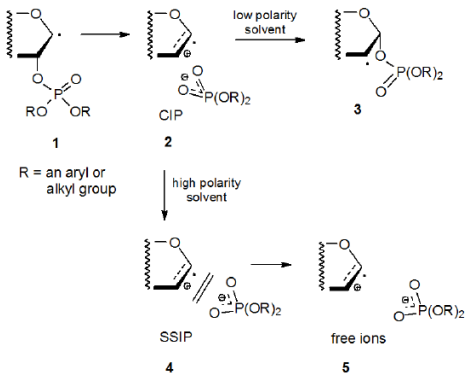
Initially two mechanisms were considered as possibilities for phosphatoxy group migration of the type shown in eq 1. (This same mechanistic choice exists for acyloxy group migration and is discussed in Section V.A of Chapter 8.) The first of these mechanisms consisted of a pair of competing, concerted reactions, each of which passed through a cyclic transition state (Scheme 1).[3–7] A basic difference between this pair was that in one reaction the same oxygen atom was bonded to the carbon-atom framework both before and after migration, but in the other the framework had a different oxygen atom attached after migration. Proposing migration via a combination of these two reactions made it possible to explain experiments with oxygen-labeled substrates in which only a portion of the labeled oxygen was attached to the carbon-atom framework after migration. The results from early studies favored this two-reaction explanation,[3–7] but those from later investigations required it to be changed because the later studies showed that ionic intermediates were involved in the migration process.

Scheme 1



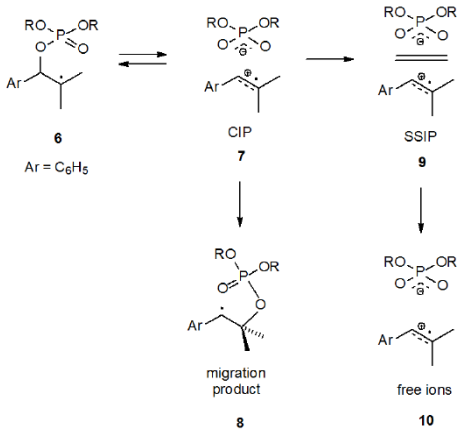
A mechanism that satisfies the ionic-intermediate requirement is shown in Scheme 2, where the β-phosphatoxy radical **1** fragments heterolytically to give the contact ion pair (CIP) **2**.[8–13] This ion pair recombines in low polarity solvents to form the group-migrated radical **3**, but in more polar solvents the CIP also can separate to become a solvent-separated ion pair (SSIP, **4**) and then free ions **5**.[10]

Scheme 2

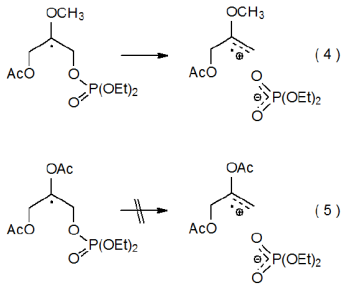


Critical support for the ion-pair mechanism for phosphatoxy group migration comes from laser-flash-photolysis (LFP) experiments. Both the SSIP **9** and the diffusively free radical cation **10** can be detected in studies where LFP generates the radical **6** (Scheme 3).[12] Evidence for the CIP in this reaction is indirect presumably because its lifetime is too short to permit direct detection. Study of reaction rates in solvents of different polarity supports the idea that the radical **6** is passing through a common intermediate in forming either the migrated radical **8** or the SSIP **9**. A reasonable conclusion is that the common intermediate is the contact ion pair **7** (Scheme 3).[12] Entropies of activation, which are the same for ion-pair formation in high polarity solvents and group migration in solvents of low polarity, also favor a common intermediate for which **7** is the prime candidate.[10,12] Generalizing these results leads to the reaction mechanism proposed in Scheme 2. (The wording in this paragraph also is found in Section V.A.5 of Chapter 8 because the information contained is pertinent to the mechanism of acyloxy group migration.)

Scheme 3

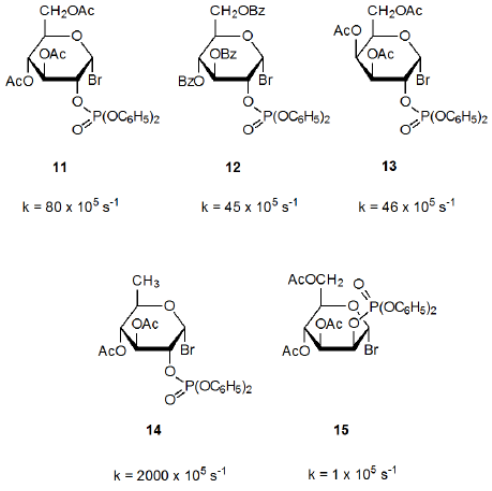


Phosphatoxy group migrations are not wide-spread in carbohydrate chemistry; in fact, all reported reactions involve migration from C-2 to C-1 in a pyranoid or furanoid ring. This situation exists because the stabilization afforded by the ring oxygen atom is critical at the transition state leading to radical-cation formation. Examining the reactivity of the noncarbohydrate radicals shown in equations 4 and 5 is instructive. An oxygen atom must be fully able to participate in radical-cation stabilization for heterolytic bond breaking to occur (eq 4).[14] Replacing the methoxy group in the substrate in the reaction shown in eq 4 with an acetyl group, as is done in the reaction shown in eq 5, prevents radical-cation formation because an oxygen atom with an electron-withdrawing group attached is unable to stabilize sufficiently the transition state leading to the radical-cation intermediate.[14]



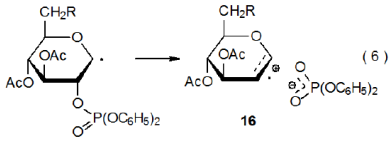
B. Relative Reaction Rates

Relative rate constants for phosphatoxy group migration in the reactions of the five hexopyranosyl bromides **11**-**15** are given in Table 1.[15] The rate constant for reaction of the 6-deoxy bromide **14** is substantially larger than those for the other bromides. Replacing the electron-withdrawing acyloxy group at C-6 with a hydrogen atom makes the radical cation **16** more stable and, in so doing, stabilizes the transition state leading to it (eq 6).



All reactions were conducted at 27 °C.

Table 1. Relative rates of phosphatoxy group migration.



R = H (more stable)

R = OAc (less stable)

The rate constant for reaction of the D-mannopyranosyl bromide **15** is decidedly smaller than those for reactions of the bromides **11-14**. One factor that contributes to this reduced reactivity is the enhanced stability of the radical **17** when compared to the corresponding radicals derived from the other bromides (**11-14**). Only **17** remains in a relatively strain-free, $^4C_1$ conformation while taking advantage of the stabilizing interaction of parallel p_o, p_c, and σ^* orbitals (Table 2).[15] To benefit from parallel-orbital stabilization, the radicals derived from bromides **11-14** must assume less stable conformations; for example, the radical derived from **11** adopts the $B_{2,5}$ boat conformation **18**.[15] As migration takes place in each of the radicals **17-19**, p_o, p_c, σ^* orbital stabilization is lost, but for radicals **18** and **19** this loss is compensated for, at least in part, by movement toward a more stable, $^4C_1$ conformation. Such compensation means that the transition states for radical-cation formation from **18** and **19** are not as high in energy as that for reaction of **17**; consequently, group migration for the radical **17** is slower than for **18** and **19**.

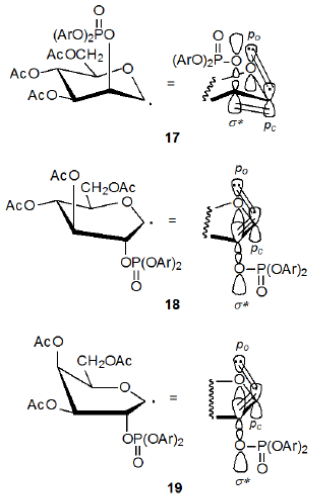
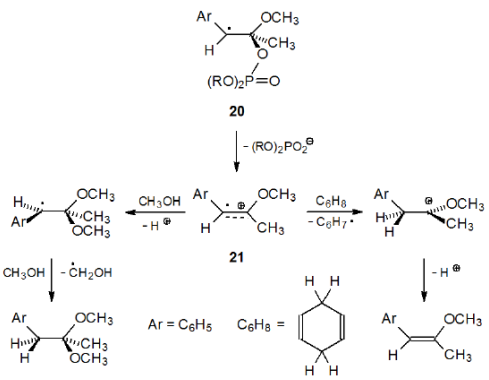


Table 2. Conformations of pyranos-1-yl radicals

Pertinent information about formation and reactivity of radical cations comes from the study of noncarbohydrate systems.[16,17] Nucleophilic trapping of the radical cation **21** by methanol ($k < 1 \times 10^3\ M^{-1}s^{-1}$) is slow compared to hydrogen-atom abstraction from 1,4-cyclohexadiene ($k = 6 \times 10^5\ M^{-1}s^{-1}$) (Scheme 4).[17] To the extent that this observation is a general one, radical cations can be expected to have greater radical reactivity than cationic reactivity.

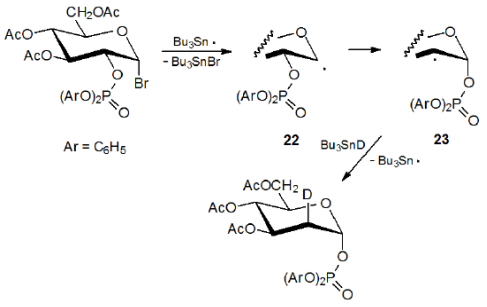
Scheme 4



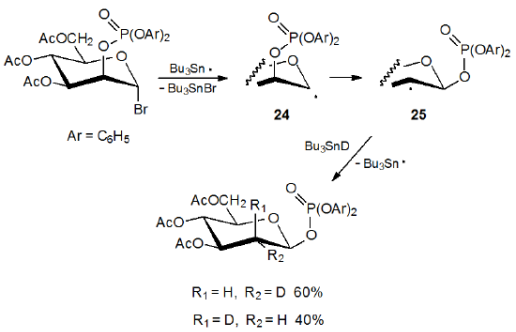
C. Stereoselectivity

The reactions pictured in Schemes 5 and 6 show that phosphatoxy group migration is a stereospecific process; thus, the epimeric radicals **22** and **24** give the product radicals **23** and **25**, respectively.[1,15] Once migration has taken place, stereoselective deuterium abstraction completes the reaction. For the radical **23** abstraction is highly stereoselective, but it is much less so for the radical **25**. Shielding of the α face of **23** by the axial phosphatoxy group causes deuterium to be abstracted from the β face of this radical (Scheme 5). The equatorial phosphatoxy group in **25** is not nearly as effective at forcing Bu_3SnD to the opposite face of the pyranoid ring (Scheme 6).

Scheme 5

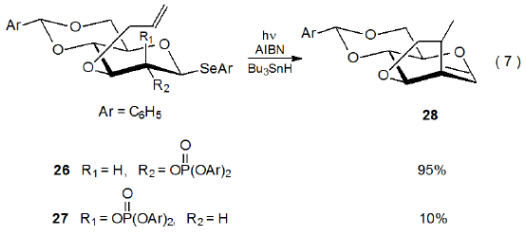


Scheme 6

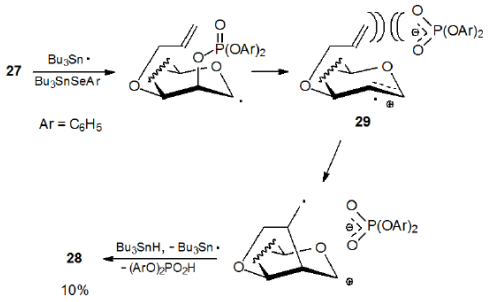


Differential shielding of the faces of a pyranoid ring affects the ability of the phosphates **26** and **27** to undergo new ring formation (eq 7). The phosphate **26** gives a decidedly higher yield of the glycal **28** than does its epimer **27**.[18] The substantially lower product yield from reaction of **27** is attributed to steric hindrance by the nearby phosphate counter ion during cyclization of the radical

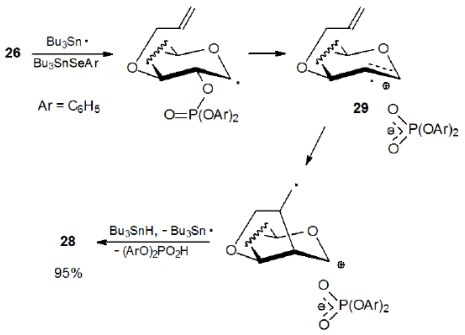
cation **29** (Scheme 7). When **29** is generated from **26**, however, the counter ion is on the opposite face of the ring and does not impede cyclization (Scheme 8).



Scheme 7



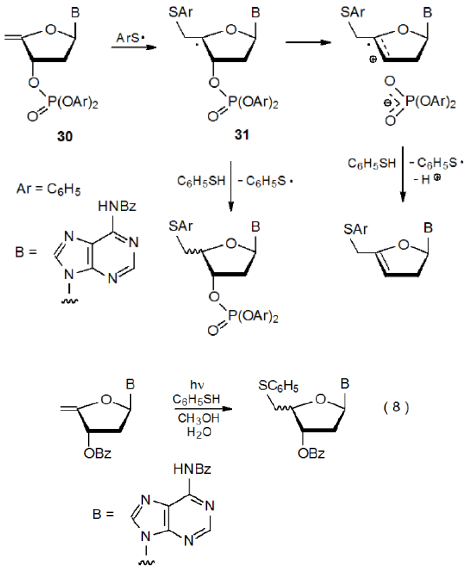
Scheme 8



III. Radical Cation Formation from Nucleotides

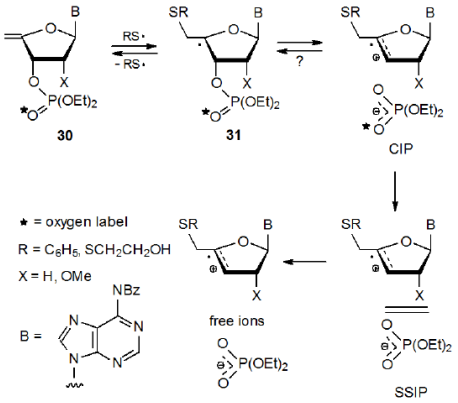
Addition of the phenylthiyl radical to the unsaturated nucleotide **30** produces the carbon-centered radical **31** (Scheme 9).[2] This radical (**31**) either abstracts a hydrogen atom to give an epimeric mixture of reduced nucleotides or fragments the C–O bond at C-3' heterolytically to give a phosphate anion and a radical cation.[19] Fragmentation is assisted by polar solvents.[20] Since heterolytic fragmentation of **31** also depends on the ability of the substituent at C-3' to stabilize a negative charge as the C–O bond breaks, forming a highly stabilized anion is critical; thus, fragmentation is competitive with hydrogen-atom abstraction when the anion produced is a phosphate (Scheme 9) but not a benzoate (eq 8).[2]

Scheme 9



Additional details concerning ion-pair formation from the unsaturated nucleotide **30** are given in Scheme 10.[21–24] A contact ion pair (CIP), a solvent-separated ion pair (SSIP), and diffusively free ions all are included in this Scheme. Labeling experiments show how the various ion pairs participate in the reaction. Since no scrambling of the oxygen label in the phosphate group in the substrate **30** occurs after partial reaction, the CIP either cannot return to the radical **31** or if it does, no reorganization occurs within this ion pair.[23] Since oxygen scrambling can take place in the SSIP, the labeling experiments show that once this intermediate is reached, there is no return to the radical **31**.

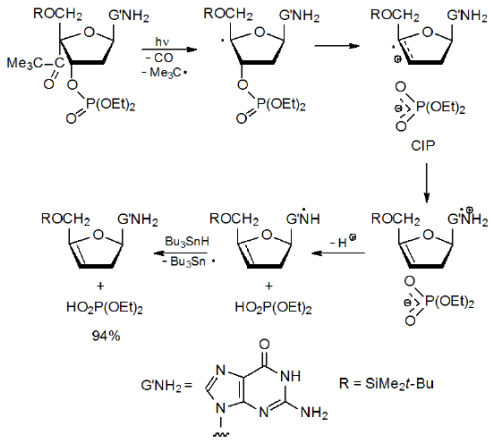
Scheme 10



Mechanistic studies using both alkyl- and arylthiols show that the equilibrium between the nucleotide **30** and the adduct radical **31** depends on the identity of the R group in the thiyl radical (Scheme 10). In this equilibrium alkylthiyl radicals favor adduct formation to a greater extent than do arylthiyl radicals. When the method of formation produces a low radical concentration, conditions can exist in which alkylthiyl radicals will form a sufficient concentration of adduct radicals (**31**) for reaction to proceed at an observable rate, but arylthiyl radicals do not produce the necessary radical concentration.[22]

Study of the rates of radical reaction of thymidine, cytidine, adenosine, and guanosine derivatives show that guanosines are by far the most reactive.[23] (The rate of reaction of guanosine derivatives is too fast to be measured.) This enhanced reactivity is attributed to rapid, internal electron transfer from the guanine moiety to the radical-cation portion of the molecule (Scheme 11).[23,25–27] Electron transfer of this type may be fast enough ($k > 1 \times 10^9\ s^{-1}$) to be taking place within the CIP.[23] One estimate of the rate constant for this type of electron transfer is $1.4 \times 10^8\ s^{-1}$.[27]

Scheme 11



IV. Migration Reactions in Other β-Ester Radicals

Other groups (sulfonyloxy,[28,29] bromo,[29] nitroxy,[28] and protonated hydroxyl[30]) that are β-related to a carbon-centered radical can react to give radical cations. The migration of acyloxy groups, discussed in Section V of Chapter 8, also is likely to involve radical cations.

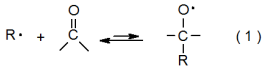
V. Summary

Under the proper conditions a phosphatoxy group that is β-related to a radical center will fragment to produce an ion pair consisting of a phosphate anion and a radical cation. This heterolytic fragmentation is favored by polar solvents and formation of radical cations at least as stable as those arising from enol ethers. When the radical center is at C-1 in a pyranoid or furanoid ring, the ion pair recombines to give a new radical in which phosphatoxy group migration to C-1 is accompanied by radical translocation to C-2. If the radical center in a nucleotide is at C-4' and a phosphatoxy group is located at C-3', heterolytic cleavage of the $C_{3'}$-O bond does not lead to group migration; rather, products arising from hydrogen-atom abstraction, solvent capture, or proton loss are observed.

CHAPTER OVERVIEW

10: Aldehydes & Ketones

Aldehydes and, to a lesser extent, ketones participate in radical reactions of carbohydrates by generating intermediate, oxygen-centered and carbon-centered radicals. The radical addition pictured below provides an example of conversion of a carbonyl compound into an oxygen-centered radical.

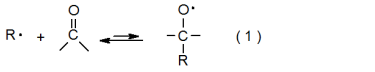


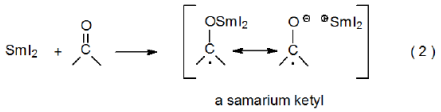
(1)

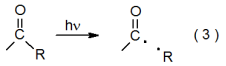
I. Introduction
II. Intramolecular Addition of Carbon-Centered Radicals to Aldehydo and Keto Groups
III. Migration of Aldehydo Groups
IV. Addition of Tin- and Silicon-Centered Radicals to Aldehydes
V. Reaction of Samarium(II) Iodide with Aldehydes and Ketones
VI. Ketone Photolysis
VII. Cyclization of Acylsilanes
VIII. Reactions of α-Acyloxyketones
IX. Summary

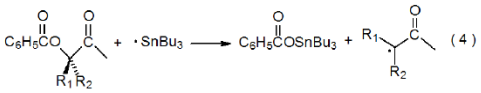
I. Introduction

Aldehydes and, to a lesser extent, ketones participate in radical reactions of carbohydrates by generating intermediate, oxygen-centered and carbon-centered radicals. The radical addition pictured in eq 1 provides an example of conversion of a carbonyl compound into an oxygen-centered radical, while that in eq 2 involves transforming an aldehyde or ketone into a carbon-centered radical. [The radicals produced in the latter reaction (eq 2) are described as samarium ketyls in recognition of their partial radical-anion character.] Other reactions that generate radicals from aldehydes and ketones are photochemical bond homolysis (eq 3) and fragmentation of α-acyloxy ketones (eq 4). The discussion in this chapter centers on the types of compounds that can be produced by these reactions and the mechanisms for their formation.







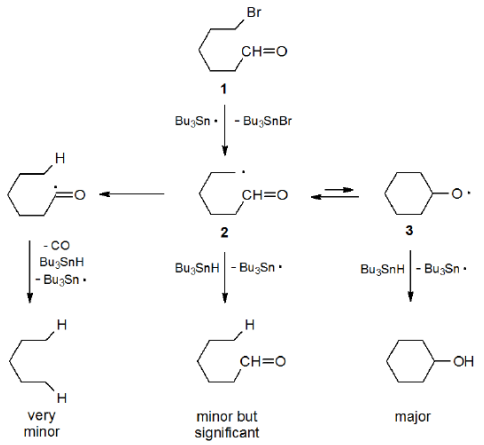


II. Intramolecular Addition of Carbon-Centered Radicals to Aldehydo and Keto Groups

The possibility of isolating a product from intermolecular addition of a carbon-centered radical to an aldehyde or ketone is small due to the ready reversibility of this reaction (eq 1), but the possibility of product isolation increases considerably if the reaction becomes an intramolecular addition of a carbon-centered radical to an aldehyde or keto group to give a radical centered on an oxygen atom that is attached to a five- or six-membered ring.

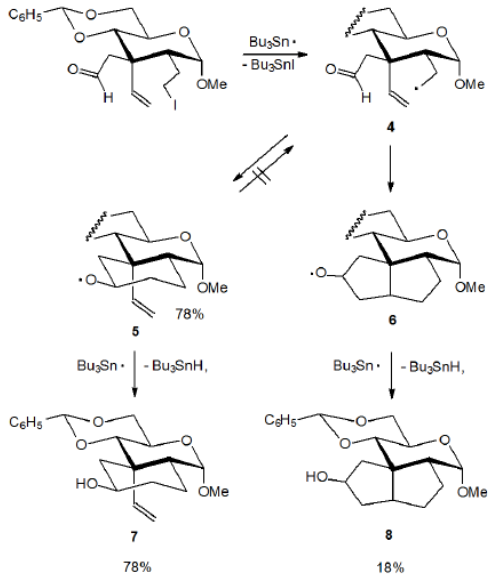
An example of such a reaction is shown in Scheme 1, where the carbon-centered radical **2**, generated from 6-bromohexanal (**1**), is converted reversibly into the cyclic alkoxy radical **3**.[1] Hydrogen-atom abstraction by **3** from tri-*n*-butyltin hydride has a substantially larger rate constant than that for abstraction by **2**; consequently, even though ring opening is more rapid than ring closure, reaction produces cyclohexanol as the major product and hexanal as a minor one.

Scheme 1



Intramolecular hydrogen-atom abstraction from the aldehydo group in **2** is a very minor process. The inability of this abstraction to compete with ring formation in a noncarbohydrate system is echoed in the reactions of carbohydrate radicals containing aldehydo groups. The reaction shown in Scheme 2 is one of several discussed in this chapter where hydrogen-atom abstraction from an aldehydo group is possible but does not take place.[2]

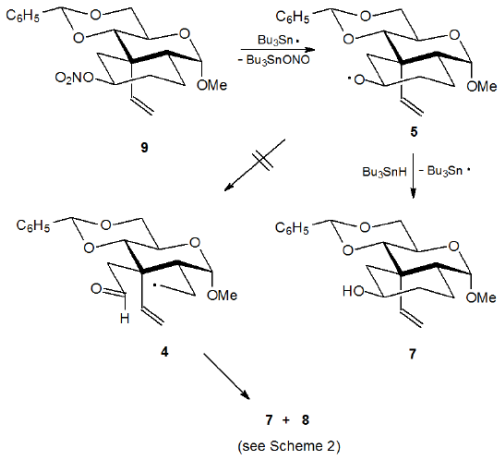
Scheme 2



Even though ring opening always is a possibility for cyclic alkoxy radicals, this transformation sometimes does not take place; for example, the reaction producing the alkoxy radical **5** from the ring-open radical **4** is not reversible (Scheme 2).[2,3] Failure of the

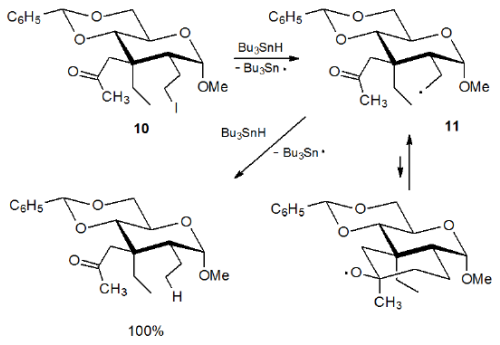
cyclohexane ring in **5** to open is demonstrated by reaction of the nitrate ester **9** (Scheme 3).[3] Treatment of **9** with Bu_3SnH produces **5** (and ultimately the product **7**) but ring opening to give **4** does not happen. If the ring-open radical **4** were formed, the product **8** also would be produced in this reaction, but since no **8** could be detected, the conclusion is that the alkoxy radical **5** does not undergo ring opening.[3]

Scheme 3

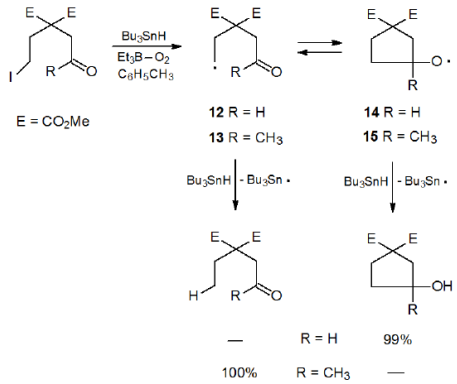


In contrast to cyclization of the aldehydo radical **4** (Scheme 2) the closely related keto radical **11** (Scheme 4) does not form a new ring system.[4] Either the greater steric hindrance inherent in producing a tertiary alkoxy radical or rapid ring opening of such a strained intermediate or both are sufficient to prevent **11** from forming a new ring system. These reasons for failure to form a new ring draw support from the reactions of noncarbohydrate radicals **13** and **14** (Scheme 5).[5] In the reaction shown in Scheme 5 where R is a methyl group, hydrogen-atom abstraction from tri-*n*-butyltin hydride is done exclusively by the open-chain radical **13**. When R is a hydrogen atom, abstraction from Bu_3SnH occurs only after conversion of the open-chain radical **12** into the cyclic alkoxy radical **14**.

Scheme 4

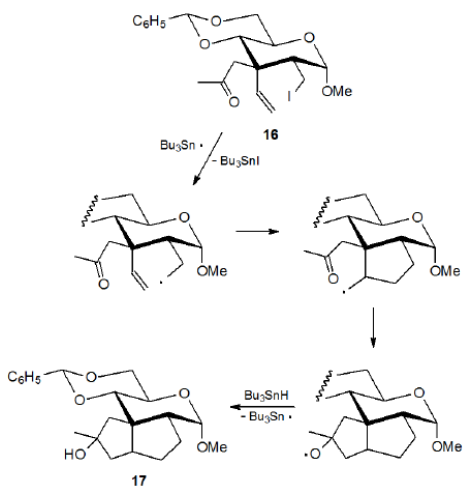


Scheme 5



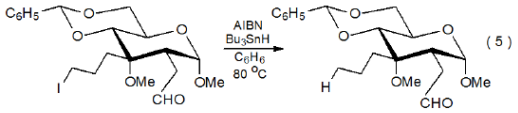
The reactivates of the aldehydo radical **4** (Scheme 2) and the keto radical **11** (Scheme 4) raise a number of questions (listed below) about participation of keto and aldehydo groups in radical cyclization reactions. Many of these questions have been answered by study of related compounds. Their answers provide insight into the factors that control the cyclization process. These questions and their answers are:

1. Scheme 6



46%

2.



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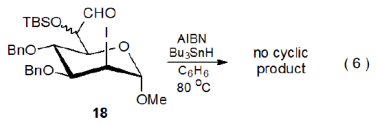
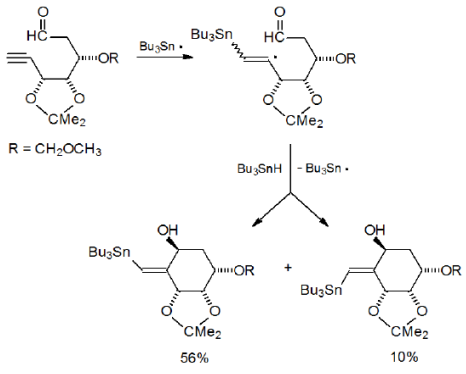
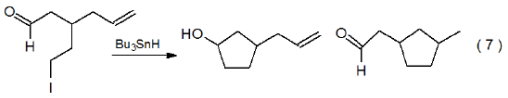
3.



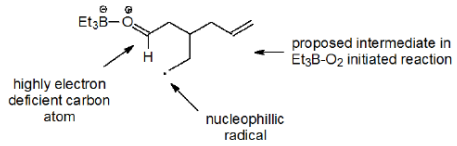
3. Scheme 7





(7)

temp	initiator		
80 °C	AIBN	21%	63%
10 °C	Et_3B, O_2	79%	0%



1.

1. Roger W. Binkley (Cleveland State University) and Edith R. Binkley (Cleveland Heights-University Heights school system)

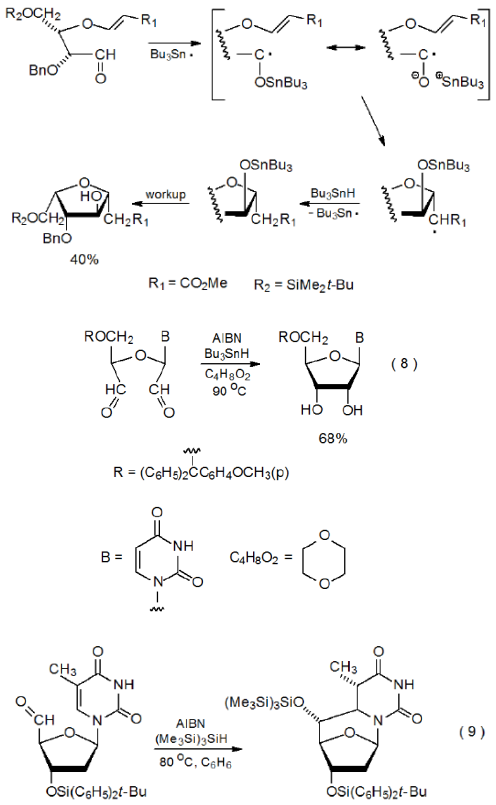
III. Migration of Aldehydo Groups

A possible fate for an alkoxy radical formed by cyclization is ring opening to produce a radical different from the one that initially formed the ring.[4,13–17] A new direction in ring opening is likely if it produces a more stable radical. In the reaction shown in Scheme 8 such a situation exists.[14,15] Ring opening of the alkoxy radical **20** gives the resonance-stabilized, benzylic radical **21** rather than the unstabilized radical **19** that reacted to produce the ring system. This alternative ring opening (**20**→**21**) completes an addition-fragmentation sequence that causes migration of the aldehydo group.

IV. Addition of Tin- and Silicon-Centered Radicals to Aldehydes

Although the reactions discussed thus far have involved addition of carbon-centered radicals to carbonyl groups, other types of radicals, including tin- and silicon-centered ones, also add to aldehydes and ketones. Reaction of the tri-*n*-butyltin radical with a carbonyl group generates a tin ketyl, a radical with considerable negative charge on the oxygen atom. As the reaction in Scheme 9[18] shows, tin ketyls undergo internal radical addition to electron-deficient, C–C multiple bonds.[18–22] These ketyls also react with C–N double bonds,[23] and they produce pinacols upon addition to carbonyl groups (eq 8).[24] Internal addition also can occur when a silicon-centered radical adds to an aldehydo group, as happens in the reaction shown in eq 9.[25]

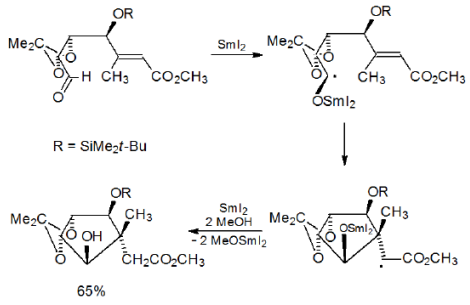
Scheme 9



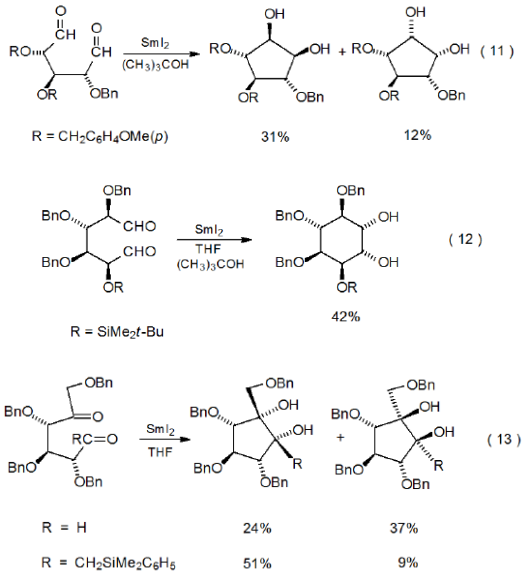
V. Reaction of Samarium(II) Iodide with Aldehydes and Ketones

Reaction of an aldehyde or ketone with samarium(II) iodide produces a samarium ketyl.[26–39] These ketyls add intramolecularly to appropriately positioned carbon–carbon[25–33] (Scheme 10)[26] and carbon–nitrogen[34–37] (eq 10)[34] double bonds. Such reactions are reminiscent of the addition of typical carbon-centered radicals to multiple bonds.

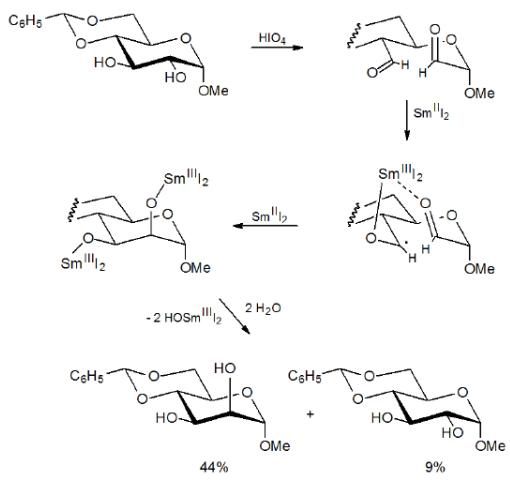
Scheme 10



When samarium(II) iodide reacts with compounds containing two aldehydo groups, the first is converted into a samarium ketyl that then adds to the second. This addition depends upon proper separation between the reacting groups;[40–53] accordingly, pinacols with five-membered[40,49-53] (eq 11)[40] and six-membered[41–48] (eq 12)[41] rings form easily. It is not necessary for both interacting groups in a molecule to be aldehydo groups; pinacols also arise when one[49–52] (eq 13, R = H)[49] or both (eq 13, R = $CH_2SiMe_2C_6H_5$)[53] are keto groups. Complexation of the ketyl and carbonyl oxygen atoms with SmI_2 forces a cis relation between the hydroxyl groups in the products (Scheme 11).[42] Pinacol formation and other reactions of aldehydes and ketones with samarium(II) iodide is revisited in Chapter 20, where a broader discussion of the interaction of SmI_2 with carbohydrate derivatives takes place.



Scheme 11



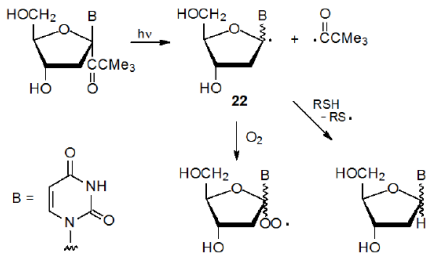
VI. Ketone Photolysis

A. α-Cleavage Reactions

When photolysis of ketones causes homolytic cleavage of a bond between the carbonyl group and one of the α carbon atoms either a pair of radicals or a diradical forms. (Such a reaction is known as an α-cleavage or Norrish Type I reaction.) α-Cleavage of simple ketones does not take place in solution, although it does occur in the gas phase. Cleavage in solution happens only when stabilized radicals are produced. This means that the reaction shown in eq 3 is successful for nonvolatile compounds such as carbohydrates only when the radical center in R· is stabilized in some way (e.g., by having an oxygen or nitrogen atom attached). Most carbohydrates that contain a keto group will have at least one pathway for forming an oxygen-stabilized radical by α-cleavage.[54]

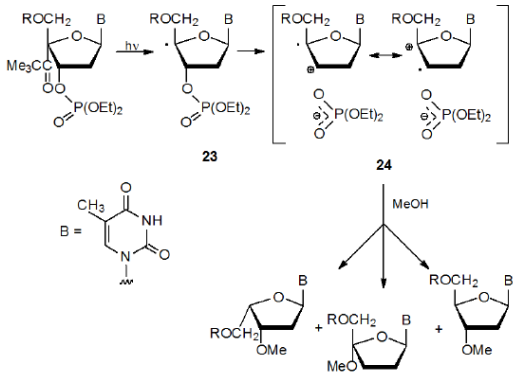
When the keto group in a carbohydrate is not part of a ring system, α-cleavage produces a radical pair. Most reactions of this type involve derivatives of nucleosides, nucleotides, or oligonucleotides.[55–67] Scheme 12 describes such a reaction, one in which the nucleoside member (**22**) of the radical pair produced by α-cleavage undergoes two characteristic radical reactions, namely, hydrogen-atom abstraction (when an effective donor, such as a thiol, is present) and addition of O_2 (when molecular oxygen is one of the reactants).[61]

Scheme 12



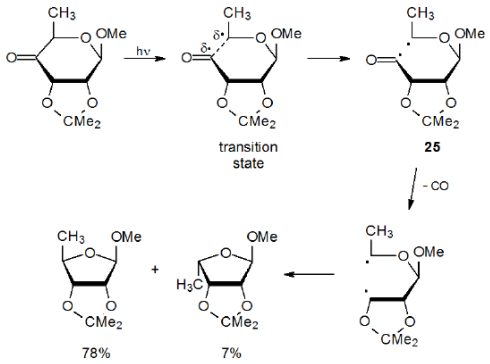
Although α-cleavage in nucleotides produces radicals that undergo typical radical reactions, such as those shown in Scheme 12, many of these radicals also undergo a heterolytic cleavage to form radical cations and phosphate anions. An example of such a reaction is shown in Scheme 13, where the radical **23** cleaves its C-3'–O bond to generate the radical cation **24** and a phosphate anion.[56] (Radical-cation formation of the type shown in Scheme 13 is discussed in Section III of Chapter 9.)

Scheme 13



α-Cleavage in a cyclic ketone, a reaction that occurs in many carbohydrates, is an internal process that produces a diradical.[68] Diradicals of this type usually reform a ring system, but often after the loss of carbon monoxide.[68] Scheme 14 describes formation of the diradical **25**, a reaction that is followed by loss of carbon monoxide to give a second diradical, one that produces a new ring system by radical combination.[69] The α-cleavage shown in Scheme 14 is driven, at least in part, by transition-state stabilization due to the developing radical center at C-6 being stabilized by an attached oxygen atom.

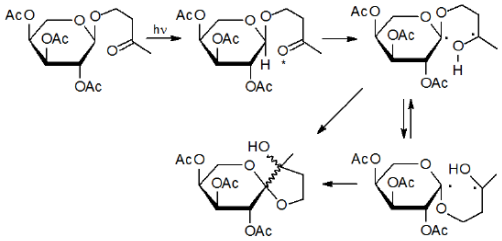
Scheme 14



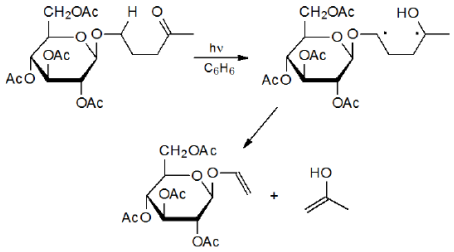
B. Hydrogen-Atom Abstraction Reactions

Ketones that do not undergo α-cleavage have another option for diradical formation, namely, internal abstraction that occurs when a hydrogen atom comes with bonding distance of an excited carbonyl group; thus, in the reaction is shown in Scheme 15, 1,6-hydrogen-atom abstraction produces a diradical that then forms a spiro compound by radical combination.[70] If a 1,5-hydrogen-atom transfer takes place, the resulting 1,4-diradical fragments as shown in Scheme 16.[71] (Many carbohydrates undergo this type of reaction, which is known as a Norrish Type II process.[72])

Scheme 15

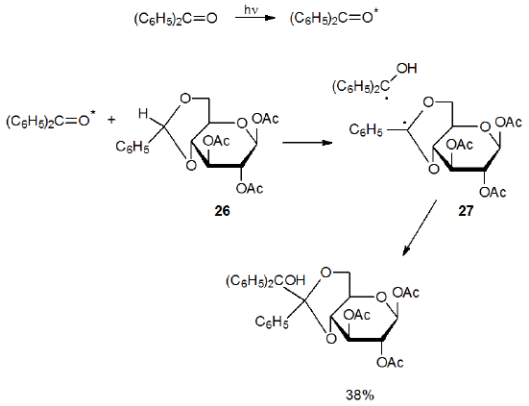


Scheme 16



If an excited ketone does not undergo internal abstraction or α-cleavage, hydrogen-atom abstraction from another molecule sometimes takes place.[73] Such abstraction requires a transition state in which there is considerable radical stabilization. Hydrogen-atom abstraction by excited benzophenone from the benzylidene acetal **26** meets this requirement by producing the highly stabilized radical **27** (Scheme 17).[74] Radical combination completes this reaction.

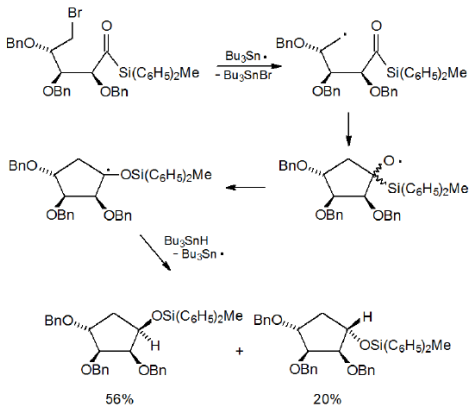
Scheme 17



VII. Cyclization of Acylsilanes

Acylsilanes undergo radical cyclization that involves addition of a carbon-centered radical to the carbonyl carbon atom in the acylsilyl group (Scheme 18).[75] This reaction is unusual in that migration of the silyl group to the radical center on oxygen stops reaction that would reverse ring formation.

Scheme 18



VIII. Reactions of α-Acyloxyketones

α-Acyloxyketones are compounds that undergo replacement of the acyloxy group with a hydrogen atom upon reaction with tri-*n*-butyltin hydride. Reactions of these compounds are discussed in Section II.A of Chapter 8 along with other reactions of carboxylic acid esters.

IX. Summary

Aldehydo and keto groups in carbohydrates react internally with carbon-centered radicals to form cyclic alkoxy radicals. Most of these reactions involve aldehydes; both five- and six-membered rings can be formed. When ring opening of the newly formed alkoxy radical takes place, it does so to produce the more stable of the two possible, carbon-centered radicals. Such ring opening can be part of a process that causes aldehydo group migration.

Tin-centered radicals add to aldehydes to generate tin ketyls, intermediates that can add to multiple bonds. Samarium ketyls, more common than their tin counterparts, undergo similar reaction. Reaction of samarium(II) iodide with carbohydrates containing two appropriately placed aldehydo groups converts one group to a ketyl that then adds to the second in route to formation of a pinacol.

Ketone photolysis forms carbon-centered radicals by breaking the bond between the carbonyl carbon atom and one of the α carbon atoms (an α-cleavage). Typical radical reactions then take place; in addition, α-cleavage in some nucleotides and oligonucleotides is followed by radical cation formation. α-Cleavage and hydrogen-atom abstraction take place in cyclic ketones to produce diradicals.

CHAPTER OVERVIEW

11: Synthesis of O-Thiocarbonyl Compounds

The first step in conducting most radical reactions is the preparation of a radical precursor. For many of such compounds (e.g., halides, esters, and acetals) this preparation needs little, if any, discussion, as the reactions involved are among the most common in organic chemistry. *O*-Thiocarbonyl compounds [xanthates, (thiocarbonyl)imidazolides, aryl thionocarbonates, cyclic thionocarbonates, and thionoesters] are different because their preparation is less common, and the potential difficulties in their formation less well known. Because these compounds are rich sources of carbon-centered radicals and because being able to prepare them efficiently is vital to their use, understanding the synthesis of *O*-thiocarbonyl compounds is integral to using them in radical formation. This chapter, targeted at the synthesis of these compounds, is a companion to the one that follows, where radical reactions of *O*-thiocarbonyl compounds are discussed.

Topic hierarchy

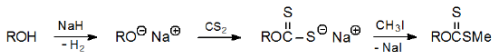
II. Xanthates
III. (Thiocarbonyl)imidazolides
IV. Aryl Thionocarbonates
V. Cyclic Thionocarbonates
VI. Thionoesters
VII. Factors Affecting O-Thiocarbonyl Compound Synthesis
VIII. Summary

II. Xanthates

A. The Carbon Disulfide–Methyl Iodide Procedure (The Standard Procedure for Xanthate Synthesis)

The most common method for synthesizing *O*-[(alkylthio)thiocarbonyl] esters of carbohydrates (carbohydrate xanthates) begins by forming an alkoxide ion from reaction of sodium hydride with a compound containing an unprotected hydroxyl group.[1] (Imidazole usually is present in the reaction mixture to promote alkoxide ion formation.) Once formed, the alkoxide ion adds to carbon disulfide, and the resulting anion is alkylated by methyl iodide. This procedure, which is the standard one for xanthate synthesis, is summarized in Scheme 1.

Scheme 1



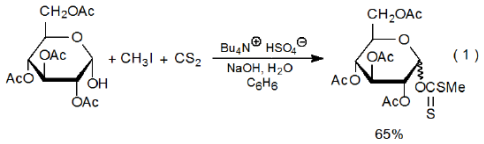
B. Modifications of the Standard Procedure

1. Reagents and Reaction Conditions

Modification of the procedure outlined in Scheme 1 sometimes is necessary to improve reactant solubility and reactivity. Minor changes take the form of replacing the normal reaction solvent (THF) with *N*,*N*-dimethylformamide[2,3] or methyl sulfoxide.[4–8] When methyl sulfoxide is the reaction solvent, sodium hydroxide usually replaces sodium hydride as the deprotonating base.[4,6,7]

2. Phase-Transfer Reaction

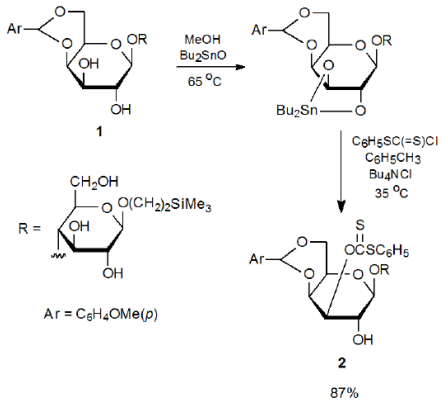
Phase-transfer reaction provides a way for synthesizing xanthates that are difficult or impossible to prepare by the standard procedure. Anomeric xanthates, compounds that provide a synthetic challenge due to their instability, can be produced by phase-transfer reaction (eq 1).[9] This reaction also demonstrates the potential of the phase-transfer procedure in preparing xanthates containing base-labile groups.



C. The Phenyl Chlorodithioformate Procedure

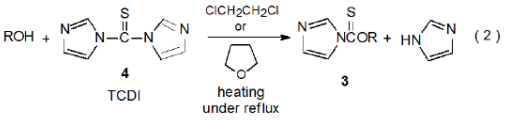
Esterification of an alcohol with an acid chloride provides another, but rarely used procedure for xanthate synthesis. Heating the partially protected disaccharide **1** with dibutyltin oxide produces a stannylene complex that then reacts regioselectively with phenyl chlorodithioformate to give the xanthate **2** (Scheme 2).[10] This reaction provides a route to carbohydrate xanthates that contain an *O*-[(arylthio)thiocarbonyl] group. These arylthio derivatives cannot be prepared by the iodide displacement that is part of the standard xanthate synthesis.

Scheme 2



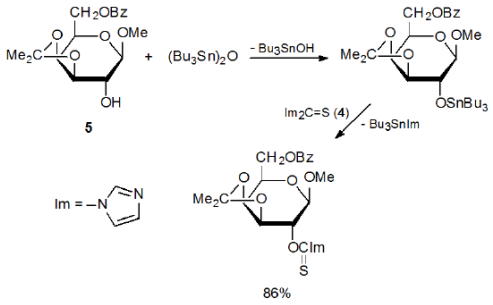
III. (Thiocarbonyl)imidazolides

Formation of a (thiocarbonyl)imidazolide (**3**) generally involves heating a partially protected carbohydrate with *N*,*N*-thiocarbonyldiimidazole (**4**, TCDI) under reflux in tetrahydrofuran (or 1,2-dichloroethane) and isolating the reaction product by chromatography (eq 2).[1,11] Nearly every synthesis of a (thiocarbonyl)imidazolide follows this procedure, although acetonitrile,[12–14] toluene,[15–17] and *N*,*N*-dimethylformamide[18,19] occasionally are used as reaction solvents.

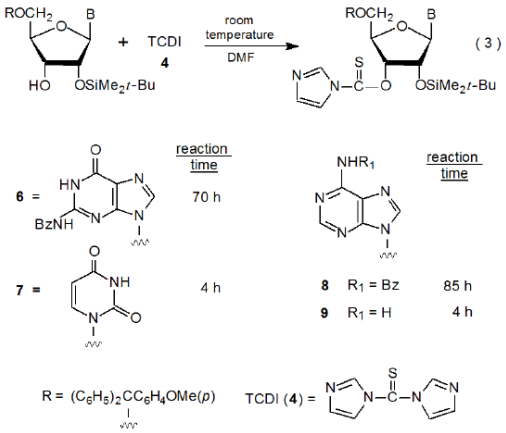


There are scattered reports of (thiocarbonyl)imidazolides forming more slowly than might be expected under typical reaction conditions. One such report concerns the methyl glycoside **5**, a compound that reacts so slowly that prior activation with bis(tributyltin)oxide is necessary to increase the nucleophilicity of **5** to the point that (thiocarbonyl)imidazolide formation proceeds at an acceptable rate (Scheme 3).[20]

Scheme 3



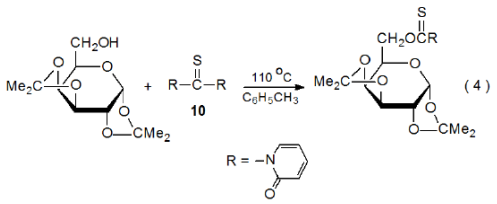
Reduced reactivity in nucleosides sometimes is brought about by *N*-benzoylation. The *N*-benzoylguanosine and adenosine derivatives **6** and **8** require treatment with TCDI (**4**) for 70 and 85 hours, respectively, for complete reaction to take place; in contrast, derivatives lacking the *N*-benzoyl group (**7** and **9**), need only four hours for reaction to reach completion (eq 3).[21]



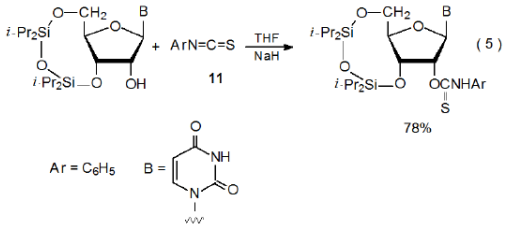
Even though (thiocarbonyl)imidazolides (**3**) can be prepared readily by the reaction shown in eq 2, this procedure has several minor drawbacks. One of these is that *N*,*N*-thiocarbonyldiimidazole (**4**, TCDI) needs to be kept in a dry atmosphere because it is unstable in the presence of atmospheric moisture.[22] Another is that imidazole, produced as a byproduct in this reaction (eq 2), may catalyze unwanted transformation of some compounds.[22] Finally, the cost of TCDI (**4**) is high enough to be a factor in deciding upon its use, particularly in large-scale reactions.

In an effort to overcome possible disadvantages associated with use of (thiocarbonyl)imidazolides, some researchers have proposed switching to related compounds. Thionocarbamates formed from 1,1'-thiocarbonyldi-2,2'-pyridone (**10**), a reagent stable to

atmospheric moisture, are effective replacements for (thiocarbonyl)imidazolides (eq 4),[22] but detracting from the use of this new reagent (**10**) is its even greater cost that TCDI.



Some thionocarbamates synthesized from the inexpensive phenyl isothiocyanate (**11**) (eq 5) are capable of radical formation.[23,24] Although producing a thionocarbamate by reacting a partially protected carbohydrate with phenyl isothiocyanate (**11**) solves the "cost problem", it has the disadvantage that this reaction requires the presence of a strong base because hydroxyl group deprotonation is needed for this reaction to occur at an acceptable rate (eq 5). Also, not all thionocarbamates prepared from **11** form radicals under typical reaction conditions.[25] None of the alternatives to (thiocarbonyl)imidazolides have been widely adopted.

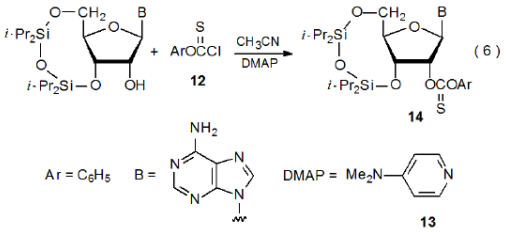


IV. Aryl Thionocarbonates

A. Reaction with Phenoxythiocarbonyl Chloride

1. DMAP-Catalyzed Reactions

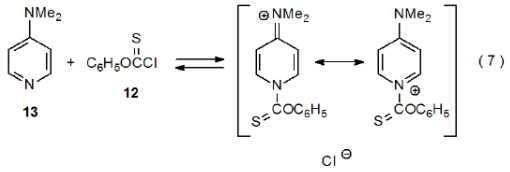
The standard procedure for synthesis of phenyl thionocarbonates is illustrated by the reaction shown in eq 6.[26,27] Phenoxythiocarbonyl chloride (**12**) in the presence of the powerful, acylation catalyst 4-dimethylaminopyridine (**13**, DMAP) esterifies most carbohydrates with ease. Even though pyridine itself can be used in some situations, the superior catalytic effect of DMAP makes it the reagent of choice. In those rare instances when thionocarbonate formation by the standard procedure is too slow, switching the reaction solvent from acetonitrile to *N*,*N*-dimethylformamide or methyl sulfoxide often is sufficient to increase the rate of reaction to a synthetically acceptable level.[28]



(6)

DMAP (**13**) causes acylation rates to increase by factors as large as 10,000 when compared to reactions catalyzed by pyridine.[29] One possibility for the greater catalytic effect of DMAP is that it is a stronger base than pyridine. (The pK_b for pyridine is 8.71 and that for DMAP is 4.30.[29]) This explanation for the difference in reactivity, however, is not sufficient to explain DMAP's superior catalytic ability because triethylamine (pK_b = 3.35), an even stronger base than DMAP, has a catalytic effect similar to that of pyridine.[29]

A better explanation for DMAP being such an effective catalyst is that it reacts with acid chlorides, such as **12,** to form high concentrations of *N*-acylpyridinium salts (eq 7).[29] These salts are better able to transfer an acyl group to a nucleophile than is the acid chloride itself. Resonance stabilization (two of the principal resonance contributors are shown in eq 7) increases the equilibrium concentration of an *N*-acylpyridinium salt, and charge delocalization increases the reactivity of this powerful acylating agent by creating loosely bound ion pairs.

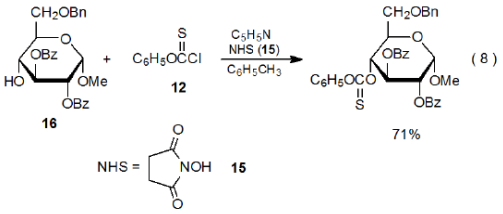


(7)

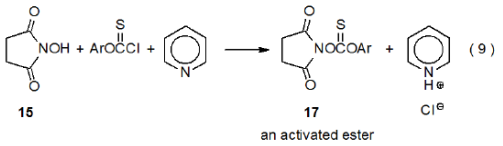
The mildly basic conditions for thionocarbonate synthesis stand in contrast to the strongly basic ones used for xanthate preparation.[26] Avoiding strongly basic conditions often is necessary in nucleoside synthesis; for example, thionocarbonates such as **14** can be prepared without difficulty (by the procedure outlined in eq 6), but attempted synthesis of the corresponding xanthates results in starting material decomposition.[27] The specific reason xanthate synthesis fails in this case is that it requires conditions too basic for the stability of nucleosides protected by the 1,1,3,3-tetraisopropyl-1,3-disiloxanediyl group, a common protecting group for nucleosides.

2. *N*-Hydroxysuccinimide-Catalyzed Reactions

Although DMAP (**13**) is the catalyst of choice in most syntheses of phenyl thionocarbonates, sometimes, in an effort to avoid an undesired, competing reaction or to improve product yield, DMAP is replaced by another reagent. The most common replacement is *N*-hydroxysuccinimide (NHS, **15**).[30–35] In the reaction shown eq 8, the methyl pyranoside **16** gives a better yield of the corresponding phenoxythionocarbonate when NHS (**15**) is the catalyst rather than DMAP.[16]

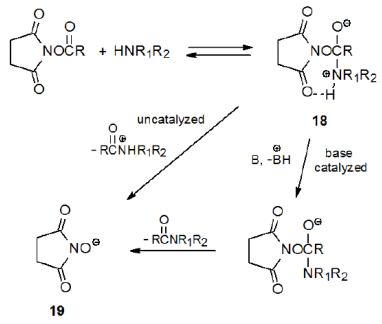


There is a similarity in the mode of action of DMAP and NHS in that each of them typically reacts with an acid chloride to produce a better acylating agent. For DMAP (**13**) this agent is the *N*-acylpyridinium salt shown in eq 7, and for NHS (**15**) the new acylating agent is the ester **17** (eq 9). Because esters of NHS react unusually rapidly with nucleophiles, they are sometimes referred to as "activated esters".[36]



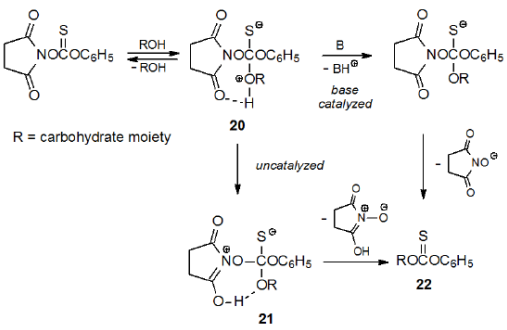
Extensive mechanistic study of esters of *N*-hydroxysuccinimide with amines has shown their reaction kinetics to be consistent with a process in which reversible formation of the zwitterionic intermediate **18** is followed by a rate-determining breakdown of this intermediate by either an uncatalyzed or base-catalyzed process (Scheme 4).[37,38] Since the hydroxyl group in NHS (**15**) is quite acidic (pK_a = 6.0[39]), its conjugate base (**19**) is more stable than most alkoxide ions. To the extent that the stability of the departing anion contributes to transition state stabilization (Scheme 4), esters derived from NHS should be particularly reactive.

Scheme 4



The mechanism shown in Scheme 5 is based on the assumption that the findings from amine acylation (Scheme 4) can be extended to thioacylation of carbohydrates. Base-catalyzed reaction seems most reasonable, but the mechanism shown in Scheme 5 also includes an uncatalyzed process in which the initially formed, tetrahedral intermediate **20** undergoes proton transfer to give the zwitterion **21**. This intermediate eliminates separation of charge by expelling a tautomer of NHS to form the desired phenyl thiono-carbonate **22**.

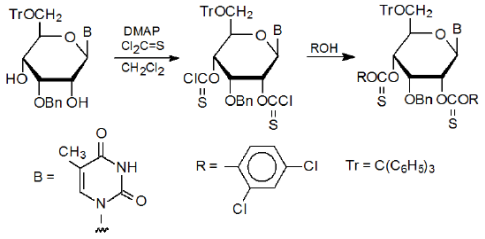
Scheme 5



B. Reaction with Thiophosgene and a Phenol

An alternative synthesis for an aryl thionocarbonate consists of treating a partially protected carbohydrate with thiophosgene and then reacting the product with a phenol (Scheme 6).[40–47] Since phenoxythiocarbonyl chloride (**12**) is commercially available, the thiophosgene procedure normally is reserved for preparing aryl thionocarbonates in which the aromatic ring contains one or more electron-withdrawing substituents. In direct reactivity comparisons, substituted aryl thionocarbonates usually give better product yields.[40] In some cases these substituents are necessary for reaction to take place.[41]

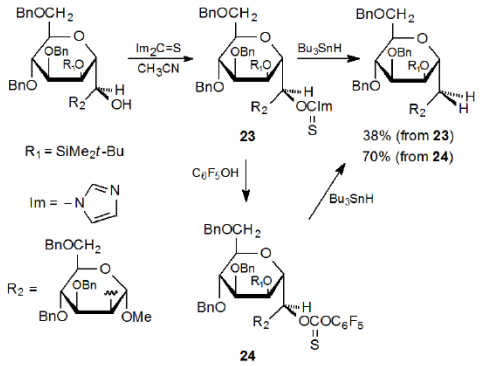
Scheme 6



C. Reaction of (Thiocarbonyl)imidazolides with Phenols

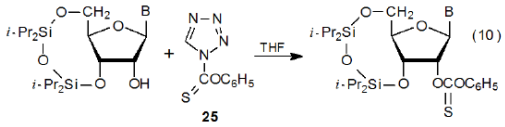
Thionocarbonates are sometimes synthesized by reacting (thiocarbonyl)imidazolides with a substituted phenol. Such a reaction converts a less reactive *O*-thiocarbonyl derivative into a more reactive one (Scheme 7).[48] It also provides another method for synthesizing aryl thionocarbonates in which the aromatic ring contains one or more electron-withdrawing substituents. Affecting the change shown in Scheme 7 causes the deoxygenated product yield to rise from 38% (starting with **23**) to 70% (starting with **24**).

Scheme 7



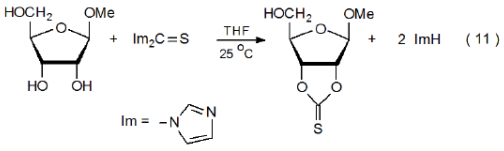
D. Reaction With Phenoxythiocarbonyltetrazole

The thioacylating agent **25** can be used to synthesize phenyl thionocarbonates under conditions that avoid the base-catalyzed side reactions that sometimes occur in the presence of DMAP (eq 10).[49]

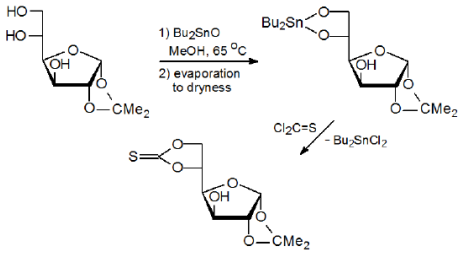


V. Cyclic Thionocarbonates

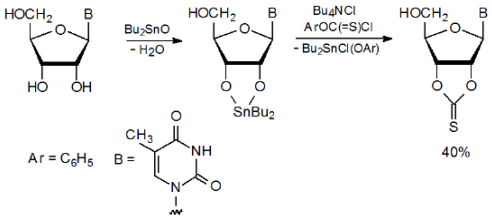
Two basic procedures for the synthesis of cyclic thionocarbonates are in common use. The first involves reacting a compound containing adjacent hydroxyl groups with *N*,*N*-thiocarbonyldiimidazole (eq 11).[50] Most cyclic thionocarbonates are synthesized by this procedure. The second approach involves initial formation of a stannylene complex and then treatment of this complex with thiophosgene (Scheme 8)[51] or phenoxythiocarbonyl chloride[52–54] (Scheme 9)[54].



Scheme 8

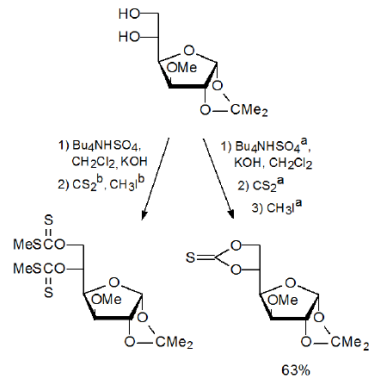


Scheme 9



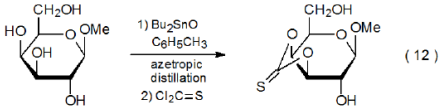
A third, but seldom used, reaction for cyclic thionocarbonate formation is one conducted under phase-transfer conditions. This synthesis is capable of producing either a bisxanthate[55] or a cyclic thionocarbonate (Scheme 10).[56] The critical factors in determining which type of product will be produced are the timing of reagent addition and the relative amounts of the reagents used. To maximize the cyclic-thionocarbonate yield, methyl iodide needs to be added to the reaction mixture after the other reagents; also, the phase-transfer catalyst, and the remaining reagents, need to be limited to molar amounts equal to that of the substrate (Scheme 10).[56]

Scheme 10



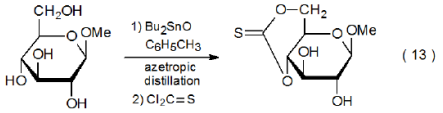
[a]Used in molar amounts equal to the reactant sugar
[b]Used in molar amounts greater than twice that of the reactant sugar

Synthesis of a cyclic thionocarbonate by initial stannylene complex formation can be complicated if more than one complex is possible because a dynamic equilibrium will exist between the possible structures.[57–59] The equilibrium population of the various complexes is determined by their stability, which is a function of factors such as ring strain, steric hindrance, and inductive effects. The relative amounts of the various complexes do not by themselves determine final product distribution because "the steric inaccessibility of the activated oxygen atoms may retard or prevent a major complex from reacting, thus allowing a minor complex to determine the product".[57] An illustration of how these factors can cause quite different cyclic thionocarbonates to form from structurally similar compounds is provided by the reactions shown in equations 12 and 13.[57]



(12)

70%



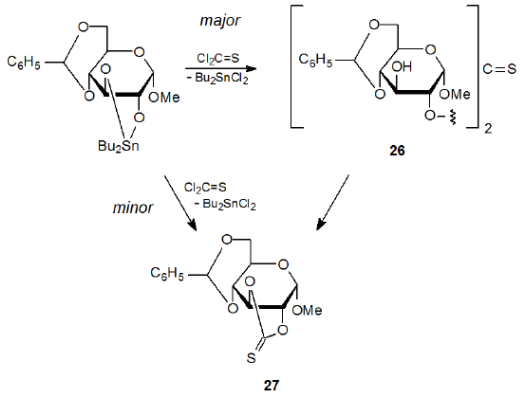
(13)

81%

Although there can be uncertainty about which cyclic thionocarbonate will form from compounds where more than one stannylene complex is possible, this uncertainty disappears for molecules with *cis*-related, vicinal hydroxyl groups. For such compounds the major (sometimes exclusive) product will come from a complex involving these *cis*-related groups (eq 12[56]).[51,52,56]

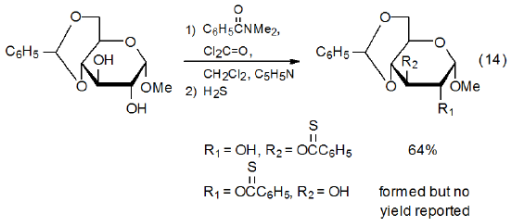
In some situations a competition exists between formation of cyclic and noncyclic thionocarbonates. In the reaction shown in Scheme 11 there is such a competition between the cyclic thionocarbonate **27** and the noncyclic thionocarbonate **26**.[57] Complete cyclic thionocarbonate formation is only temporarily delayed if reaction is allowed to continue because compound **26** is converted into **27** under the reaction conditions.

Scheme 11

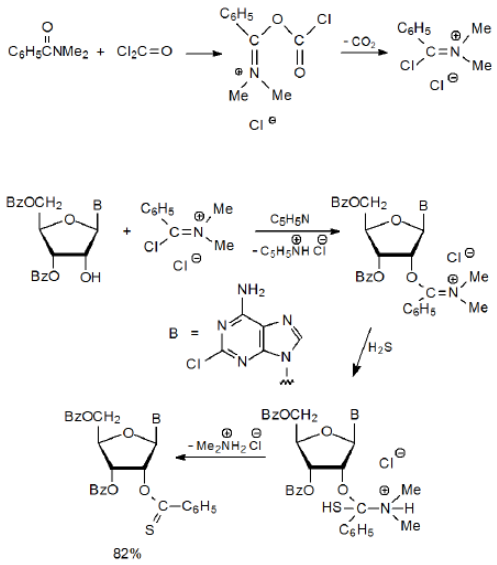


VI. Thionoesters

The standard synthesis of thionoesters is shown in eq 14. Scheme 12, which contains a more detailed picture of this sequence, includes a proposed mechanism for this reaction.[1] Although this method of thionoester preparation is effective, it requires handling the toxic gases phosgene and hydrogen sulfide.[27] This added difficulty in preparation is a factor in thionoesters being used less frequently than other, *O*-thiocarbonyl carbohydrate derivatives.

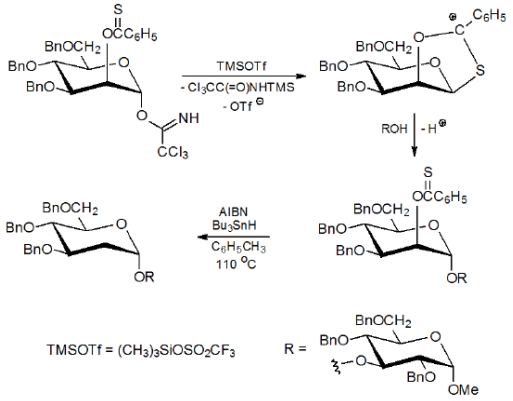


Scheme 12



Thionobenzoates are used for radical formation more often than other thionoesters. Although conditions for preparation of thionobenzoates make them less attractive starting materials that other *O*-thiocarbonyl compounds, these esters become more desirable reactants if the *O*-thiobenzoyl group has an additional role in the reaction. In the transformation shown in Scheme 13 the 2-*O*-thiobenzoyl group anchimerically assists glycoside formation prior to participating in radical reaction.[60,61.]

Scheme 13

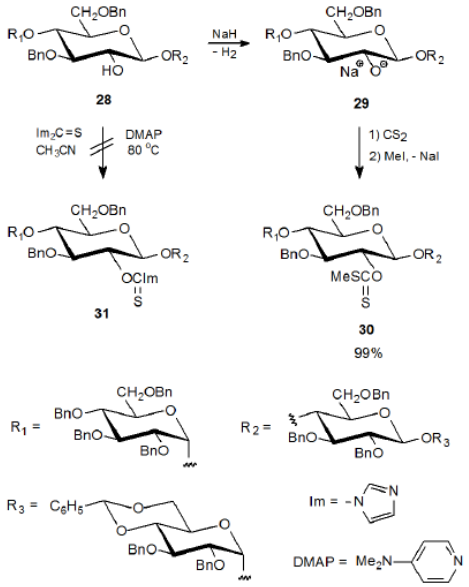


VII. Factors Affecting O-Thiocarbonyl Compound Synthesis

A. The Strength of the Participating Nucleophile

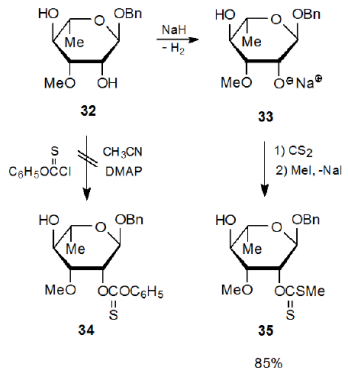
Some compounds do not form every type of *O*-thiocarbonyl derivative. The tetrasaccharide **28**, for example, does not produce a (thiocarbonyl)imidazolide (**31**) but does form a xanthate (**30**) (Scheme 14).[62] A possible explanation for this difference in behavior is based upon the reactivity of the nucleophiles involved in preparation of each derivative. The first step in xanthate formation is conversion of **28** into the powerful nucleophile **29** by deprotonation of the C-2' hydroxyl group with sodium hydride. These reaction conditions stand in contrast to those for (thiocarbonyl)imidazolide synthesis, which depends upon the less effective nucleophile **28**. (The small equilibrium concentration of the alkoxide ion **29**, produced by DMAP deprotonation of **28**, is insufficient to cause the (thiocarbonyl)imidazolide **31** to form in detectable amounts).

Scheme 14



Another example illustrating the role of nucleophilicity in producing *O*-thiocarbonyl compounds concerns the phenoxythionocarbonate **34**, which cannot be prepared from the diol **32**, even though the xanthate **35** easily forms from this compound (**32**) by way of the alkoxide ion **33** (Scheme 15).[63] Once again, greater ease in xanthate formation can be linked to greater nucleophilicity of an alkoxide ion when compared to its corresponding alcohol.

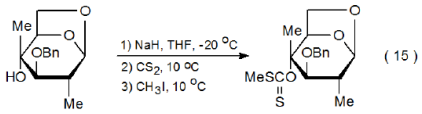
Scheme 15



A method for increasing the nucleophilicity of a partially protected carbohydrate without converting it into a fully ionic compound consists of forming a derivative containing a tin–oxygen bond. This is the approach adopted in several of the reactions (Schemes 2, 3, 8, and 11 and equations 12 and 13) discussed thus far. In the derivatization shown in Scheme 3, for example,

combining the methyl glycoside **5** with bis(tributyltin)oxide forms a nucleophile able to produce a (thiocarbonyl)imidazolide, but reaction of **5** without increasing its nucleophilicity is unsuccessful.[20]

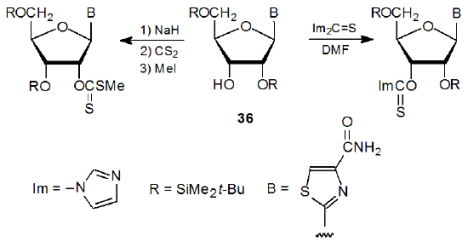
Another advantage of the nucleophilicity of an alkoxide ion when participating in xanthate synthesis is that reaction can take place at low temperatures.[64,65] Reaction occurring under these conditions is particularly important for forming tertiary xanthates (eq 15[64]) because these compounds readily undergo thermal rearrangement and elimination reactions.[66]



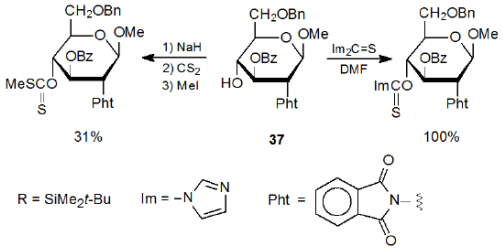
B. Protecting-Group Migration and Loss

Although increasing the nucleophilicity of a hydroxyl group by deprotonation is sometimes helpful in forming an *O*-thiocarbonyl compound, deprotonation also promotes protecting group migration. Compound **36**, for example, forms a (thiocarbonyl)imidazolide with the silyl group remaining in place, but attempted synthesis of the corresponding xanthate causes complete O-2' to O-3' silyl-group migration (Scheme 16).[67] In another example, compound **37** forms a xanthate in only 31% yield, but (thiocarbonyl)imidazolide formation is quantitative (Scheme 17).[68] Group migration (Scheme 16) and reduced product yield (Scheme 17) (possibly through benzoyl group loss or migration or both) are linked to the nucleophilicity of the alkoxide ions formed during xanthate synthesis.

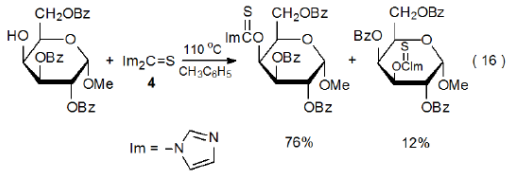
Scheme 16



Scheme 17



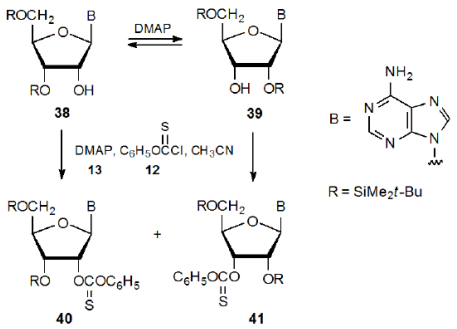
Even though the absence of a strong base during (thiocarbonyl)imidazolide formation reduces the likelihood of group migration, it does not eliminate this possibility entirely. Whenever a carbon atom bearing a hydroxyl group has an acyloxy or silyloxy group on a neighboring (or nearby) atom, group migration is a possibility[15,69,70] because the organic base (and catalyst) imidazole is generated as the reaction proceeds (eq 2). An example of a migration reaction that takes place during (thiocarbonyl)imidazolide synthesis is shown in eq 16, where the benzoyl group at O-3 in the starting material migrates to O-4 in forming the minor product.[15]



The possibility that imidazole causes group migration during (thiocarbonyl)imidazolide formation garners support from the observation that DMAP causes such reaction during thionocarbonate synthesis. Phenyl thionocarbonates **40** and **41** both form when

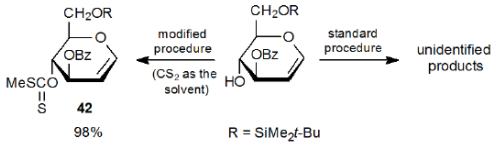
either nucleoside **38** or **39** reacts with phenoxythiocarbonyl chloride (**12**) (Scheme 18).[71] The formation of this mixture of products (**40** and **41**) is the result of DMAP-catalyzed, silyl-group migration in compounds **38** and **39** prior to esterification (Scheme 18).

Scheme 18



Group migration sometimes can be avoided by modification in the reaction conditions. The xanthate **42**, for instance, cannot be synthesized by the standard procedure, but it forms in excellent yield when carbon disulfide is the reaction solvent (Scheme 19).[72] When carbon disulfide is present in large excess, the increased rate of xanthate formation suppresses competing, unimolecular reactions such as group migration.

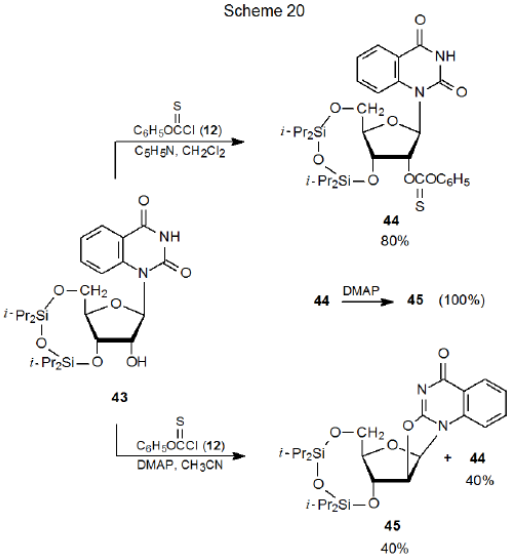
Scheme 19



C. Displacement Reactions

O-Thiocarbonyl groups can function as nucleofuges in displacement reactions. They are not particularly effective in this role; consequently, their participation is limited to internal reaction in which the nucleophile is created by deprotonation and is held in an advantageous position for reaction. An example of internal displacement of this type is shown in Scheme 20 where the thionocarbonate **44** forms in good yield from reaction of the nucleoside **43** with phenoxythiocarbonyl chloride (**12**) in the presence of pyridine, but when the stronger base DMAP (**13**) is used, internal S_N2 displacement produces the anhydro nucleoside **45**.[73] Support for the idea that **44** is an intermediate in this reaction comes from its quantitative conversion into **45** by reaction with DMAP.

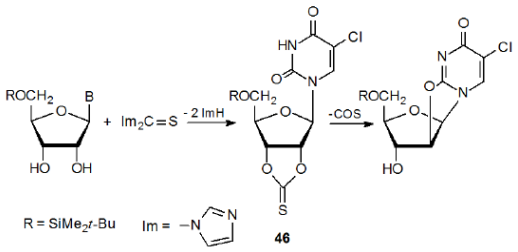
Scheme 20



Cyclic thionocarbonates also can be substrates in nucleophilic substitution reactions.[74,75] In the reaction shown in Scheme 21, for example, formation of the 2',3'-*O*-thiocarbonyl derivative **46** places nucleofuges at C-2' and C-3'. The C-2' substituent then is

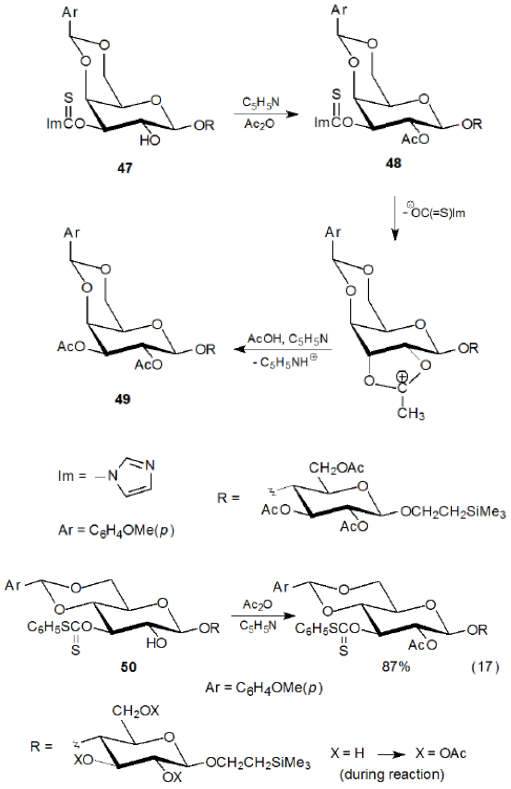
displaced by an oxygen atom in the nitrogenous base portion of the molecule.[74]

Scheme 21



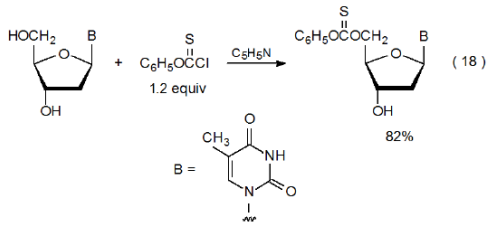
Another example of nucleophilic substitution involving an *O*-thiocarbonyl compound is found in Scheme 22, where attempted acetylation of the disaccharide **47** causes replacement of the *O*-imidazol-1-ylthiocarbonyl group with an acetyl group.[10] A reasonable assumption is that the desired acetate **48** actually forms, but the *O*-imidazol-1-ylthiocarbonyl group is a sufficiently good nucleofuge that it is displaced by the neighboring *O*-acetyl group in a reaction that leads to the pentaacetate **49**. Acetylation of the closely related xanthate **50** (eq 17) without internal displacement indicates that the *O*-[(phenylthio)thiocarbonyl] group is a less effective nucleofuge.[10]

Scheme 22

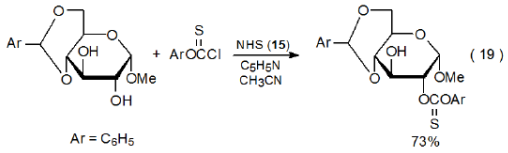


D. Regioselective Reactions

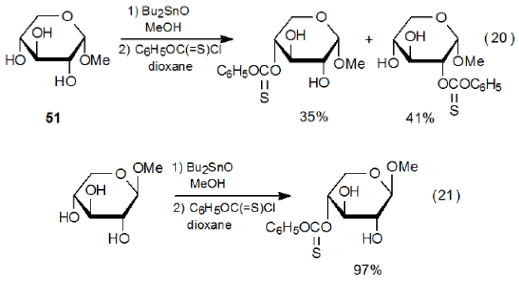
In a carbohydrate with more than one unprotected hydroxyl group, it is sometimes possible to predict which group will react preferentially with a limited amount of a thioacylating agent. For example, reaction of the less hindered of two hydroxyl groups will occur if there is a substantial difference in their steric shielding; thus, in the reaction shown in eq 18, regioselective thioacylation takes place at the primary, rather than the secondary, hydroxyl group.[76]



Even if there is little difference in steric shielding of two hydroxyl groups, site selectivity sometimes can be predicted if one of the groups is attached to C-2 and deprotonation is the first step in the reaction. Under these conditions the typically greater acidity of the C-2 hydroxyl group determines which of the two possible alkoxide ions will form to a greater extent. This preferential formation leads to regioselective reaction at C-2 (Scheme 15[63] and eq 19[30]). Comparing the reaction shown in eq 19[30] with that in eq 14[1] demonstrates that predicting regioselective reaction at C-2 must be done cautiously. In these two reactions the same compound exhibits different selectivity when the reagents and the reaction conditions change.



Regioselectivity extends to reactions where esterification is preceded by formation of a stannylene complex (equations 12 and 13). Since this selectivity is dependent upon the stability and reactivity of the various stannylene complexes that are in equilibrium in the reaction mixture, predicting or even rationalizing the formation of reaction products is complicated by esterification being a two-step process with selectivity involved in each step. Although regioselective reaction of stannylene complexes is often high, it is far from assured, as is illustrated by the nearly unselective reaction of the methyl glycoside **51** (eq 20).[52] The difficulty in predicting site selectivity is underscored when comparing the reaction shown in eq 20 with that in eq 21, where an essentially unselective reaction becomes highly selective upon changing the configuration of the methoxy group at C-1.[52] Under carefully selected conditions reaction of organotin complexes of a variety of unprotected methyl glycosides with phenoxythiocarbonyl chloride leads to highly regioselective thionocarbonate formation.[53]



VIII. Summary

Synthesis of *O*-thiocarbonyl compounds [(xanthates, (thiocarbonyl)imidazolides, aryl thionocarbonates, cyclic thionocarbonates, thionoesters)] is the first step in using them to generate carbon-centered radicals.

Xanthates usually are prepared by deprotonating a partially protected carbohydrate and then reacting the resulting alkoxide ion with carbon disulfide and methyl iodide. The primary limitation of this approach is that it involves conditions in which base-sensitive compounds are unstable. Xanthate synthesis by phase-transfer reaction or by reaction with phenyl chlorodithioformate avoids this difficulty.

(Thiocarbonyl)imidazolides are formed by reacting a partially protected carbohydrate with *N*,*N*-thiocarbonyldiimidazole. These conditions for synthesis are much less basic that those used for preparing xanthates.

Aryl thionocarbonates typically come from reaction of a partially protected carbohydrate with phenoxythiocarbonyl chloride in the presence of DMAP (4-dimethylaminopyridine). Side reactions are rare and tend to arise when DMAP promotes base-catalyzed reactions that compete with thionocarbonate formation. Phenyl thionocarbonates also can be prepared in reactions catalyzed by *N*-hydroxysuccinimide (NHS). This alternative procedure normally is implemented to improve product yields or avoid side reactions caused by DMAP. An additional option for phenyl thionocarbonate preparation consists of reacting a partially protected sugar with thiophosgene and treating the product with a phenol. This procedure is useful in preparing phenyl thionocarbonates with groups, usually electron-withdrawing ones, in the aromatic ring.

If a partially protected carbohydrate has vicinal, cis-related hydroxyl groups, reaction with *N*,*N*-thiocarbonyldiimidazole will form a cyclic thionocarbonate. A second procedure for synthesis of these compounds consists of formation of a stannylene complex of a carbohydrate, and then reaction of this complex with thiophosgene or phenoxythiocarbonyl chloride.

Thionoesters are less frequently used in deoxygenation reactions than other *O*-thiocarbonyl compounds, in part, due to the difficulty in their preparation. The only thionoesters used to a significant extent in deoxygenation are thionobenzoates.

When *O*-thiocarbonyl compounds are unable to form under the standard reaction conditions, sometimes they can be synthesized by converting the partially protected carbohydrate reactant into its corresponding alkoxide ion. Forming an alkoxide ion also increases the possibility that group migration will compete with formation of an *O*-thiocarbonyl, carbohydrate derivative.

CHAPTER OVERVIEW

12: Reactions of O-Thiocarbonyl Compounds

Reaction of an *O*-thiocarbonyl derivative of a carbohydrate with a tin- or silicon-centered radical generates a carbon-centered radical that undergoes reactions typical of such an intermediate. These reactions include abstracting a hydrogen atom from a donor molecule (almost always a tin or silicon hydride), adding to a compound containing a multiple bond, or forming a new ring system by adding internally to a multiple bond within the radical. These reactions place *O*-thiocarbonyl compounds among the most useful substrates for radical formation from carbohydrates. The current chapter, where the reactions of these compounds are discussed, is a close companion to the preceding one (Chapter 11), where synthesis of *O*-thiocarbonyl carbohydrate derivatives is described.

Topic hierarchy

II. Deoxygenation: The Barton-McCombie Reaction

III. Radical Addition

IV. Radical Cyclization

V. Comparing the Reactivity of O-Thiocarbonyl and O-Carbonyl Carbohydrates

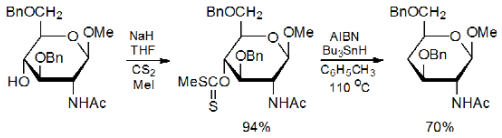
VI. Summary

II. Deoxygenation: The Barton-McCombie Reaction

A. A Two-Step Sequence

In 1975 Barton and McCombie reported a two-step sequence for hydroxyl-group replacement by a hydrogen atom.[1] The first step in this process was the conversion of the hydroxyl group into an *O*-thiocarbonyl group, and the second step (the Barton-McCombie reaction) was a free-radical chain reaction that replaced the *O*-thiocarbonyl group with a hydrogen atom. A typical example of this widely used, reaction sequence is shown in Scheme 1.[2]

Scheme 1



Various types of *O*-thiocarbonyl compounds undergo the Barton-McCombie reaction. Initially this group consisted of xanthates (**1**), thionobenzoates (**2**), thiocarbonylimidazolides (**3**), and thionoformates (**4**) (Figure 1).[1] Subsequently, this list was expanded to contain phenyl thionocarbonates (**5**),[3,4] including those with electron-withdrawing substituents in the aromatic ring (**6**-**8**),[5,6] and cyclic thionocarbonates (**9**).[7,8]

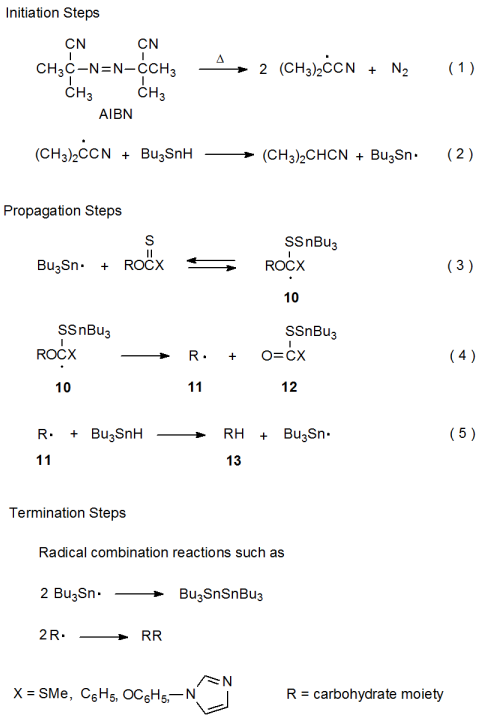
Compound	Number	Compound	Number
ROCSMe	**1**	$ROCOC_6F_5$	**6**
$ROCOC_6H_5$	**2**	$ROCOC_6H_4F(p)$	**7**
ROCN(C=CN)	**3**	$ROCOC_6H_2Cl_3(2,4,6)$	**8**
ROCH	**4**	R, R', O, O, S	**9**
$ROCOC_6H_5$	**5**		

Figure 1. *O*-Thiocarbonyl derivatives that undergo the Barton-McCombie reaction

B. Proposed Reaction Mechanisms

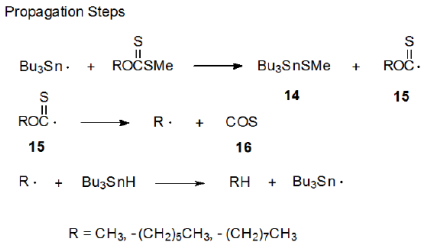
A proposed mechanism for the Barton-McCombie reaction is shown in Scheme 2.[1,9] In the initiation phase of this reaction thermal decomposition of 2,2'-azobis(isobutyronitrile) (AIBN) (eq 1), the most common initiator for the Barton-McCombie reaction, produces a radical that abstracts a hydrogen atom from tri-*n*-butyltin hydride (eq 2). In the first propagation step the tri-*n*-butyltin radical adds to a carbon–sulfur double bond to create the adduct radical **10** (eq 3). Reaction reaches a critical stage at this point because its success requires **10** to fragment to give the radical **11** (eq 4) before competing reactions can intervene. Once fragmentation takes place, hydrogen-atom abstraction by **11** from tri-*n*-butyltin hydride completes the overall reaction and generates a new, chain- carrying, tri-*n*-butyltin radical (eq 5). (Equations 1-5 are found in Scheme 2.)

Scheme 2



The propagation steps for a revised mechanistic proposal for the Barton-McCombie reaction are shown in Scheme 3.[10] (The initiation and termination steps for this mechanism are the same as those pictured in Scheme 2.) The primary change introduced in the revised mechanism (Scheme 3) is that $Bu_3Sn\cdot$ does not add to the thiocarbonyl group but rather abstracts the SCH_3 group. Identification of the radical **15** in the ESR spectrum of the reaction mixture supports the revised mechanism; however, an argument against mechanistic significance of **15** is that this intermediate is observed under conditions quite different from those of the Barton-McCombie reaction (e.g., no effective hydrogen-atom donor (Bu_3SnH) was present in the reaction mixture because the tri-*n*-butyltin radicals were generated from photolysis of $Bu_3SnSnBu_3$.[10])

Scheme 3



Subsequent competition experiments returned support to the original mechanism (Scheme 2).[11–13] In addition to these experiments, ^{119}Sn NMR identification of the intermediate **12** (R = SCH_3) in a Barton-McCombie reaction mixture provided evidence for the addition of $Bu_3Sn\cdot$ to the thiocarbonyl group, as proposed in Scheme 2, rather than abstraction of SCH_3, as proposed in Scheme 3.[13] Further mechanistic analysis led to the conclusion that the tri-*n*-butyltin radical must be adding reversibly to the thiocarbonyl group to give the radical **10**, which then fragments as shown in eq 4 (Scheme 2). Additional support for this mechanism is based on a ring-forming reaction that is described at the end of this chapter, after cyclization reactions have been discussed.

C. Hydrogen-Atom Donors/Chain-Transfer Agents

Critical to the success of the Barton-McCombie reaction is the compound that donates a hydrogen atom to the carbohydrate radical (eq 5) to complete the propagation sequence. Tri-*n*- butyltin hydride is particularly well suited for this role because it rapidly donates a hydrogen atom to a carbon-centered radical, and in the same reaction generates the chain-carrying radical $Bu_3Sn\cdot$, an

intermediate needed to begin a new sequence of propagation steps (eq 3). (A critical feature of the reactivity of $Bu_3Sn\cdot$ is that it does not cause side reactions by abstracting hydrogen atoms from carbon-hydrogen bonds.)

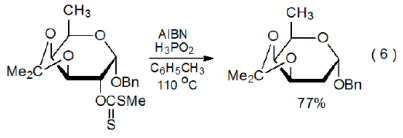
Although use of tri-*n*-butyltin hydride has significant advantages, it also suffers from substantial drawbacks. There are serious problems associated with the toxicity of tin-containing compounds and the difficulty in removing residues of these compounds from reaction products. A variety of solutions to these problems have been proposed. Because these solutions apply not just to *O*-thiocarbonyl compounds but also to a broad range of carbohydrate derivatives, they will not be discussed here; rather, they have been gathered together and are found in Appendix I.

D. The Scope and Reactivity of *O*-Thiocarbonyl Compounds

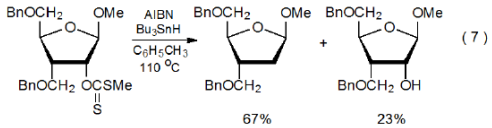
The number of *O*-thiocarbonyl carbohydrate derivatives that undergo the Barton-McCombie reaction is large and continues to grow. Although all of these compounds react basically in the same way, some are better suited than others for particular situations. The following several sections focus on the scope and special reactivity of various *O*-thiocarbonyl compounds. To emphasize their broad range of reactivity, references are provided to Barton-McCombie reaction taking place at various positions in substituted carbohydrates. These references are not meant to represent the total number that exists, but rather to provide examples of the reactions possible in cyclic and open-chain carbohydrates.

1. Xanthates

A striking feature of xanthate reactivity is the number and variety of carbohydrates that can be deoxygenated by xanthate formation followed by Barton-McCombie reaction. This sequence replaces hydroxyl groups at the 2-,[14,15] 3-,[16,17] 4-,[2,18] and 6-[19,20] positions with hydrogen atoms in compounds containing pyranoid rings, as well as the 1-,[21] 2-,[22,23] 3-,[24,25] 5-,[26] and 6-[27]positions in those with furanoid rings. Equations 6[15] and 7[28] provide typical examples of reactions of carbohydrates containing pyranoid and furanoid rings, respectively. (Hypophosphorous acid, one of the substitutes for tri-*n*-butyltin hydride mentioned in Appendix I, is the hydrogen-atom donor in the reaction shown in eq 6.) Xanthates also are used in Barton-McCombie reaction of alditols,[29,30] cyclitols,[31,32] and nucleosides.[33,34]



(6)



(7)

2. Thionocarbamates

Among thionocarbamates the (thiocarbonyl)imidazolides (**3**, Figure 1) are easily the most frequently used substrates for the Barton-McCombie reaction. The range of types of compounds involved is broad and includes (thiocarbonyl)imidazolides formed from carbohydrates with hydroxyl groups at the 2-,[35] 3-,[36–38] 4-,[39–41] and 6-[42] positions in compounds with pyranoid rings, and at the 2-,[43,44] 3-,[45,46] and 5-[47,48] positions in compounds with furanoid rings. There also are numerous reports of Barton-McCombie reactions of nucleosides with *O*-imidazol-1-ylthiocarbonyl groups at C-2'-[49,50] and C-3'.[51,52]

3. Thionocarbonates

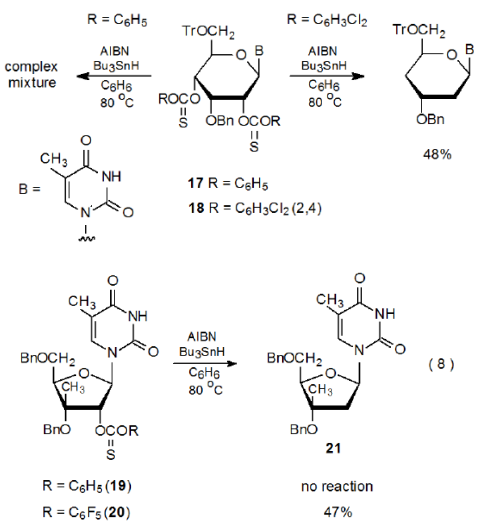
a. Phenyl Thionocarbonates

Phenyl thionocarbonates are yet another *O*-thiocarbonyl, carbohydrate derivative that undergoes the Barton-McCombie reaction. These derivatives participate in reaction at C-2,[53,54] C-3,[55,56] C-4,[57,58] and C-6[59,60] in compounds with pyranoid rings, and C-1,[61,62] C-2,[63,64] C-3,[65,66] and C-5[67,68] in compounds with furanoid rings. Further, phenyl thionocarbonates are the preferred intermediates for nucleoside deoxygenation. They are involved in reaction at the 2'-position not only for a large number of 1,1,3,3-tetraisopropyl-1,3-disiloxanediyl-protected nucleosides,[69,70] but also for compounds protected by benzyl,[71] benzoyl,[72,73]t-butyldimethylsilyl,[74] and pivaloyl groups.[75] Similar reactions take place at the 3'- and 5'-positions.[65,76]

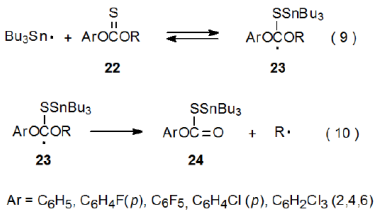
b. Substituted Phenyl Thionocarbonates

Phenyl thionocarbonates typically undergo a Barton-McCombie reaction that produces deoxygenated products in good yield; however, when product yields are low, introducing one or more electron-withdrawing substituents into the aromatic ring often raises these yields.[77–80] Two examples illustrate the effect of these substituents. First, attempted Barton-McCombie reaction of the phenyl thionocarbonate **17** produces a complex mixture of products, but the 2,4-dichlorophenyl analog **18** forms the desired dideoxy nucleoside (Scheme 4).[77] In the second example, the phenyl thionocarbonate **19** is unreactive under typical Barton-McCombie conditions, but its pentafluorophenyl analog **20** reacts with tri-*n*-butyltin hydride to give the corresponding deoxy nucleoside **21** (eq 8).[78]

Scheme 4



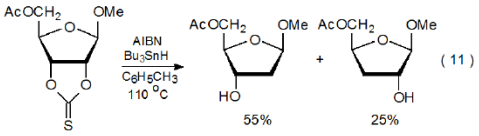
In light of the better yields produced by the substituted phenyl thionocarbonates **18** and **20**, it is surprising to find that the *p*-fluoro-, pentafluoro-, *p*-chloro-, 2,4,6-trichloro-, and pentachlorophenoxythiocarbonyl derivatives of cyclododecanol all react more slowly than the unsubstituted compound.[6] In attempting to understand such a finding it is useful to consider the various ways in which ring substituents might influence reactivity. Evidence from the study of *O*-thiocarbonyl compounds suggests that the formation of the radical **23** (eq 9) is a reversible process and that the rate-determining step in this reaction sequence (equations 9 and 10) is the fragmentation of **23** shown in eq 10.[9] An aromatic ring substituent is likely to impact this process in several ways. These include altering the radicophilicity of **22**, the stability of **23**, and the strength of the carbon–oxygen bond being broken to produce R· and **24** (eq 10); therefore, since an aromatic-ring substituent can exert influence on reactivity in several ways, understanding and predicting the overall effect that such a substituent will have on a reaction can be difficult.



c. Cyclic Thionocarbonates

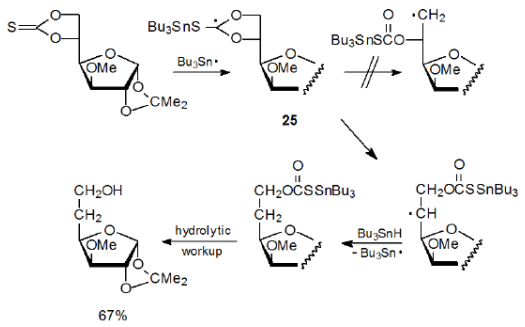
Cyclic thionocarbonates undergoing Barton-McCombie reaction include compounds in which 2,3-*O*-thiocarbonyl,[81–83] 3,4-*O*-thiocarbonyl,[53,84] and 4,6-*O*-thiocarbonyl[85] groups are attached to pyranoid rings. This reaction also takes place with 2,3-*O*-thiocarbonyl[7,8] and 5,6-*O*- thiocarbonyl[67,86] groups in compounds with furanoid rings. Cyclic thionocarbonates, formed from acyclic structures, also undergo the Barton-McCombie reaction.[87]

Reaction of a cyclic thionocarbonate is more complex than reaction of other *O*-thiocarbonyl compounds because it also involves ring opening. Since ring opening potentially can place a radical center on either of two carbon atoms, reaction often produces a mixture of products (eq 11).[7,8] Formation of this mixture not only can reduce the amount of the desired product but also can complicate its isolation.

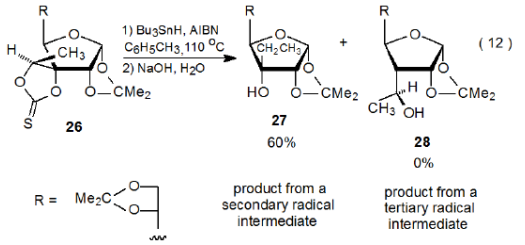


A proposed mechanism for reaction of a cyclic thionocarbonate with tri-*n*-butyltin hydride is given in Scheme 5.[8] A "key" intermediate in this reaction is the radical **25**, formed by addition of the tri-*n*-butyltin radical to the thiocarbonyl group. Radical stability usually controls the direction of ring opening; thus, even though **25** can produce either a primary or a secondary radical by ring opening, the pathway followed leads exclusively to the secondary radical (Scheme 5).[7,8,88,89]

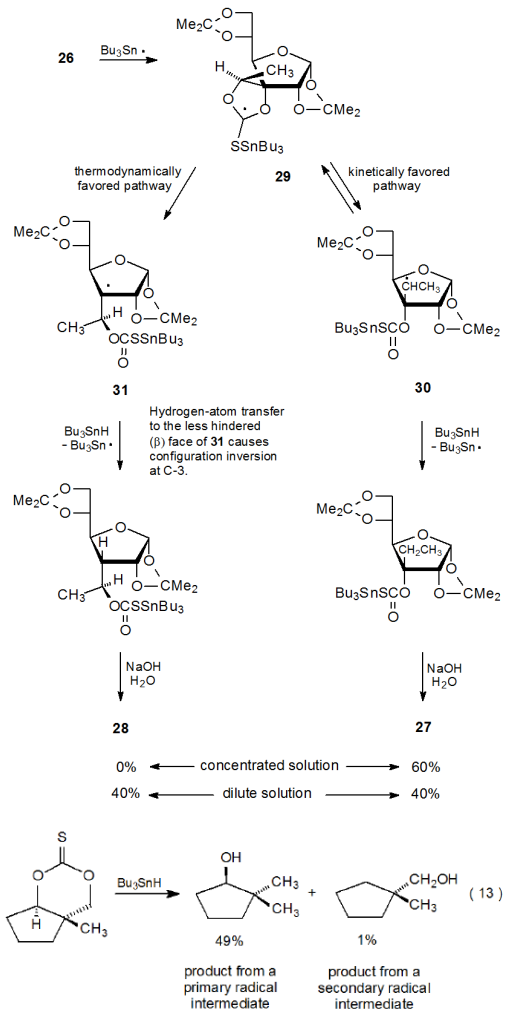
Scheme 5



Although radical stability normally controls the direction of ring opening in a cyclic thionocarbonate, relief of angle strain in the transition state sometimes is the major factor.[90] Ring opening of compound **26**, for example, leads to the product derived from a secondary, rather than a tertiary, radical (eq 12).[91] (A mechanism for this reaction is shown in Scheme 6.) Molecular mechanics calculations on noncarbohydrates indicate that fragmentation to give a less stable radical will occur if relief of ring strain in the transition state is great enough (eq 13).[90] This relief of strain provides an explanation for the unexpected conversion of **26** into **27** rather than **28** (eq 12).



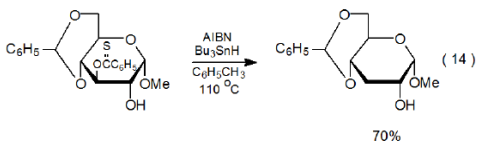
Scheme 6



There is a concentration effect associated with the reaction of the cyclic thionocarbonate **26**. In concentrated Bu_3SnH solution only the kinetically favored product **27** is formed, but in dilute solution some of the thermodynamically favored isomer **28** is produced (Scheme 6). One explanation for this behavior is based on reversible formation of the secondary radical **30** from the cyclic radical **29**. In concentrated solution **30** abstracts a hydrogen atom rapidly enough from Bu_3SnH to prevent significant return to **29**. Under these conditions only the product **27** is formed. In dilute solution hydrogen-atom abstraction by **30** is slowed to the point that reversible formation of **29** becomes significant and creates greater opportunity for **29** to be converted (irreversibly) into the thermodynamically favored tertiary radical **31**. Since in dilute Bu_3SnH solution both kinetically and thermodynamically favored pathways are followed, a mixture of the products **27** and **28** is produced.

4. Thionoesters

Primarily because their synthesis is more challenging, thionoesters are selected less frequently as starting materials for the Barton-McCombie reaction than are other *O*-thiocarbonyl derivatives. Thionoesters with *O*-thiocarbonyl groups at C-2[92] and C-3[1] in pyranoid rings and C-2[28] in furanoid rings are known substrates for deoxy sugar formation. A typical example is shown in eq 14.[1] The thionoesters that undergo reaction are, with rare exception,[93] thionobenzoates.[28,92,94–101]

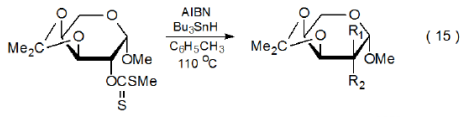


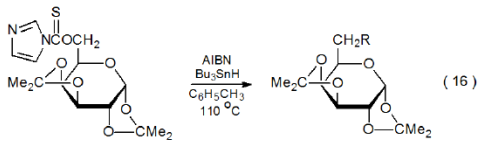
E. Competing Reactions

Frequent application of the Barton-McCombie reaction in carbohydrate chemistry occurs because this reaction has a variety of attractive features. These include the broad range of compounds that undergo this reaction, the generally good product yields, and the freedom, in most cases, from significant, competing reactions. Even though side reactions usually do not represent a major concern, Barton-McCombie reaction has been conducted on so many compounds that quite a number of these reactions have been identified. They range in importance from alcohol regeneration, a common but usually minor side reaction, to phenyl-group migration, a rare event.

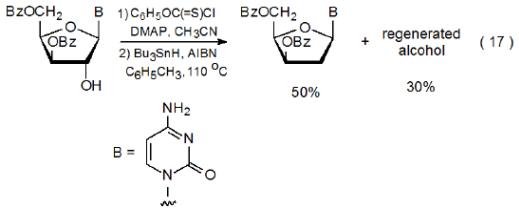
1. Alcohol Regeneration

Regenerating the alcohol from which an *O*-thiocarbonyl compound originally was synthesized is a side reaction sometimes accompanying deoxygenation. An example of such a reaction is shown in eq 15.[102] In rare instances alcohol regeneration is the major reaction pathway (eq 16).[42]





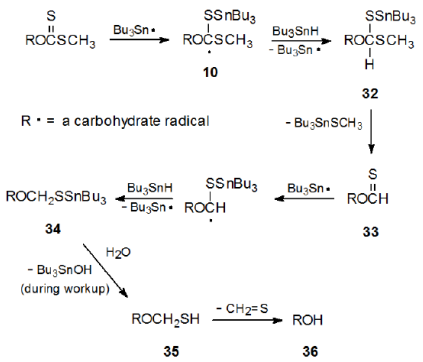
Not all *O*-thiocarbonyl derivatives of carbohydrates are equally prone to alcohol regeneration. One of the advantages initially associated with phenyl thionocarbonates was that they did not undergo this reaction.[3,4] Continued study of these compounds, however, showed that they are not immune to the alcohol-reforming process (eq 17).[103]



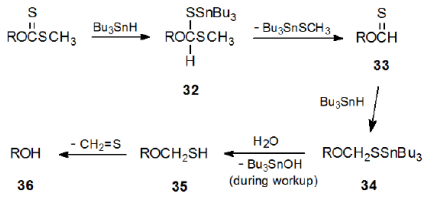
a. Proposed Reaction Mechanisms

Although alcohol regeneration is the most common competing process during Barton-McCombie reaction, there is not general agreement on how the regeneration process proceeds. The two most frequently cited possibilities are both multi-step processes with many intermediates in common. The difference between these two rests with thiocarbonyl group reduction, one mechanism (Scheme 7) involves radical intermediates and the other (Scheme 8) does not.

Scheme 7



Scheme 8

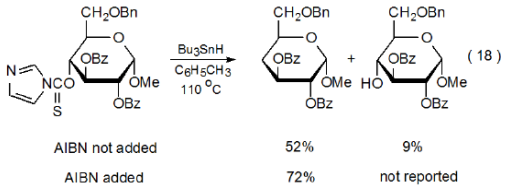


(1). A Radical-Based Process

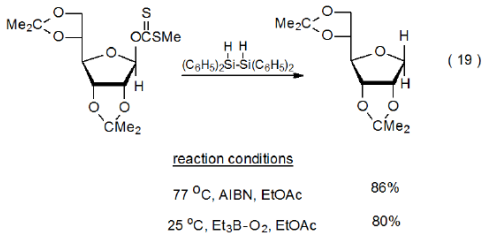
If one assumes that the radical **10** is an intermediate in the Barton-McCombie reaction (Scheme 2, X = SCH_3), the possibility exists that before this radical fragments, it could abstract a hydrogen atom. Such a reaction would produce the intermediate **32** (Scheme 7).[1,9] Formation of **32** not only would reduce the deoxygenated product yield, but it also could provide an explanation for the formation of the regenerated alcohol **36** as a side-product in the reaction.[1,9] When viewed in this way, **32** is the beginning point in a series of events that leads first to the thionoformate **33**, which reacts with tri-*n*-butyltin hydride to give the tin-containing intermediate **34**, a substance that hydrolyzes during workup to the hemithioacetal **35**. Compound **35** then decomposes spontaneously to give the alcohol **36** and thioformaldehyde (Scheme 7).[9]

(2). A Hydride-Transfer-Based Reaction Sequence

The conditions originally used for the Barton-McCombie reaction did not include an added initiator; rather, reaction depended upon adventitious initiation. Within a few years, however, adding 2,2'-azobis(isobutyronitrile) (AIBN) became standard procedure because dependable initiation was recognized as a significant factor in maximizing deoxygenation.[4,13] The reaction shown in eq 18 is one that provides an illustration of the improvement in product yield brought about by an added initiator.[104] The observation that alcohol regeneration occurs in the absence of an initiator in the reaction shown in eq 18, supports the idea that a radical reaction may not be involved in the alcohol-reforming process.[4]



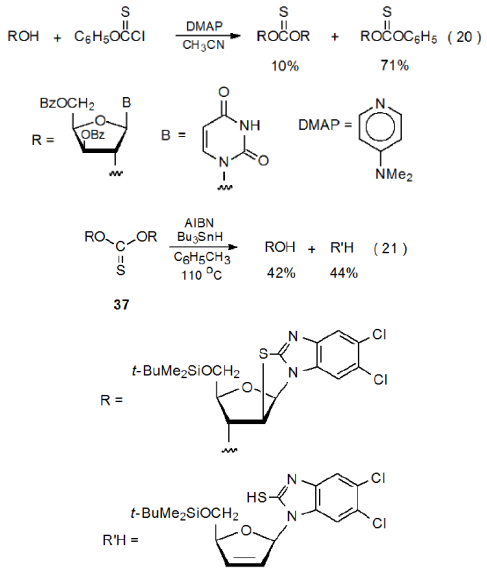
When the Barton-McCombie reaction is initiated by $Et_3B–O_2$,[105,106] it can take place at temperatures much lower than those required for AIBN initiation (eq 19).[21] Because it was originally thought that reducing the temperature of a Barton-McCombie reaction to about 80 °C caused alcohol regeneration to begin to become important,[12] further lowering the reaction temperature would be expected to increase alcohol formation. When reactions were conducted at lower temperature using $Et_3B–O_2$ initiation, Barton-McCombie reaction took place with little or no alcohol regeneration. This finding was not consistent with the idea that **10** (Scheme 7) was increasingly likely to abstract a hydrogen atom from Bu_3SnH as the reaction temperature decreased.[13] If the conversion of **10** into **32** by hydrogen-atom abstraction were not taking place, it raised the possibility that **32** was formed in a different, perhaps nonradical, reaction (Scheme 8).



Several investigators have proposed that hydride transfer may be responsible for alcohol regeneration.[13,107,108] As a part of the most detailed of these proposals, it was suggested that nonradical addition of tri-*n*-butyltin hydride to an *O*-thiocarbonyl group occurs in the first step in alcohol regeneration, and it occurs later in the reaction sequence when the thionoformate **33** is converted into the thioacetal **34** (Scheme 8).[108]

b. Alcohols from Dimeric Esters

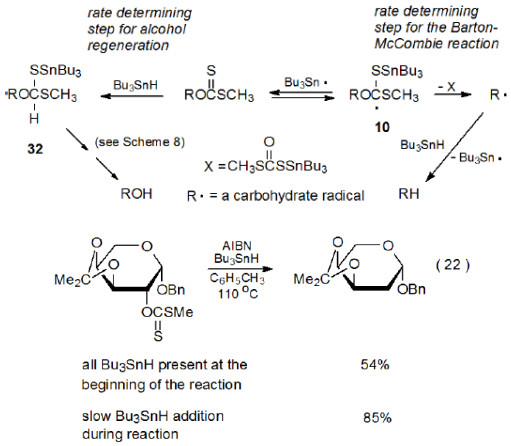
The observation that minor amounts of "dimeric' esters were formed during the phenyl thionocarbonate synthesis shown in eq 20 raised the possibility that if these esters were not removed prior to Barton-McCombie reaction, an alcohol could be formed because each dimeric ester reasonably could be expected to react with tri-*n*-butyltin hydride to give a molecule of a deoxygenated compound and one of the starting alcohol.[103] This expectation was confirmed when the dimeric ester **37** was found to undergo the reaction shown in eq 21.[109]



c. Minimizing Alcohol Regeneration

The rate determining step in the Barton-McCombie reaction is believed to be the unimolecular fragmentation of the radical **10** to give the carbon-centered radical R· (Scheme 9).[9] For alcohol regeneration, however, the rate is more likely to depend upon a bimolecular reaction involving Bu_3SnH. This analysis (Scheme 9) is consistent with the finding that keeping the concentration of Bu_3SnH at a low level during reaction (i.e., adding the tin hydride slowly as the reaction proceeds) is associated with maximizing deoxygenation; for example, the xanthate shown in eq 22 reacts to give a deoxy sugar in 54% yield when all the Bu_3SnH is present at the beginning of the reaction, but the yield rises to 85% when Bu_3SnH is added over a period of 1.5 h.[36] Part of the reduced deoxy sugar yield in the reaction where all the Bu_3SnH was added at the beginning is due to recovery of the alcohol from which the xanthate was synthesized.[36]

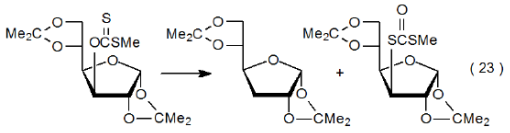
Scheme 9



2. *O*-Thionocarbonyl Group Conversions and Rearrangements

a. Conversion of a Xanthate into a Dithiocarbonate

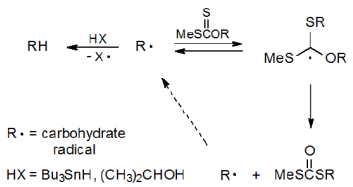
When Bu_3SnH is the hydrogen-atom donor in the reaction shown in eq 23,[1] a deoxy sugar forms in the normal manner, but if a less effective donor is used, xanthate conversion to a dithiocarbonate competes with the deoxygenation process. This conversion-becomes significant when reaction is conducted with 2-propanol serving as both solvent and hydrogen-atom donor. When benzene is the solvent, dithiocarbonate formation is the major reaction pathway.[110] Benzene is, in fact, such a poor hydrogen-atom donor that any carbohydrate present in solution is a more likely hydrogen-atom source for the small amount of deoxy sugar formed.



hydrogen donor	xanthate concentration		
Bu_3SnH	0.2 M	85%	0%
$(CH_3)_2CHOH$	0.2 M	70%	20%
$(CH_3)_2CHOH$	0.1 M	not reported	8%
C_6H_6	0.2 M	12%	70%

The reaction shown in eq 23 begins with formation of the carbohydrate radical R·. As pictured in Scheme 10, this radical (R·) then either adds to a molecule of starting material, leading to a dithiocarbonate, or abstracts a hydrogen atom, producing a deoxy sugar. The data presented in eq 23 confirm the expectation from the proposed mechanism (Scheme 10) that deoxy sugar formation is favored when effective hydrogen-atom donors are used, and dithiocarbonates form more easily in reactions run at high xanthate concentrations in the presence of poor hydrogen-atom donors.[110]

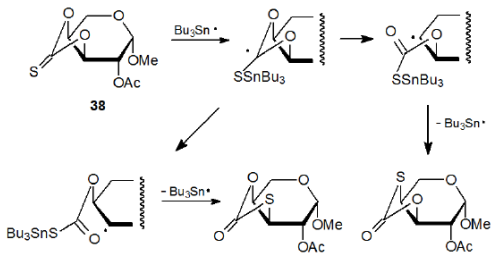
Scheme 10



b. Thionocarbonate-Thiocarbonate Rearrangement

A reaction closely related to the xanthate-dithiocarbonate rearrangement just discussed is the conversion of a thionocarbonate into a thiocarbonate. When a hydrogen-atom donor is present in a reaction mixture in an amount less than that needed to supply a hydrogen atom to each carbohydrate radical, thionocarbonate to thiocarbonate rearrangement can take place.[82,88,89,111,112] In the reaction shown in Scheme 11 this rearrangement represents the major reaction pathway when the amount of tri-*n*-butyltin hydride is significantly less than that required for complete reduction.[111] Rearrangement is, of course, undesirable when simple reduction is the goal of a reaction, but it can be useful if the purpose of the reaction is to convert a sugar into a thiosugar.[112]

Scheme 11

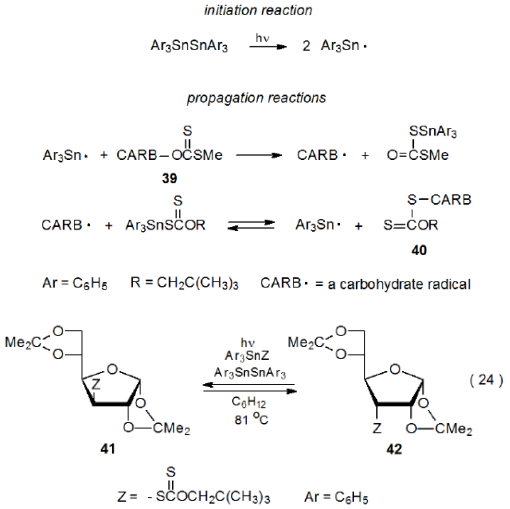


38	Bu_3SnH		
1.0 eq	1.0 eq	9%	6%
1.0 eq	0.3 eq	40%	32%

c. Conversion of an *S*-Alkyl Xanthate into an *O*-Alkyl Xanthate

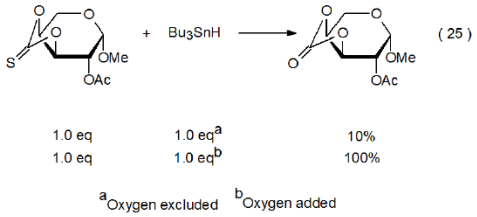
Reaction of the carbohydrate xanthate **39** (an *S*-alkyl xanthate) with the triphenyltin radical is the first step in a propagation sequence (Scheme 12) that converts **39** into a xanthate with the carbohydrate portion of the molecule bonded to sulfur (**40**, an *O*-alkyl xanthate).[113,114] The second step in this sequence is reaction of the carbohydrate radical with triphenyltin xanthate to produce **40** and the chain-carrying, triphenyltin radical. This second step must be reversible in order to account for the epimers **41** and **42** being interconverted under the reaction conditions (eq 24).[114] Effective hydrogen-atom donors, such as triphenyltin hydride, must be excluded to prevent simple reduction. Excluding triphenyltin hydride but still having the triphenyltin radical needed to initiate the reaction is accomplished by photolysis of bis(triphenyltin) (Scheme 12).

Scheme 12



3. Reaction With Molecular Oxygen

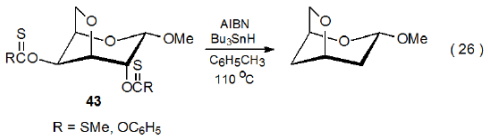
Reaction conducted in the presence of molecular oxygen leads to rapid capture of O_2 by carbon-centered radicals. This capture is faster than hydrogen-atom abstraction from Bu_3SnH. Radical capture of O_2 is suppressed by the normal procedure of excluding oxygen from the reaction mixture, but when O_2 is deliberately added, its combination with a carbohydrate radical becomes a major or even the exclusive reaction pathway (eq 25).[89]

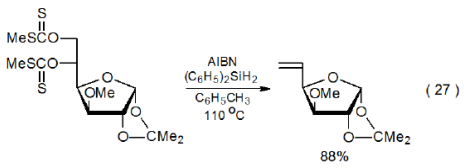


4. Elimination Reactions

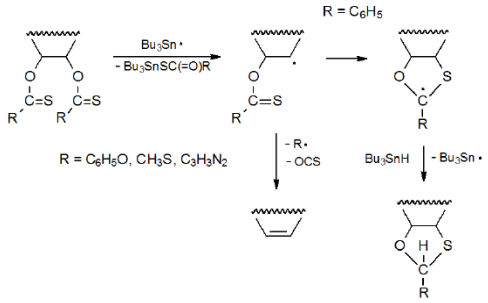
a. Reactions of Compounds with Two *O*-Thiocarbonyl Groups

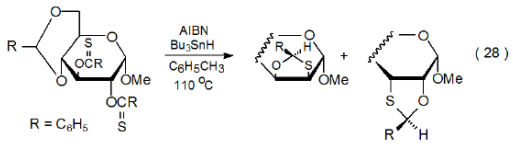
If there are two *O*-thiocarbonyl groups in the same molecule, their physical separation affects whether or not Barton-McCombie reaction will take place.[1,115–134] In the reaction of compound **43**, for example, the substituents are sufficiently well separated to allow replacement of each group by a hydrogen atom to proceed in the normal manner (eq 26[115]).[115,130] When *O*-thiocarbonyl groups are attached to adjacent carbon atoms, reaction of one of these groups produces a carbon-centered radical that forms a double bond by elimination of the second group.[117–129,131,133] An example is shown in eq 27.[117–119] As indicated in Scheme 13, elimination takes place when R = OC_6H_5 or SCH_3, but in the rare event that R = C_6H_5, the elimination pathway leads to the unstable phenyl radical; as a consequence, radical cyclization takes place instead of elimination (eq 28).[1] If two *O*-thiocarbonyl groups are not on adjacent carbon atoms, but the radical produced by reaction of the first is centered on an atom in close proximity to the second, internal addition will take place.[115,116,132,134] Because the new radical formed by this reaction does not have a clear path to an elimination product, more complex reaction, such as that shown in eq 29,[115] is likely to take place.

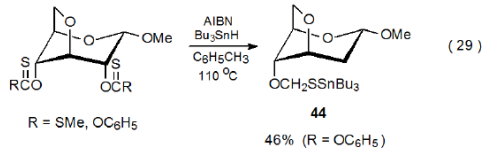




Scheme 13

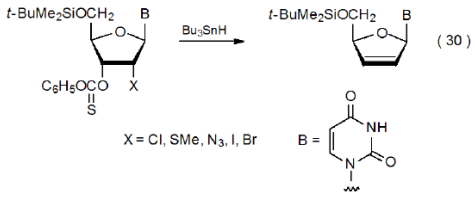




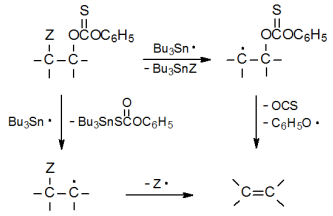


b. Reactions of Compounds with a Single *O*-Thiocarbonyl Group

As described in the previous section, elimination reactions take place when compounds with *O*-thiocarbonyl groups on adjacent carbon atoms react with tin or silicon hydrides. Similar reaction takes place when an *O*-thiocarbonyl group is attached to a carbon atom that has an azido,[135] bromo,[135–137] chloro,[135,138,139] iodo,[135] isocyano,[140] methylthio,[135] or phenylthio,[141] substituent bonded to an adjacent carbon atom. An example is given in eq 30.[135] This process begins with formation of a carbon-centered radical and ends with radical expulsion from an adjacent carbon atom (Scheme 14). In some instances it is reaction of the *O*-thiocarbonyl group that generates the carbon-centered radical, but in others, particularly those involving compounds containing bromine and iodine, halogen-atom abstraction is the first reaction to take place.



Scheme 14



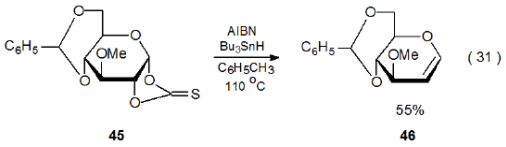
Z = Cl, CH_3S, N_3, I, Br

c. Use of Sacrificial Olefins

One of the difficulties associated with the synthesis of unsaturated compounds by radical reaction is that a radical intermediate may add to a recently formed double bond in a product molecule. When such an unwanted addition occurs, it may be reduced in importance to an acceptable level by adding an alkene such as 1-dodecene to the reaction mixture. This alkene, a compound described as a “sacrificial olefin”, protects the elimination product by scavenging radicals before they add to product molecules.[142]

d. Cyclic Thionocarbonates

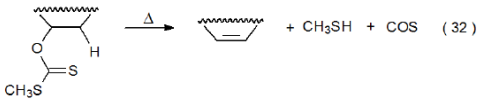
One way to view cyclic thionocarbonates is as compounds that have adjacent *O*-thiocarbonyl groups and, consequently, might undergo radical elimination. Since Barton-McCombie reactions of cyclic thionocarbonates generally give good yields of deoxy compounds, an elimination reaction can be expected only if such a reaction benefits from a special driving force. This driving force can come from reaction producing an unsaturated compound with a double bond stable enough that its formation significantly lowers transition-state energy. Consistent with this idea is formation of the glycal **46** as the only product from reaction of the cyclic thionocarbonate **45** with tri-*n*-butyltin hydride (eq 31).[143] 2',3'-*O*-Thiocarbonyl nucleoside derivatives undergo similar reaction to give unsaturated nucleosides, but only as minor products.[144–146]



45 **46** (31)

e. Preventing Thermal Elimination

The Barton-McCombie reaction of xanthates is most successful when these compounds are prepared from secondary alcohols. Xanthates formed from tertiary alcohols are prone to thermal elimination (eq 32, Chugaev elimination[147]) at temperatures normally used in the Barton-McCombie reaction. When reaction is initiated by triethylboron–oxygen, however, it can be conducted at room temperature, where reaction of tertiary xanthates occurs without competing elimination.[106,148]

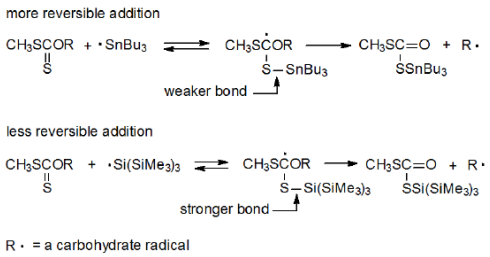


(32)

5. Reversible Addition to an *O*-Thiocarbonyl Group

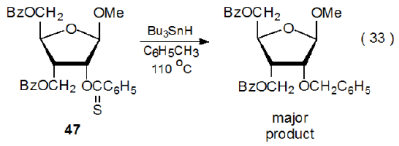
Xanthates synthesized from primary alcohols usually require higher temperatures in the Barton-McCombie reaction and often give lower product yields.[149,150] These problems can be overcome in some instances by changing the hydrogen-atom donor from Bu_3SnH to $(Me_3Si)_3SiH$. Tri-*n*-butyltin hydride is a less effective donor than tris(trimethylsilyl)silane in these reactions due to greater reversibility of $Bu_3Sn\cdot$ addition to a thiocarbonyl group (Scheme 15).[149] Because the S–Si bond [90 kcal mol^{-1} (377 kJ mol^{-1})][151] is stronger than the S–Sn bond [65 kcal mol^{-1} (272 kJ mol^{-1})],[151] reversal of addition of $(Me_3Si)_3Si\cdot$ is less likely to occur. Reduced reversibility means that once a silyl radical has added to an *O*-thiocarbonyl group, a difficult forward reaction (e.g., one producing a primary radical[149] and, sometimes, one producing a secondary radical[152,153]) can compete more effectively with reverse reaction to give the starting materials. Limiting reversibility is even more effective when reaction take place under the low temperature conditions made possible by Et_3B–O_2 initiation.[33]

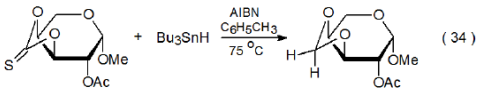
Scheme 15



6. Reduction of a Thiocarbonyl Group to a Methylene Group

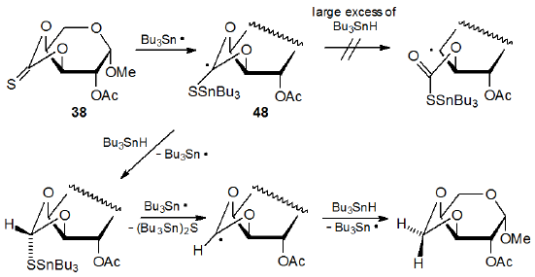
Conversion of a thiocarbonyl group into a methylene group represents a rare type of competition for the Barton-McCombie reaction. This transformation changes the *O*-phenylthiocarbonyl group in **47** into an *O*-benzyl group (eq 33),[28] and it is responsible for a similar change in the cyclic thionocarbonate **38** (eq 34).[89,111] The reaction shown in eq 34 occurs in much higher yield when a large excess of tri-*n*-butyltin hydride is present. One effect of a large excess of Bu_3SnH is to increase the rate of hydrogen-atom abstraction by the radical **48** (Scheme 16) to the point that ring opening by this radical is too slow to be detected.





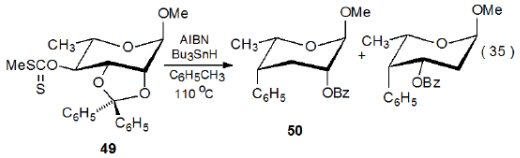
1.0 eq	0.3 eq	0%
1.0 eq	1.0 eq	16%
1.0 eq	5.0 eq	75%

Scheme 16

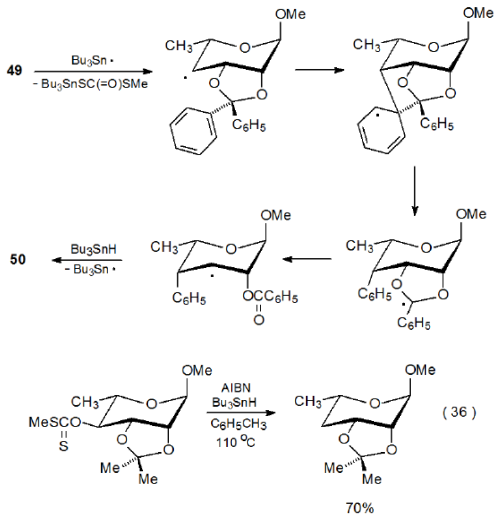


7. Phenyl-Group Migration

Compound **49**, a xanthate with an *O*-[(alkylthio)thiocarbonyl] group at C-4 and 2,3-*O*-diphenylmethylene protection, undergoes phenyl group migration and ring opening during reaction (eq 35).[154] According to the mechanism proposed in Scheme 17, this reaction depends upon the presence of substituents in the protecting group that can undergo migration by an addition-elimination process. Consistent with this mechanistic proposal is the observation that if the 2,3-*O*-diphenylmethylene group is replaced by a 2,3-*O*-isopropylidene group, normal reaction occurs (eq 36).[155]

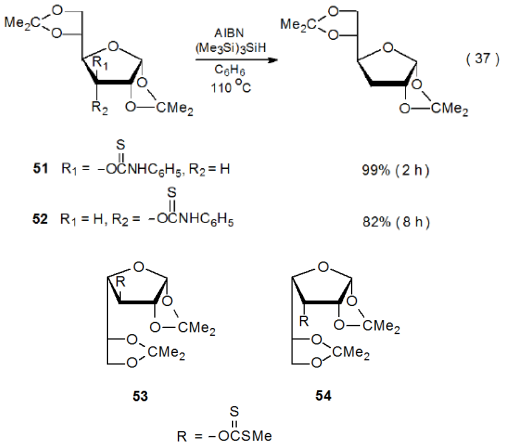


Scheme 17



F. Influence of Steric Effects on Reactivity

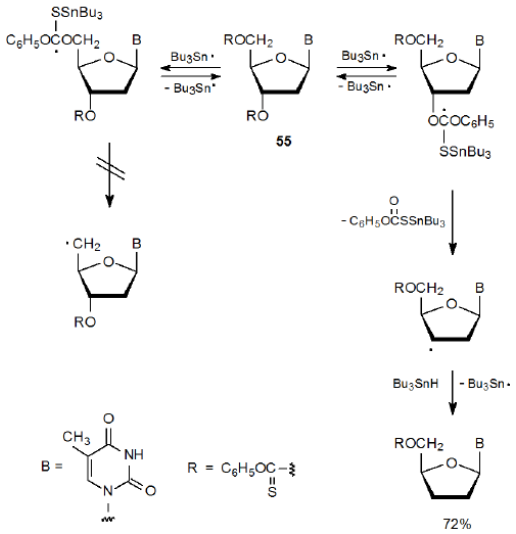
Reaction of the epimeric thionocarbamates **51** and **52** with Bu_3SnH illustrates the role that steric effects play in the Barton-McCombie reaction (eq 37).[156] The dramatically different steric environment for the C-3 substituents in **51** and **52** does not have a substantial impact on their reactivity; specifically, the difference of a factor of four in reaction times (reaction rates were not measured) is consistent with only minor influence by steric effects. A possible explanation for this modest difference in reactivity is that although the steric congestion around C-3 in compounds **51** and **52** is substantially different, it is not dramatically different in the area of the sulfur atom, where the reaction is taking place. Comparing the reactivity of the xanthates **53** and **54** provides another example of the modest role of steric effects in the Barton-McCombie reaction. The decidedly more hindered *O*-[(methylthio)thiocarbonyl] group in **54** renders this xanthate (**54**) only about five times less reactive than its epimer **53**.[157]



G. Regioselectivity

One of the characteristics of the Barton-McCombie reaction is that when it is conducted in the normal manner (i.e., with Bu_3SnH as the hydrogen-atom donor and AIBN as the initiator), higher temperature is required for reaction of a primary *O*-phenoxythiocarbonyl group than a secondary one.[76,158] This difference in reactivity can become the basis for regioselective reaction; thus, as pictured in Scheme 18, group replacement takes place only at the 3'-position in the nucleoside **55**.[76]

Scheme 18

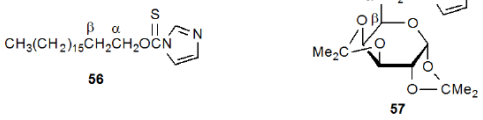


H. Chemoselectivity

Chemoselectivity in reactions of compounds containing *O*-thiocarbonyl groups is discussed in Section II.B of Chapter 9 in Volume I.

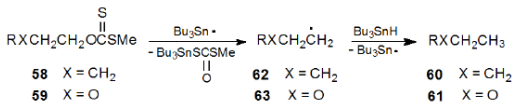
I. The β-Oxygen Effect

An observation about the Barton-McCombie reaction is that some carbohydrates react more easily than would be expected on the basis of model compound behavior. This greater reactivity is observed when the carbon atom in a C–O bond is β-related to a carbon atom bearing an *O*-thiocarbonyl group.[93] Comparison of the reactivities of **56** and **57** illustrates this difference. Compound **56** does not react with tri-*n*-butyltin hydride at 110 °C (it does at 130 °C),[93] but **57**, which also is a primary (thiocarbonyl)imidazolide, does react under these conditions[42,93] This and similar observations led to the proposal that "oxygen bonded to the β-carbon of a carbon radical has a marked stabilizing effect; this permits radical reactions not seen, except at much higher temperatures, in non-oxygenated model compounds."[93] When first proposed, this "β-oxygen effect" represented a potentially important factor in carbohydrate chemistry because many carbon-centered radicals would be stabilized by its existence.



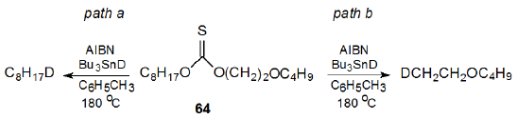
Considerable effort has been invested in studying the β-oxygen effect. This work has established that the presence of a β-related, carbon–oxygen bond does not necessarily increase the rate of formation of a developing, carbon-centered radical. For example, reaction of a mixture of the xanthates **58** and **59** with a limited amount of tri-*n*-butyltin hydride gave products **60** and **61** in approximately equal amounts (Scheme 19).[159,160] Since this result meant that xanthates **58** and **59** were reacting at essentially the same rate, a β-related, carbon–oxygen bond was providing little, if any, transition-state stabilization for the developing radical **63**.[160]

Scheme 19



A related experiment involved the thionocarbonate **64**, which could react along either of two competing pathways (Scheme 20). If the β-oxygen effect existed, reaction by path b would be favored. Experimentation showed that reaction along each pathway was equally likely; consequently, the conclusion again was that no evidence existed for a β-oxygen effect.[149]

Scheme 20



Although these experiments dispelled the idea that a β-related oxygen atom generally provides stabilization to a radical center, they did not explain why the carbohydrate derivative **57** is more reactive than the model compound **56**. An explanation for this behavior, however, does come from study of the equatorial and axial isomers **65** and **66**, respectively. The axial epimer (**66**) with its gauche (synclinal) dipoles is more reactive than the equatorial epimer (**65**) with trans dipoles (Figure 2). The greater reactivity of compound **66** is attributed to eliminating an unfavorable dipole-dipole interaction during bond breaking. Removing such an interaction then appears to be the primary reason for the rate differences that originally were attributed to the β-oxygen effect.[149]

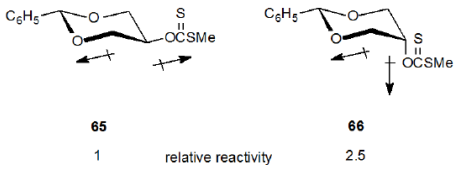


Figure 2. Relative reactivity of axial and equatorial substituents in xanthates **65** and **66**

III. Radical Addition

Addition reactions can be organized on the basis of the process that follows the initial reaction of a carbon-centered radical with a multiple bond to form an adduct radical. For an adduct radical that traces it beginning back to an *O*-thiocarbonyl compound, observed further reactions include atom abstraction and radical elimination. Chapter 18 contains a more general discussion of radical addition reactions, one that focuses more on the compound to which addition is occurring rather than on the radical precursor.

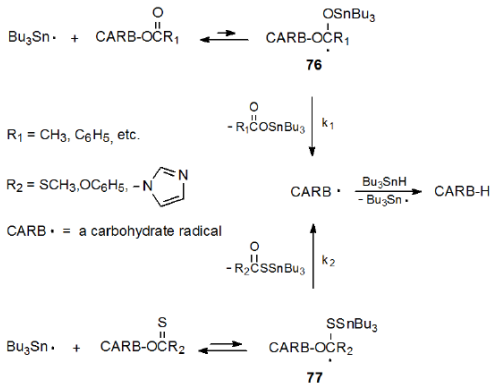
IV. Radical Cyclization

It is convenient to organize cyclization reactions on the basis of the locations of the reacting multiple bond and the radical center. These two can be either in the carbohydrate framework or in a substituent group. More information about radical cyclization is found in Chapter 19, which is devoted entirely to ring-forming reactions.

V. Comparing the Reactivity of O-Thiocarbonyl and O-Carbonyl Carbohydrates

When one considers the success of *O*-thiocarbonyl compounds as substrates in the Barton- McCombie reaction, a reasonable question to ask is "Why don't *O*-carbonyl carbohydrate derivatives (in particular, *O*-acylated compounds) exhibit similar reactivity?" An answer to this question can be framed in terms of the reactions shown in Scheme 28.[223–225] According to this explanation, the equilibrium involving addition of $Bu_3Sn\cdot$ to a compound with an *O*-thiocarbonyl group produces a far greater concentration of the adduct radical **77** than the concentration of the radical **76** produced by addition of $Bu_3Sn\cdot$ to the corresponding *O*-carbonyl carbohydrate. The dramatically greater equilibrium concentration of **77** leads to a corresponding increased rate of carbohydrate radical (CARB·) formation.[223–225]

Scheme 28



Detectable reaction of simple esters with $Bu_3Sn\cdot$ becomes possible only if the low equilibrium concentration of **76** can be increased in some manner or compensated for by rapid further reaction of this radical (k_1 large). Due to these requirements, no reaction takes place under normal Barton-McCombie conditions, but replacement of an acyloxy group with a hydrogen atom does occur when acylated carbohydrates react with $(C_6H_5)_3Si\cdot$ under vigorous conditions [$(C_6H_5)_3SiH$, 140 °C, 12 h, benzoyl peroxide].[226] Also, under quite different conditions (HMPA, H_2O, UV light, room temperature) photochemical electron transfer leads to reduction of acylated carbohydrates to the corresponding deoxy compounds.[227] These and other reactions of esterified carbohydrates are discussed in detail in Chapter 8.

VI. Summary

An effective procedure for deoxygenation begins with the conversion of a hydroxyl group in a carbohydrate into an *O*-thiocarbonyl group and ends with a radical reaction (the Barton- McCombie reaction) that replaces the *O*-thiocarbonyl group with a hydrogen atom. Xanthates, (thiocarbonyl)imidazolides, and thionocarbonates are the most common substrates for the Barton- McCombie reaction. Although a number of hydrogen-atom donors can be used in this reaction, the usual choice is tri-*n*-butyltin hydride. Safety concerns about tin hydrides and problems with product purification have caused chemists to turn increasingly to other hydrogen atom sources, in particular, tris(trimethylsilyl)silane. Barton-McCombie reaction is sometimes complicated by competing reactions, the most common of which regenerates the partially protected carbohydrate from which the *O*-thiocarbonyl-containing substrate was synthesized.

Differences in reactivity sometimes favor selecting a particular type of *O*-thiocarbonyl compound. Phenyl thionocarbonates are particularly valuable for hydroxyl group replacement by a hydrogen atom during nucleoside synthesis, and they are the least likely *O*-thiocarbonyl derivative to undergo alcohol regeneration. If reaction of a xanthate is attempted with a hydrogen-atom donor much less effective than tri-*n*-butyltin hydride, xanthate-dithiocarbonate rearrangement can take place. Reactions of tertiary xanthates can be complicated by Chugaev elimination unless these reactions are conducted at low temperature.

Deoxygenation involving cyclic thionocarbonates differs from that of other *O*-thiocarbonyl compounds because reaction involves ring opening. The direction of ring opening determines which of the two carbon atoms in the ring system will become the radical center. A high yield of a single product, therefore, depends on high regioselectivity in the ring-opening process. Cyclic thionocarbonates generally react to give deoxy compounds resulting from formation of the more stable intermediate radical. In some instances release of ring strain during ring opening becomes a factor in determining where the radical center will be located. Mixtures of products are a common result when the two radicals produced by ring opening are comparable in stability.

Radicals produced by reaction of *O*-thiocarbonyl compounds undergo addition reactions when a compound with a reactive multiple bond is present, and they undergo cyclization when the radical itself has a properly positioned multiple bond. In either situation the reactions that take place are of the addition-abstraction or addition-elimination type. The latter includes reactions with double bond migration and those without. Observed radical cyclizations are all addition- abstraction reactions. Most of these involve addition of a framework radical to either a framework multiple bond or to a substituent multiple bond.

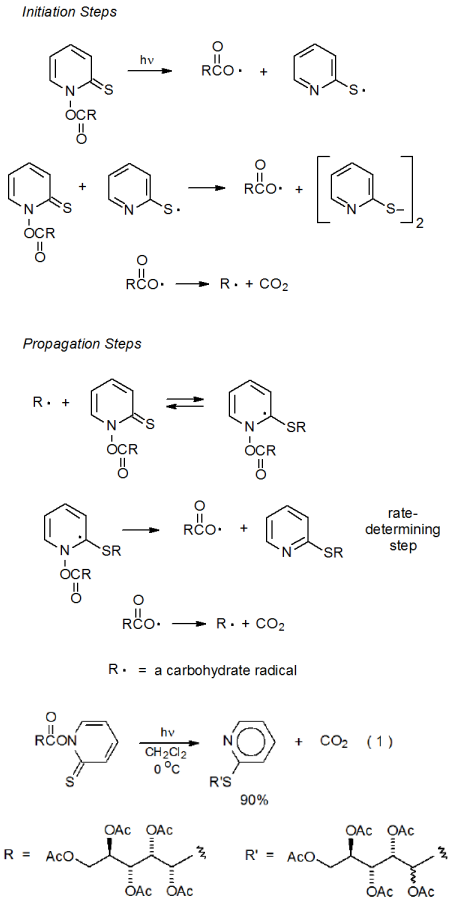
CHAPTER OVERVIEW

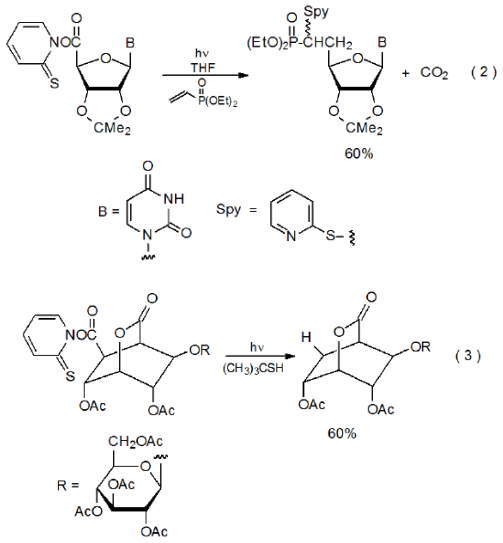
13: Carboxylic Acid Esters of N-Hydroxypyridine-2-thione

The discussion in Chapter 12 focused on reactions of *O*-thiocarbonyl compounds prepared by derivatization of hydroxyl groups in partially protected carbohydrates. The current chapter is concerned with reactions of another type of thiocarbonyl compound, one prepared by carboxyl group esterification. The compounds of interest are esters of *N*-hydroxypyridine-2-thione, sometimes referred to as *O*-acyl-*N*-hydroxy-2-thiopyridones or "Barton esters".

Barton esters generate carbon-centered radicals in photochemically initiated reactions in which the esters themselves produce the chain-carrying radicals needed for the chain reaction to continue (Scheme 1).[1–4] Radical formation from these esters is followed by loss of carbon dioxide and, in the absence of additional reactants (e.g., a compound with an electron-deficient double bond), formation of a product with a sulfur atom bonded to the carbon atom in the carbohydrate framework where the radical was centered (eq 1).[5] The carbon–sulfur bond in the product from Barton ester reaction provides greater flexibility in further synthetic transformation than does the carbon–hydrogen bond that forms when tin or silicon hydrides are present. The synthetic potential of this type of reaction is greater than that indicated in eq 1 because the intermediate, carbon- centered radical also can add to a multiple bond (eq 2),[6,7] abstract a hydrogen atom from a suitable donor (eq 3),[8] or undergo other radical reactions. In effect, through formation and reaction of *N*-hydroxypyridine-2-thione esters it is possible to replace a carboxyl group in a molecule with a carbon-atom chain or with one of a variety of functional groups.

Scheme 1





Since relatively few carbohydrates contain the carboxyl group needed for radical formation by Barton ester photolysis, the requirement that a carbohydrate first be converted into a carboxylic acid places a barrier to the general usefulness of this procedure. In spite of this limitation a number of addition and group replacement reactions exist that are based on radical formation from *N*-hydroxypyridine-2-thione esters of carbohydrates that have been modified to contain a carboxyl group.

Topic hierarchy

II. Reaction Mechanism
III. Group Replacement Reactions
IV. Addition Reactions
V. Cyclization Reactions
VI. Generating Methyl Radicals
VII. Summary

II. Reaction Mechanism

The mechanism proposed in Scheme 1 for reaction of an *N*-hydroxypyridine-2-thione ester is supported by a number of experimental observations. The carbon-centered radical R· is detectable by ESR spectroscopy,[9] and flash photolysis experiments identify the 2-pyridylthiyl radical (PyS·) as one of the transients formed by ester photolysis.[10,11] Also, the radical-chain nature of the reaction is attested to by quantum yields that range between 6 to 35, depending upon the reaction conditions.[12]

There are several characteristics of reactions of *N*-hydroxypyridine-2-thione esters that have "come to light" as a result of mechanistic studies. One of these is that addition of R· to the carbon–sulfur double bond is reversible (Scheme 1).[13] Another is that the 2-pyridylthiyl radical, produced by photolysis in the first initiation step (Scheme 1), can add to a molecule of the starting ester in the second initiation step to provide another pathway for acyloxy radical formation.[14]

Several factors contribute to the driving force for the rate-determining step in the reaction shown in Scheme 1. One of these is conversion of a nonaromatic starting material into an aromatic product.[15,16] Another is that a weak N–O bond (BDE = 43 kcal $mole^{-1}$)[17] in the substrate is being replaced with a stronger N–C bond (BDE ≅ 76 kcal $mole^{-1}$ for the second bond between carbon and nitrogen atoms)[18] in the product.

III. Group Replacement Reactions

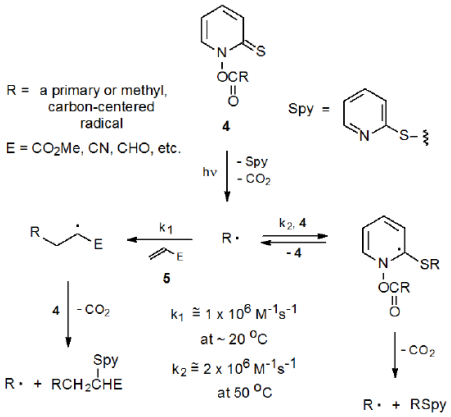
Since the reaction pictured in Scheme 1 depends upon R· adding to a molecule of the starting ester, one way to change the course of this reaction is to introduce a compound that will react more rapidly with R· than does the ester. Thiols meet this requirement.[8,19–25] Hydrogen-atom abstraction by a carbon-centered radical from a thiol is rapid enough (k_H = 1.4 x 10^8 $M^{-1}s^{-1}$ at 25 °C for abstraction from C_6H_5SH by Bu·)[26] to occur in preference to radical reaction with the starting ester.

IV. Addition Reactions

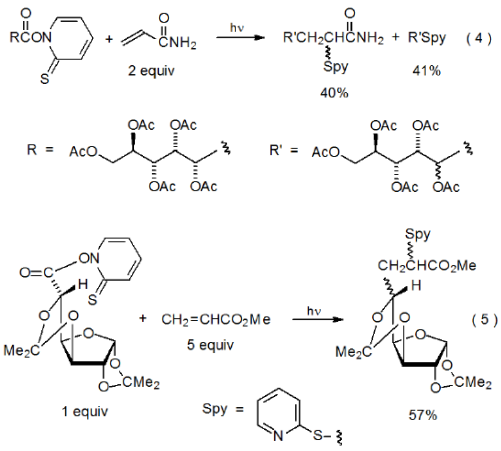
A. A Competition Always Present

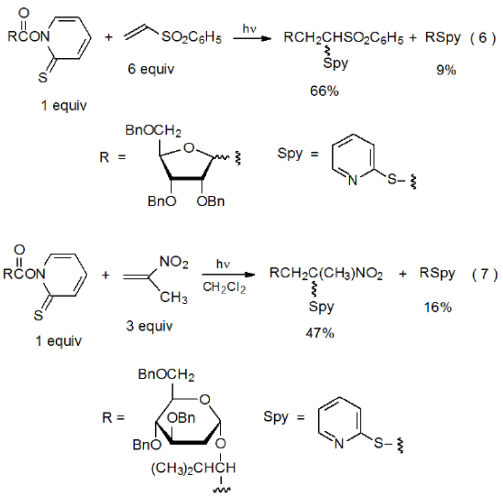
The rate constant for addition of a typical carbon-centered radical to an ester of *N*-hydroxypyridine-2-thione ($k_r \cong 2 \times 10^6\ M^{-1}s^{-1}$ at 50 °C)[29,30] is large enough that competing addition of such a radical to a reactant with a carbon–carbon multiple bond occurs only for compounds with the most reactive bonds (i.e., those with electron-withdrawing substituents attached.) (The rate constants for addition to these unsaturated reactants are approximately $1 \times 10^6\ M^{-1}s^{-1}$ at 20 °C[31]) In practice this means that unless the multiple bond has an electron-withdrawing substituent, the rate of addition of a carbon-centered radical will be too slow to compete effectively with addition to a Barton ester. As is emphasized in Scheme 4, a similarity in rate constants means that the competition between addition of a radical to the unsaturated compound **5**, as opposed to addition to a second molecule of the Barton ester **4**, depends heavily upon the relative concentrations of these two reactants (**4** and **5**).

Scheme 4



Examples of the competition between radical addition to a molecule with an electron deficient double bond or to a molecule of unreacted starting ester are found in the reactions shown in equations 4-7. In the first of these (eq 4) acrylamide is present in two-fold excess; yet, products from addition of R· to the amide and to the starting ester are formed in essentially equal amounts.[32] In the second reaction (eq 5) a good yield of the product from radical addition to methyl acrylate requires a five-fold excess of the unsaturated ester.[33] In the reaction shown in eq 6 even a six-fold excess of phenyl vinyl sulfone does not suppress completely addition to the starting ester of some of the carbohydrate radicals.[34] Radical addition to 2-nitropropene is similar to addition to other unsaturated compounds (eq 7).[35,36]

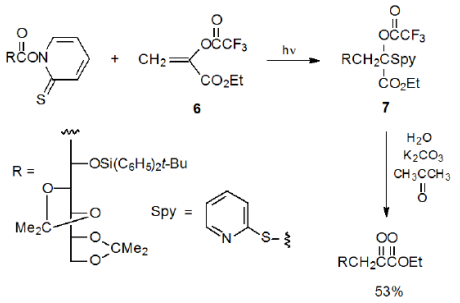




B. Compounds With Electron-Deficient Multiple Bonds

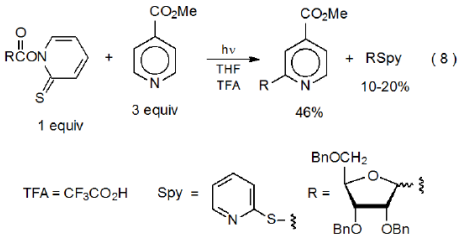
Generalizing the information in equations 4-7 leads to the conclusion that carbohydrate radicals formed from esters of *N*-hydroxypyridine-2-thione add to compounds with electron- deficient multiple bonds; specifically, these reactions include radicals combining with α,β-unsaturated amides[32,37,38] and esters[33,35,39–41] as well as with compounds in which a double bond has either a phenylsulfonyl [34,39,42] or nitro[35,36] substituent. Among reactive compounds addition to the carbon–carbon double bond in ethyl α-(trifluoroacetoxy)acrylate (**6**)[32,35,43–47] is reported more often than addition to any other compound (Scheme 5). One reason for this is that the resulting adduct (**7**) hydrolyzes under very mild conditions to give an α-keto ester; thus, radical addition extends the carbon chain by two atoms and introduces easily manipulated functional groups (Scheme 5).[47]

Scheme 5



C. Heteroaromatic Compounds

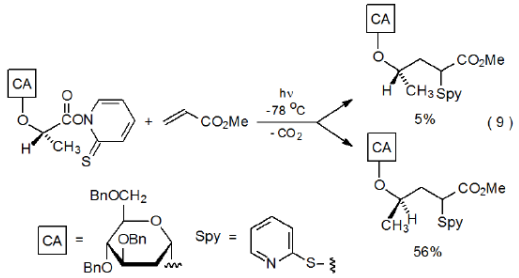
As the reaction in eq 8 shows, radicals generated from *N*-hydroxypyridine-2-thione esters also add to aromatic amines.[34,42,48,49] Since this type of reaction occurs only when an acid such at trifluoroacetic acid is present in the reaction mixture, the assumption is that the radical is adding to the protonated amine. [In the absence of an acid only RSPy (eq 8) is formed.] Such an assumption is reasonable because a nucleophilic radical would be expected to react more rapidly with an electron-deficient π system.



D. Carbohydrates as Chiral Auxiliaries

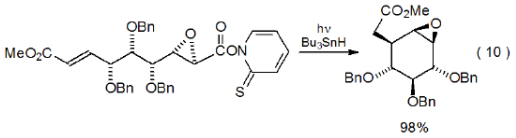
One synthetic application of carbohydrate-containing esters of *N*-hydroxypyridine-2-thione uses the carbohydrate moiety as a chiral auxiliary during radical addition.[35,36,40,41,43] The reaction shown in eq 9 illustrates the diastereoselectivity possible in this type of

process.[35] Selectivity in this case results primarily from steric interactions between methyl acrylate and the C-6 substituent in the reactant sugar.[35]



V. Cyclization Reactions

A radical generated from a Barton ester undergoes cyclization if it contains a properly positioned multiple bond (eq 10[50]).[50,51] Such reactions are not common because unless the needed carboxylic acid is readily available, the steps involved in its synthesis often make this process less attractive than others for generating the carbohydrate radical needed for ring formation.



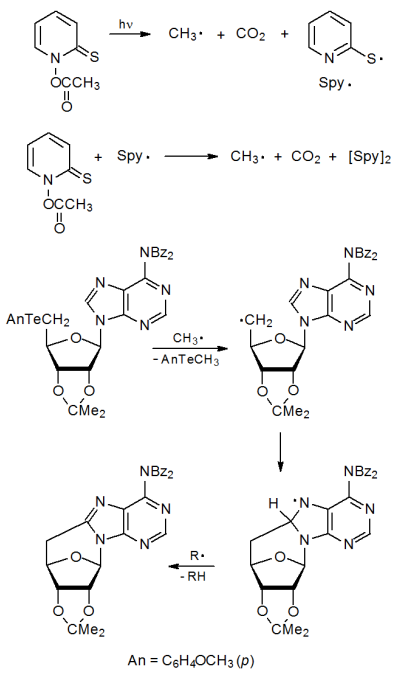
(10)

98%

VI. Generating Methyl Radicals

Photolysis of acetylated *N*-hydroxypyridine-2-thione produces a methyl radical (Scheme 6).[52] Methyl radicals generated in this way react with tellurium-containing nucleosides to generate the corresponding, carbon-centered radicals.[52–56] In the reaction shown in Scheme 6, radical formation from photolysis of *O*-acetyl-*N*-hydroxypyridine-2-thione is the first step in producing a new ring system.[52]

Scheme 6



VII. Summary

Radical reaction of a carboxylic acid ester of *N*-hydroxypyridine-2-thione causes the weak N–O bond to fragment to produce acyloxy and 2-pyridylthiyl radicals. The acyloxy radical then loses carbon dioxide to form a carbon-centered, carbohydrate radical. Carbon-centered radicals produced in this way abstract hydrogen atoms from highly reactive donors, such as thiols, and they combine with 2-pyridylthiyl radicals formed in the initial N–O bond homolysis. These carbohydrate radicals also can add to α,β-unsaturated esters and amides, to compounds with phenylsulfonyl- or nitro-substituted multiple bonds, and to protonated aromatic amines. Photolysis of acetylated *N*-hydroxypyridine-2-thione provides a source of methyl radicals that react readily with tellurium-containing carbohydrates to produce carbohydrate radicals.

CHAPTER OVERVIEW

14: Nitro Compounds

Carbohydrates contain two types of nitro groups. The first type has the nitrogen atom in this group attached to a carbon atom in the carbohydrate framework (creating a deoxynitro or *C*-nitro carbohydrate) and the second has the nitrogen atom bonded to an oxygen atom in the carbohydrate structure (making an *O*-nitro carbohydrate or a carbohydrate nitrate). Radical reactions of nitro compounds are highly dependent upon the atom to which the nitro group is bonded.

Topic hierarchy

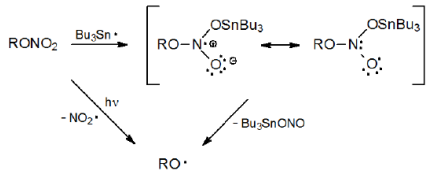
II. Reaction Mechanisms
III. C-Nitro Carbohydrates
IV. O-Nitro Carbohydrates
V. Reactions of Nitro Compounds with Silanes
VI. Summary

II. Reaction Mechanisms

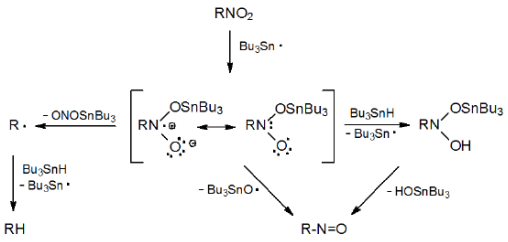
A. Addition-Elimination Reaction

The first step in the reaction of the tri-*n*-butyltin radical with a nitro compound is the addition of the radical to one of the oxygen atoms in the nitro group. The reaction that takes place after this initial addition depends upon whether the reactant is an *O*-nitro or a *C*-nitro compound. *O*-Nitro carbohydrates fragment to give alkoxy radicals (Scheme 1). *C*-Nitro carbohydrates have more varied possibilities. The adduct radical either breaks the C–N bond to give a carbon-centered radical, cleaves an O–N bond to form a nitroso compound, or abstracts a hydrogen atom from an available donor, usually Bu_3SnH (Scheme 2).

Scheme 1



Scheme 2

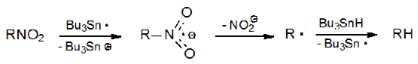


R· = a carbon-centered,carbohydrate radical

B. Electron Transfer

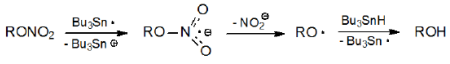
Early investigations raised the possibility that reaction of a *C*-nitro compound with the tri-*n*-butyltin radical could involve electron transfer (Scheme 3).[1–3] Later investigation, however, did not support this possibility because the electron transfer between $Bu_3Sn\cdot$ and $(CH_3)_2CHNO_2$ (Scheme 3) was found to be endothermic by at least 12 kcal mol^{-1} . This endothermic electron transfer was inconsistent with the large rate constant ($k = 9.5 \times 10^7\ M^{-1}s^{-1}$) observed for reaction between this pair [$Bu_3Sn\cdot$ and $(CH_3)_2CHNO_2$].[4] The conclusion from this latter study was that the addition-elimination mechanism (Scheme 2)[5–8] provided a better explanation for the reaction between $Bu_3Sn\cdot$ and a *C*-nitro compound. The possibility that electron transfer could be involved in reaction of *O*-nitro compounds (Scheme 4) has not been addressed and, thus, remains open.

Scheme 3



R· = a carbon-centered, carbohydrate radical

Scheme 4



RO· = an oxygen-centered, carbohydrate radical

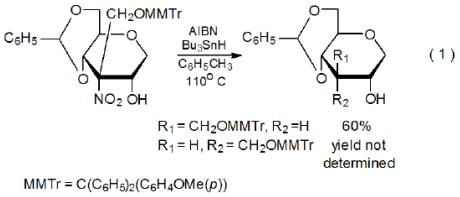
C. Photochemical Reaction

Photolysis of an *O*-nitrocarbohydrate fragments the N–O bond in the nitro group to produce nitrogen dioxide and the corresponding alkoxy radical (Scheme 1).

III. C-Nitro Carbohydrates

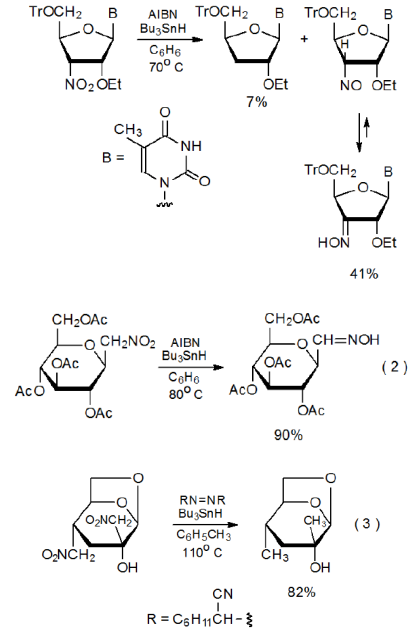
A. Group Replacement

Since in the reaction of a *C*-nitro compound the stability of the developing radical (R·) affects the ease of cleavage of the carbon–nitrogen bond (Scheme 2), group replacement occurs more easily for tertiary nitro compounds[9–14] than for secondary[15–19] and, especially, primary ones.[20–22] Reaction of Bu_3SnH with a compound containing a tertiary nitro group is given in eq 1.[9] If the nitro group in the substrate is secondary, reaction usually follows the same pathway and replaces this group with a hydrogen atom,[15–18] but sometimes breaking a C–O bond leading to a nitroso compound (which isomerizes to an oxime) offers significant competition (Schemes 2 and 5).[19] When a nitro group is primary, the elimination phase of the reaction is more likely to produce only the nitroso compound (eq 2),[20,21] even though replacement of a primary nitro group with a hydrogen atom has been observed (eq 3).[22]



(1)

Scheme 5

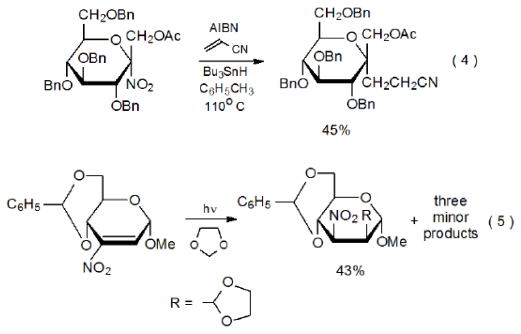


(2)

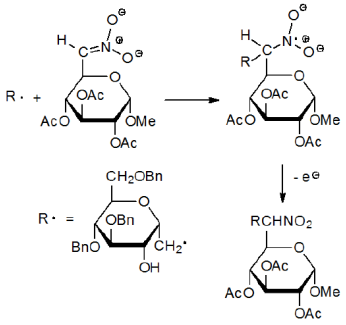
(3)

B. Addition Reactions

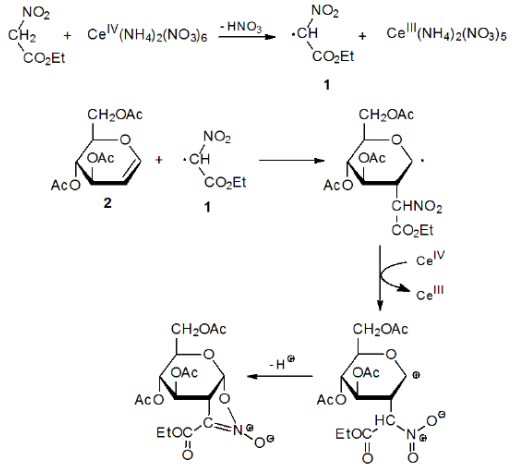
A nitro group in a reactant molecule can be involved in radical addition in several ways. First, denitration can produce a carbon-centered radical that undergoes typical addition to an electron-deficient multiple bond (eq 4).[3] In a different role, nitro groups activate multiple bonds toward addition by nucleophilic radicals and affect the regioselectivity of such reactions (eq 5).[23] Deprotonation of a carbon atom bearing a nitro group creates an unsaturated system to which a carbon-centered radical can add to form a new, C–C bond (Scheme 6[24]).[24–26] Finally, the electron-withdrawing character of a nitro group can contribute to turning a normally nucleophilic radical into one that is electrophilic; thus, the philicity of the radical **1**, which has both nitro and ethoxy-carbonyl groups attached to the radical center, is reflected in its ability to add to the electron-rich double bond in the glycal **2** (Scheme 7).[27]



Scheme 6

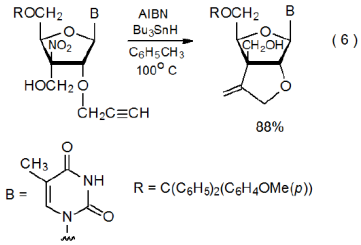


Scheme 7



C. Cyclization Reactions

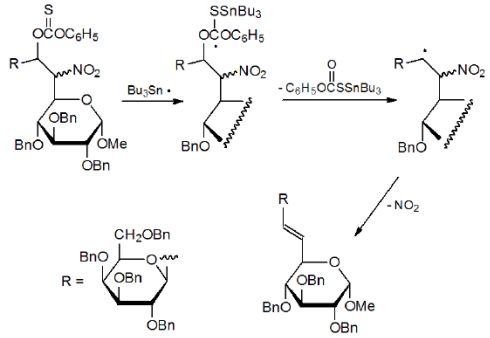
A cyclization reaction that begins with a *C*-nitro carbohydrate is shown in eq 6.[28] The high yield of this reaction, which involves a radical centered on a tertiary carbon atom adding to a multiple bond, illustrates that radical addition can be relatively insensitive to steric congestion at the radical center.[28,29]



D. Elimination Reactions

A deoxynitro sugar can undergo an elimination reaction, if a radical center develops on a carbon atom adjacent to that bearing the nitro group.[30–32] In the reaction shown in Scheme 8,[30] such a radical forms and then eliminates nitrogen dioxide to give an unsaturated compound.

Scheme 8



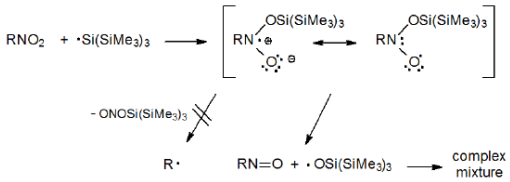
IV. O-Nitro Carbohydrates

Reaction of an *O*-nitro carbohydrate with a tri-*n*-butyltin radical or with ultraviolet light produces the corresponding alkoxy radical, an intermediate that is reactive enough to abstract a hydrogen atom from most C–H bonds. Also characterizing the reactivity of alkoxy radicals is rapid carbon–carbon bond cleavage to produce both a compound with a carbonyl group and a carbon-centered radical. Examples of these reactions are discussed in the next several sections.

V. Reactions of Nitro Compounds with Silanes

Concerns with the toxicity of tri-*n*-butyltin hydride and the purification problems that accompany its use have spawned a variety of attempts to replace this reagent with a less troublesome one (see Appendix I). Tris(trimethylsilyl)silane normally is an attractive alternative to Bu_3SnH, but it fails completely in this role in group replacement reactions in nitro compounds. The reason for failure is that the radical formed by addition of $(Me_3Si)_3Si\cdot$ to a nitro group does not break the carbon–nitrogen bond required for group replacement but rather cleaves a nitrogen–oxygen bond to begin a sequence of reactions leading to a complex reaction mixture (Scheme 13).[48]

Scheme 13



A more effective procedure for reducing the amount of tri-*n*-butyltin hydride needed for nitro-group replacement with a hydrogen atom consists of regenerating Bu_3SnH from the Bu_3SnNO_2 formed during the substitution process. A pair of reactions that achieve group replacement and regenerate Bu_3SnH are given in equations 11 and 12. This alternative method requires only 10% of the tri-*n*-butyltin hydride needed in the standard procedure.[49]

$$RNO_2 + Bu_3SnH \longrightarrow RH + Bu_3SnONO \quad (11)$$

$$Bu_3SnONO + C_6H_5SiH_3 \longrightarrow Bu_3SnH + C_6H_5SiH_2ONO \quad (12)$$

VI. Summary

The type of radical produced by reaction of a nitro group in a carbohydrate depends upon whether this group is bonded to a carbon or an oxygen atom. A nitro group bonded to an oxygen atom invariably fragments to produce an alkoxy radical, but a nitro group attached to a carbon atom either fragments to generate a carbon-centered radical, expels an oxygen-centered radical to form a nitroso compound, or abstracts a hydrogen atom.

The alkoxy radicals produced from *O*-nitro carbohydrates rapidly abstract hydrogen atoms either internally or from molecules present in solution. Competing with or, in some instances, superseding hydrogen-atom abstraction is carbon–carbon bond cleavage to give a carbonyl group and a carbon-centered radical.

The carbon-centered radicals derived from reaction of *C*-nitro carbohydrates form most readily if the radical being produced is tertiary. These radicals undergo typical replacement, addition, and cyclization reactions. Primary radicals are much less likely to form from *C*-nitro carbohydrates; instead, these carbohydrate derivatives usually produce nitroso compounds.

CHAPTER OVERVIEW

15: Azides & Azo Compounds

Radicals are involved in both the synthesis and reactions of carbohydrate azides and, to a much lesser extent, azo compounds. The primary contribution of radicals to azide synthesis is in the formation of 2-azido-2-deoxy sugars by addition of azide radicals to glycals. The principal radical reaction of azides is their conversion to amines by reduction with an organotin hydride, often tri-*n*-butyltin hydride. The most important contribution of azo compounds to radical chemistry is in their role as reaction initiators.

Topic hierarchy

II. Azides

III. Azo Compounds

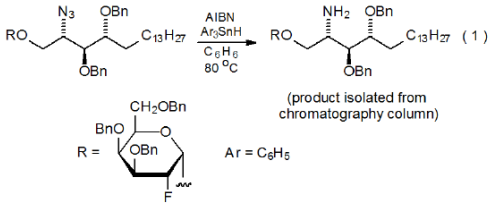
IV. Summary

II. Azides

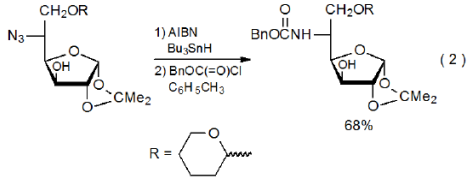
A. Reactions

1. Reduction

Azides are reduced to tin-substituted amines by reaction with tin hydrides.[1–9] These tin-containing compounds generally are not isolated; rather, each is converted into either the corresponding amine or an amine derivative. Amine derivatives include compounds formed by reaction of a tin-containing product with an acid halide,[1,2] anhydride,[3] or ester.[4] Free amines are liberated from tin-containing products by a hydrolysis that often takes place during chromatographic purification.[5–9] Examples of reactions producing amine and amine derivatives are found in equations 1[7] and 2,[1] respectively. Conversion of an azide into the corresponding amine also can take place when tri-*n*-butyltin hydride is replaced by tris(trimethylsilyl)silane.[10]

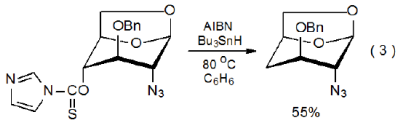


(1)

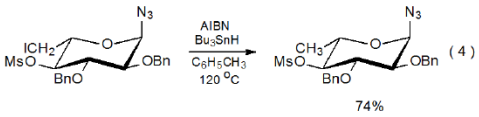


(2)

Treatment of azides with tri-*n*-butyltin hydride does not always cause reaction of the azido group.[11–13] Carbohydrates containing *O*-thiocarbonyl substituents (eq 3)[11,12] or iodine atoms (eq 4)[13] undergo chemoselective reaction that leaves the azido group intact. If the amount of Bu_3SnH is sufficient and the conditions are conducive, azido groups will react after the replacement of more reactive groups is complete.[13]



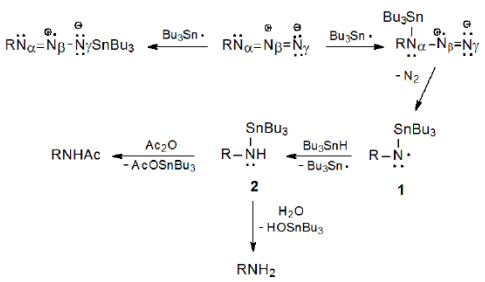
(3)



(4)

The tri-*n*-butyltin radical potentially can add to either N_α or N_γ in an azido group (Scheme 1), but since the intermediate radical **1** is thought to be a precursor to the tin-containing product **2**, it is assumed that the initial addition of $Bu_3Sn\cdot$ is to N_α.[14–16] As mentioned above and indicated in Scheme 1, normal procedure calls for either hydrolysis or derivatization prior to product isolation.

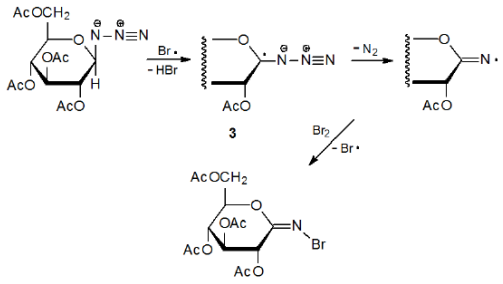
Scheme 1



2. Bromination

Free-radical bromination of a glycosyl azide produces the corresponding *N*-bromoglycosylimine.[17,18] The reaction shown in Scheme 2 begins such a process when H-1 is abstracted regioselectively to give the radical **3**, an intermediate that is stabilized by both the ring oxygen atom and the azido group. Loss of molecular nitrogen, followed by bromine-atom abstraction, completes the reaction.

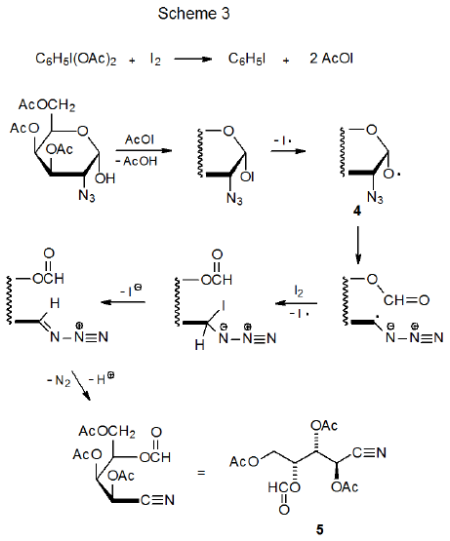
Scheme 2



3. Nitrile Formation

If an oxygen-centered radical and an azido group are attached to adjacent carbon atoms, the bond between the carbon atoms cleaves in a reaction leading to a nitrile.[19] In the example shown in Scheme 3, the alkoxy radical **4** fragments to open a six-membered ring; a sequence of steps then leads to the nitrile **5**. Similar ring opening occurs in compounds with five-membered rings.[19]

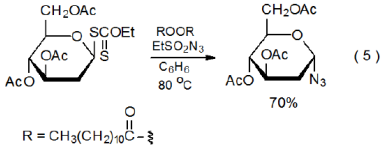
Scheme 3



B. Synthesis

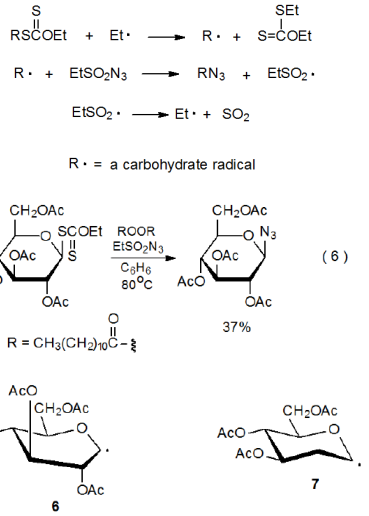
1. Carbohydrate Radical Addition to Ethanesulfonyl and Benzenesulfonyl Azides

It is possible to synthesize a carbohydrate azide by reaction of the corresponding xanthate with ethanesulfonyl azide[20] or benzenesulfonyl azide[20,21] (eq 5[21]). The propagation steps for this type of reaction are outlined in Scheme 4.[21] As shown in eq 6, the presence of an acetoxy group at C-2 reduces product yield when compared to reaction in which such a group is absent (eq 5). The intermediate pyranos-1-yl radical **6**, which adopts a $B_{2,5}$ boat conformation, is more hindered at C-1 than the pyranos-1-yl radical **7**, which lacks a C-2 substituent and has a chair conformation. (Section IV of Chapter 6 in Volume I contains more information about the conformation of pyranos-1-yl radicals.) In addition to being more hindered at C-1, the radical **6** is less nucleophilic due to the electron-withdrawing nature of the C-2 acetoxy group.



(5)

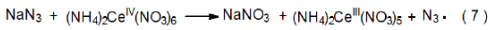
Scheme 4

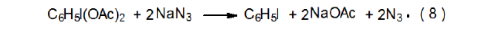


2. Azide Radical Addition to an Unsaturated Carbohydrate

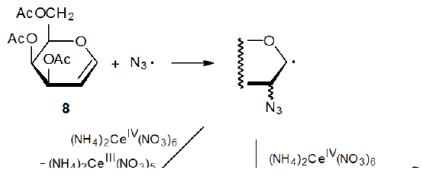
a. Azide Radicals

Azide ion is converted into azide radical by reaction with oxidizing agents that include ammonium cerium(IV) nitrate (eq 7)[22] and (diacetoxyiodo)benzene (eq 8).[23] The electrophilic nature of the azide radical is attested to by its addition to electron-rich double bonds such as those found in glycals.[24–47] Atomic orbital coefficients can be critical in determining regioselectivity in a reaction with an early transition state because the rate constant for the bond-forming process between two atoms depends in its early stages on the magnitude of the coefficients of the interacting frontier orbitals.[28,29] In the azide radical addition pictured in Scheme 5, the frontier orbitals are the SOMO of the azide radical and the HOMO of the D-galactal **8**. The more reactive position for addition to the double bond in **8** is at C-2 because, based on simple model systems,[30] the atomic orbital coefficient for the HOMO is larger at C-2 than at C-1 (Figure 1).





Scheme 5



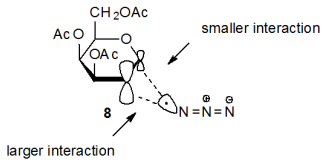
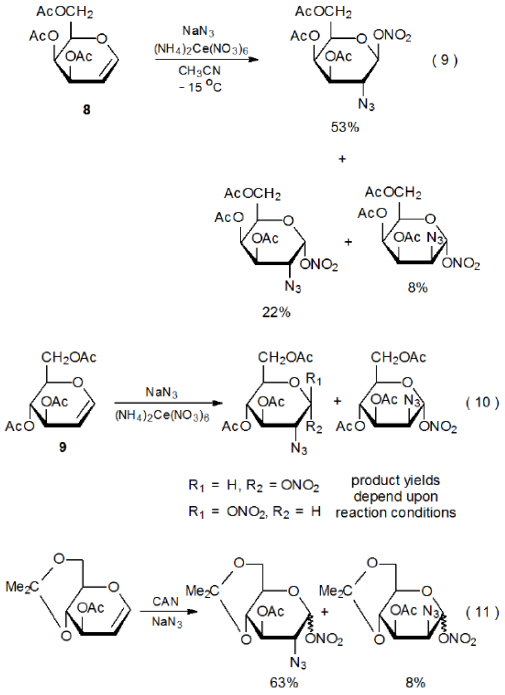


Figure 1. Orbital interactions in addition of the azide radical to the glycal **8**

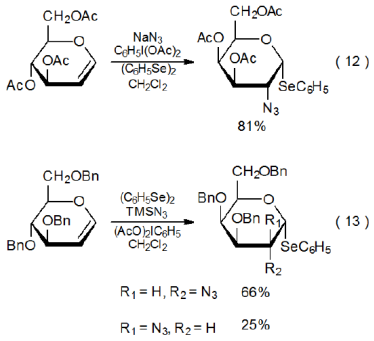
b. Azidonitration

Azidonitration takes place when the azide radical is produced by oxidation of the azide ion by ammonium cerium(IV) nitrate in the presence of a glycal.[24–27,31–39] The stereoselectivity of azide radical addition is dependent on glycal structure; thus, $N_3\cdot$ adds in a highly selective fashion to the α face of the D-galactal **8** because the β face is well protected by ring substituents (eq 9).[24] Less effective protection of the β face, which occurs when **8** is replaced by the D-glucal **9**, leads to stereoselectivity that varies as the reaction conditions change (eq 10).[37] When a 4,6-*O*-isopropylidene group is incorporated into the D-glucal structure, it creates a compound that is conformationally less mobile. With this reduction in conformational mobility comes greater stereoselectivity in addition of the azide radical to the D-glucal derivative (eq 11).[37]



c. Azidophenylselenylation

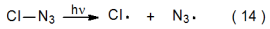
When azide ion is oxidized by (diacetoxyiodo)benzene, the resulting azide radical will add to a glycal to produce a phenyl selenide if diphenyldiselenide is present in the reaction mixture (eq 12[40]).[39–48] The normal solvent for this reaction is dichloromethane, but due to limited solubility of sodium azide in this solvent, reaction usually is heterogeneous, a situation that causes product yields to suffer except in quite dilute solutions. If, however, the azide radical is generated from trimethylsilyl azide, solutions are homogeneous and good product yields are realized (eq 13).[49]



d. Azidohalogenation

The azide radical also forms by photolysis of chloroazide (eq 14). When this reaction takes place in the presence of a glycal, azido-chlorination results (eq 15).[50] The stereoselectivity of glycal addition by the azide radical formed from photolysis is similar to that observed when this radical is generated by azide ion oxidation. The photochemical reaction is different, however, in that a small amount (13%) of addition occurs in which the positions of the azido and chloro substituents are interchanged. Since photolysis of

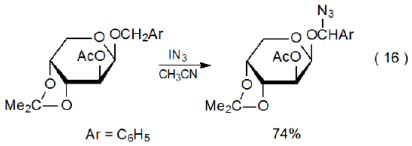
chloroazide also produces the electrophilic chlorine atom (eq 14), it is reasonable to expect that sometimes a chlorine atom would add to a glycal at C-2.



(14)

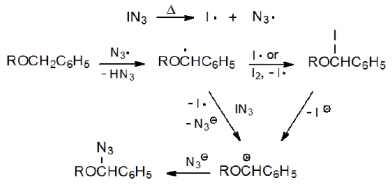
3. Atom Replacement by an Azido Group

Reaction between iodoazide and a carbohydrate containing a benzyloxy group leads to hydrogen atom replacement by an azido group (eq 16).[51] In this reaction the azide radical abstracts one of the reactive hydrogen atoms from the benzyloxy group to form a benzylic radical. The azido group then can be introduced by one of the proposed pathways shown in Scheme 6.



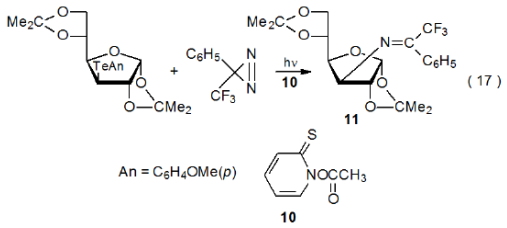
(16)

Scheme 6



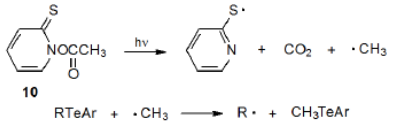
III. Azo Compounds

Azo compounds, in particular 2,2'-azobis(isobutyronitrile), are ubiquitous initiators in radical reactions, but they rarely participate in these reactions in other ways. One reaction that includes an azo compound in a role other than that as an initiator is shown in eq 17, where the imine **11** is produced by reaction of a carbohydrate radical with an azo compound.[52,53] The dimer **12** is a suggested intermediate in the proposed mechanism for this reaction, which is pictured in Scheme 7.[52,53] After radical reaction is complete, the imine **11** can be hydrolyzed to produce an aminodeoxy sugar.

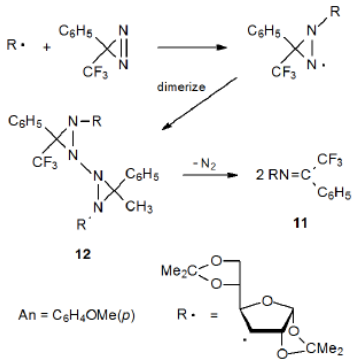


Scheme 7

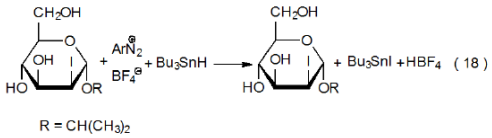
carbohydrate radical formation



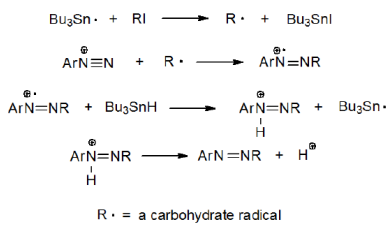
radical addition to an azo compound



It is also possible to synthesize an azo compound in a radical reaction. Such a compound is formed when a carbohydrate radical, generated from a deoxyiodo sugar, adds to a diazonium salt (eq 18).[54] The propagation steps for a proposed mechanism for this reaction are shown in Scheme 8.[54]



Scheme 8



IV. Summary

The principal radical reaction of carbohydrate azides is reduction to tin-substituted amines by reaction with tri-*n*-butyltin hydride. Products from this reaction are isolated either as free amines or amine derivatives. Three radical reactions for synthesis of carbohydrate azides are known. One of these involves the addition of a carbohydrate radical to ethanesulfonyl azide. A second is the azidonitration that takes place when an azide radical adds to a glycal in the presence of ammonium cerium(IV) nitrate. Finally, reaction of a glycal with an azide radical and diphenyldiselenide, results in azidophenylselenylation.

CHAPTER OVERVIEW

16: Nitriles & Isonitriles

Radical reactions of carbohydrate nitriles and isonitriles are not widespread. Isonitrile reactions are rare because these compounds themselves are not common. Their primary reaction is replacement of the isocyano group with a hydrogen atom. Nitriles are more plentiful than isonitriles but less reactive in radical reactions. They typically are involved in radical cyclization. Both nitriles and isonitriles can be synthesized by radical reaction.

II. Isonitriles
III. Nitriles
IV. Summary

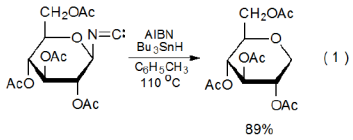
II. Isonitriles

A. Reactions

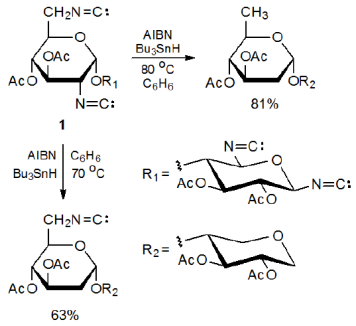
1. Group Replacement

a. Isocyano Groups

Reaction of tri-*n*-butyltin hydride with carbohydrates containing isocyano groups replaces each of these groups with a hydrogen atom. Such replacement is known to occur when isocyano groups are attached to anomeric,[1,2] secondary,[3–9] and primary[7–9] carbon atoms. An example of replacement at an anomeric carbon atom is shown in eq 1,[5] while both primary and secondary groups are replaced in the reaction described in Scheme 1.[7,9]



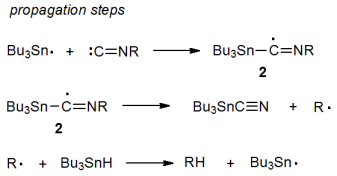
Scheme 1



Isocyano group replacement is remarkably temperature sensitive. Reaction of the secondary groups in **1** takes place at 70 °C, but the primary isocyano group is unreactive (Scheme 1).[7,9] When the temperature of the reaction mixture is raised to 80 °C, both groups are replaced. This temperature dependence provides a basis for regioselective reaction.

A mechanism for isocyano group replacement with a hydrogen atom is pictured in Scheme 2.[10] In the first step of this process the tri-*n*-butyltin radical adds to the carbon atom of the isocyano group to produce an imidoyl radical (**2**). Fragmentation of this radical (**2**) then generates the carbon-centered radical R·, which abstracts a hydrogen atom from Bu_3SnH to complete the reaction sequence. If R represents a phenyl or substituted-phenyl group, fragmentation to give an aryl radical does not occur; rather, an addition reaction takes place.[11] When tris(trimethylsilyl)silane replaces tri-*n*-butyltin hydride in reduction of isonitriles, compounds containing primary, secondary, or tertiary isocyano groups all are reactive.[12]

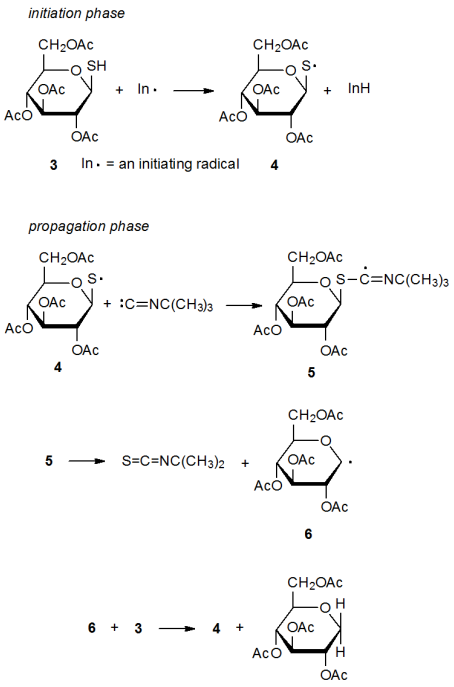
Scheme 2



b. Sulfhydryl Groups

An isonitrile can participate in replacement of a sulfhydryl group by a hydrogen atom.[13] Such a reaction is pictured in Scheme 3, where replacement begins when the sulfur-centered radical **4** forms from the thiol **3** by hydrogen-atom abstraction. Addition of **4** to *t*-butyl isocyanide gives the adduct radical **5**, which then fragments to produce the pyranos-1-yl radical **6**. Hydrogen-atom abstraction by **6** from another molecule of the starting thiol (**3**) completes the cycle and begins a new reaction sequence. Sulfhydryl group replacement represents another pathway for generating carbon-centered, carbohydrate radicals.

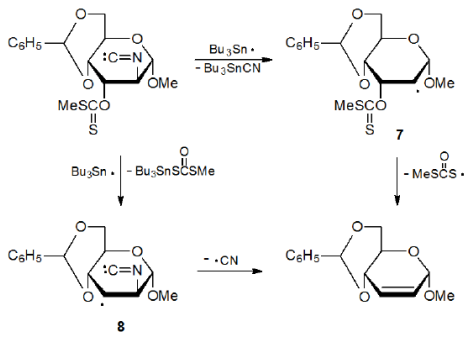
Scheme 3



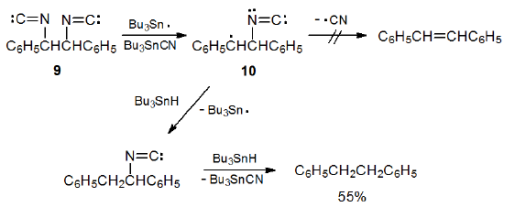
2. Elimination Reactions

Reaction of tri-*n*-butyltin hydride with a carbohydrate that has adjacent isocyano and *O*-thiocarbonyl groups generates a product with a C–C double bond (Scheme 4).[4] In this reaction radicals **7** and **8** are both possible intermediates. Study of the diisonitrile **9** provides information helpful in choosing between **7** and **8**. Reaction of **9** with $Bu_3Sn\cdot$ produces a carbon-centered radical (**10**) with an isocyano group attached to the carbon atom adjacent to the radical center (Scheme 5).[8] The intermediate **10** does not expel a cyano radical to form a multiple bond but rather abstracts a hydrogen atom from tri-*n*-butyltin hydride. Extrapolating the behavior of **10** to the reaction shown in Scheme 4 leads to the conclusion that the radical **8** is an unlikely intermediate in this process.

Scheme 4



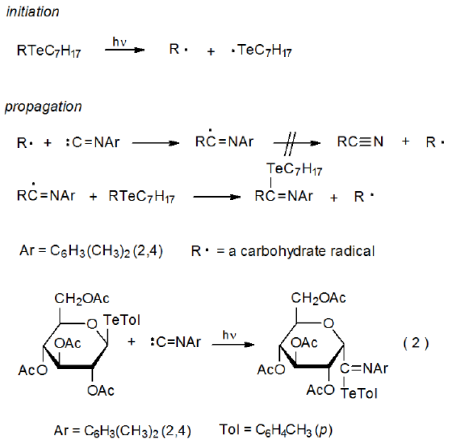
Scheme 5



3. Addition Reactions

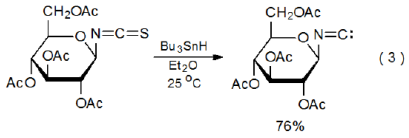
As a part of the replacement process shown in Scheme 2, an isonitrile reacts with $Bu_3Sn\cdot$ to produce an intermediate, carbon-centered radical R·. Normal completion of this reaction involves hydrogen-atom abstraction by R· from Bu_3SnH; however, if R· is formed without a hydrogen-atom transfer present, it will add to a molecule of isonitrile (Scheme 6). A specific example of this type of reaction is found in eq 2, which describes the α addition of a pyranos-1-yl radical, formed from a carbohydrate telluride, to an aromatic isonitrile.[14]

Scheme 6

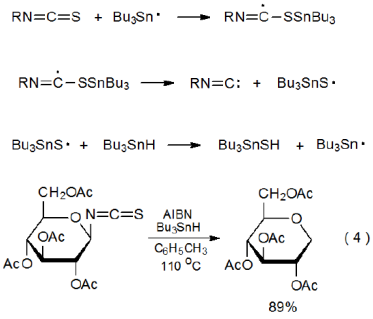


B. Synthesis

It is possible to produce isonitriles from isothiocyanates by radical reaction (eq 3).[2] A proposed mechanism for such a structural change is shown in Scheme 7. Isonitrile formation results when reaction is conducted at room temperature (eq 3), but if the reaction temperature is raised to 110 °C, the isonitrile is not isolated because it undergoes isocyano group replacement by a hydrogen atom (eq 4).[2,15]



Scheme 7

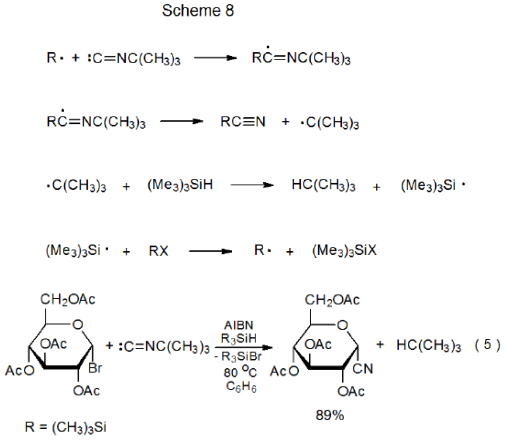


III. Nitriles

A. Synthesis

When *t*-butyl isonitrile reacts with a carbon-centered radical, an addition-elimination process takes place that results in the formation of a nitrile (Scheme 8).[16–23] This type of nitrile synthesis is illustrated by the reaction shown in eq 5.[20] (Scheme 10 in Chapter 2 describes another example of this type of reaction.[22])

Scheme 8

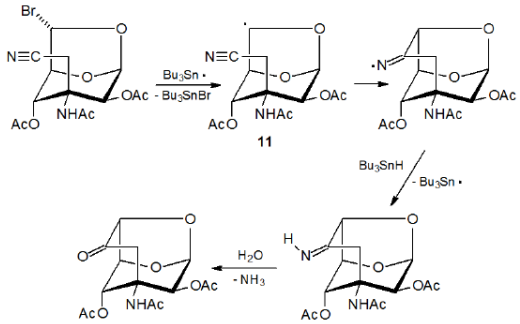


B. Reactions

1. Addition to a Cyano Group

Radical reactions of carbohydrate nitriles usually involve internal addition in which a carbon-centered radical generated in close proximity to a cyano group forms a new ring system.[24–31] An example is shown in Scheme 9, where the radical centered on C-6 in **11** adds to the cyano group as a part of this sequential process.[24] Carbohydrate radical formation in this type of reaction typically begins with the tri-*n*-butyltin radical abstracting a halogen atom or an *O*-thiocarbonyl group. After cyclization, the radical abstracts a hydrogen atom from Bu_3SnH to produce an imine, which in some cases is isolated and in others is hydrolyzed to the corresponding carbonyl compound before isolation.

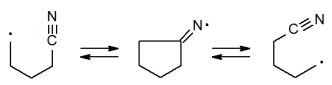
Scheme 9



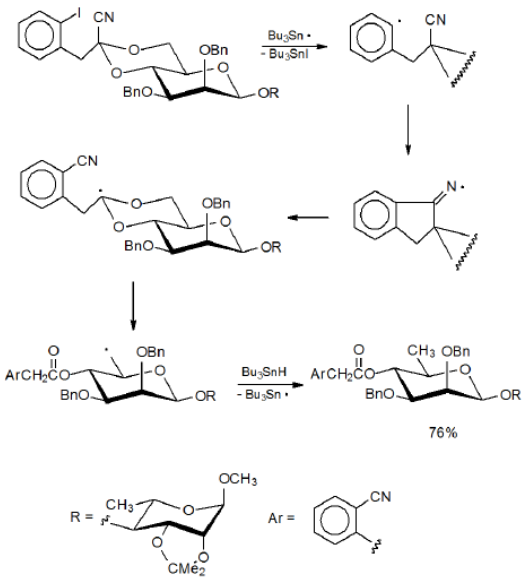
2. Cyano Group Migration

When a cyclic imino radical forms during carbon-centered radical addition to a cyano group, the possibility exists that ring opening will lead to cyano group migration (Scheme 10).[32–34] Such a reaction is shown in Scheme 11, where migration accompanies ring opening of a benzylidene acetal.[32]

Scheme 10



Scheme 11



IV. Summary

When compared to reactions of halogenated carbohydrates or *O*-thiocarbonyl compounds, radical reactions of nitriles and isonitriles are few in number. The primary reaction for isonitriles is isocyano group replacement by a hydrogen atom. For nitriles the only reaction of significance is internal addition of a carbon-centered radical to a cyano group to form a cyclic imino radical.

Radical reactions can be involved in nitrile and isonitrile synthesis. Isonitriles are formed from reaction of isothiocyanates with tri-*n*-butyltin hydride. Nitriles are produced by addition of a carbon-centered radical to *t*-butyl isonitrile and subsequent elimination of the *t*-butyl radical.

CHAPTER OVERVIEW

17: Oxime Ethers & Related Compounds

Carbon-centered radicals add to compounds containing carbon–nitrogen double bonds. Most reactions of this type are internal additions involving oxime ethers, but similar transformations of hydrazones, ketonitrones, and protonated heteroaromatics also take place.[1,2] When compared to addition to carbon–carbon double bonds, reactions of their carbon–nitrogen counterparts are similar in that they are rarely reversible[1] but different in that the rate constants for addition are larger. Also, the final products from addition to carbon–nitrogen double bonds contain functional groups that more easily undergo further modification.[1]

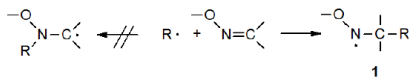
II. Oximes
III. Hydrazones and Imines
IV. Ketonitrones
V. Protonated Heteroaromatics
VI. Protected Amines
VII. Summary

II. Oximes

A. Addition Reactions

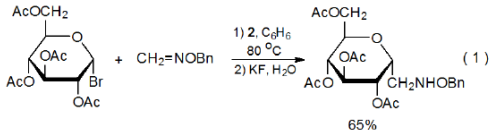
A carbon-centered radical adds preferentially to the carbon atom in the carbon–nitrogen double bond of an oxime ether (Scheme 1). The regioselectivity of this reaction is consistent with a radical adding to the oxime ether to produce the more stable of the two possible adduct radicals; that is, the radical stabilized by an oxygen atom attached to the radical center. Examples of this type of reaction are found in the addition of a pyranos-1-yl radical to *O*-benzylformaldoxime (eq 1),[3] and reaction of a nucleoside radical centered at C-3' to a nucleoside-containing oxime ether (eq 2).[4,5]

Scheme 1



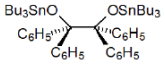
1

R· = carbohydrate radical

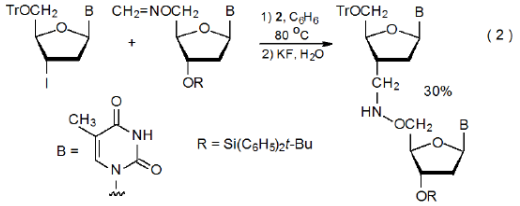


(1)

65%



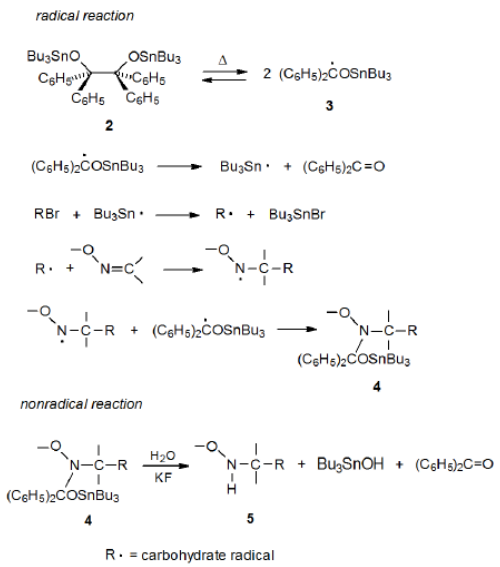
2



(2)

The carbon-centered radicals that add to oxime ethers typically are formed from the corresponding iodides and bromides by reaction with $Bu_3Sn\cdot$. Because simple reduction offers significant competition to radical addition, Bu_3SnH is not the best source for the tin-centered radicals participating in these reactions. Addition is more successful when $Bu_3Sn\cdot$ is generated from bis(tri-*n*-butyltin)benzpinacolate (**2**), a compound that produces $Bu_3Sn\cdot$ but suppresses simple reduction by not introducing an effective hydrogen-atom transfer into the reaction mixture (Scheme 2).[3] In the absence of such a donor the radical phase of this reaction is thought to produce the tin-containing compound **4**, which then is hydrolyzed to the benzyloxyamine **5** in a nonradical reaction (Scheme 2).

Scheme 2

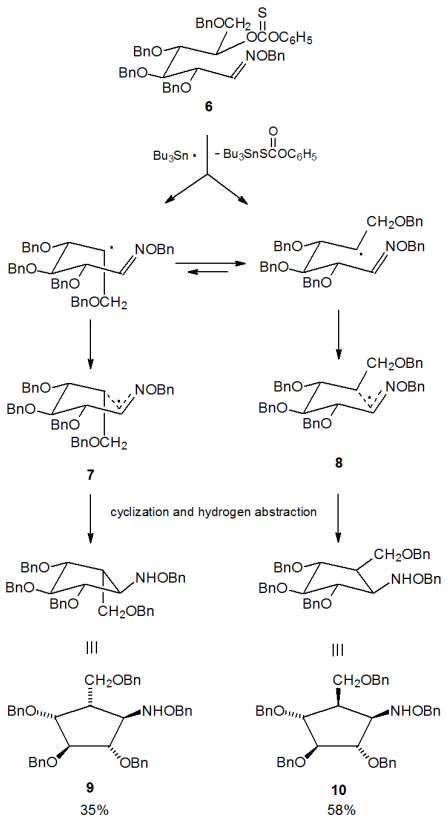


B. Cyclization Reactions

1. Regioselectivity

An example of regioselective radical cyclization involving an oxime ether is shown in Scheme 3.[6] One factor important in determining regioselectivity in this type of reaction is the energetically favored addition of a radical to the carbon atom of the carbon–nitrogen double bond (Scheme 1). Also of importance is the preference during radical cyclization of oxime ethers for forming five-membered rather than six-membered rings when both are possible and six-membered rather than seven-membered rings when either one could be formed.[7]

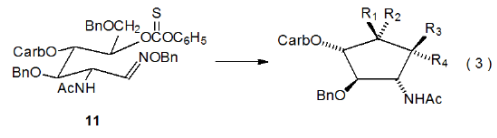
Scheme 3



2. Stereoselectivity

Radical cyclization converts open-chain oxime ethers into highly substituted, alkoxyamino cyclopentanes[6,8–14] and cyclohexanes.[7,15–17] As is often the case in radical cyclization reactions, stereoselectivity can be understood, if one assumes that the lowest energy transition state is a chair-like structure that maximizes the number of pseudoequatorial substituents. The reaction shown in Scheme 3, for example, generates compounds with two new chiral centers but produces only two (**9** and **10**) of the four possible stereoisomers.[6] These two isomers arise from the chair-like transition states **7** and **8**, respectively. The transition state **8**, leading to the major product **10** has the greater number of pseudoequatorial substituents.

In light of the reaction of the oxime ether **6** (Scheme 3) one might expect the structurally similar oxime ether **11** (eq 3) also to produce only the two stereoisomers **14** and **15**, that is, the products expected from reaction via chair-like transition states. Actually, **11** produces all four possible stereoisomers (eq 3), and neither **14** nor **15** is the major product.[11] The major product (**12**) arises from reaction involving the boat-like transition state **16** (Scheme 4). Similar amounts of energy often are required to reach chair-like and boat-like transition states in radical cyclization reactions (Section IV.A in Chapter 11 of Volume I); consequently, differences in structure near the reactive centers can affect product distribution significantly.

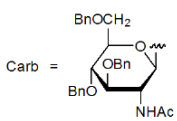


$R_1 = CH_2OBn, R_2 = H, R_3 = H, R_4 = NHOBn$ **12** (31%)

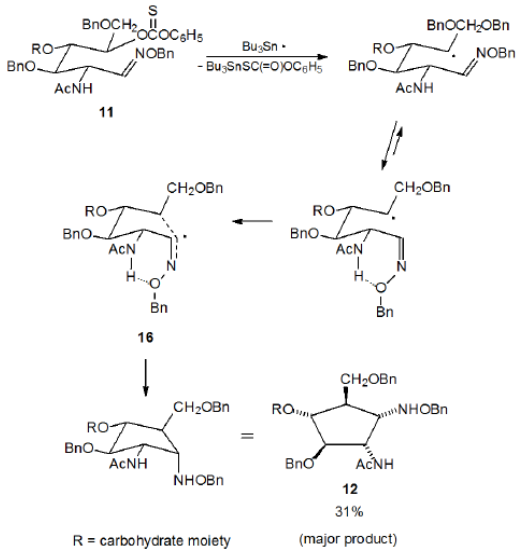
$R_1 = H, R_2 = CH_2OBn, R_3 = H, R_4 = NHOBn$ **13** (2%)

$R_1 = H, R_2 = CH_2OBn, R_3 = NHOBn, R_4 = H$ **14** (23%)

$R_1 = CH_2OBn, R_2 = H, R_3 = NHOBn, R_4 = H$ **15** (15%)



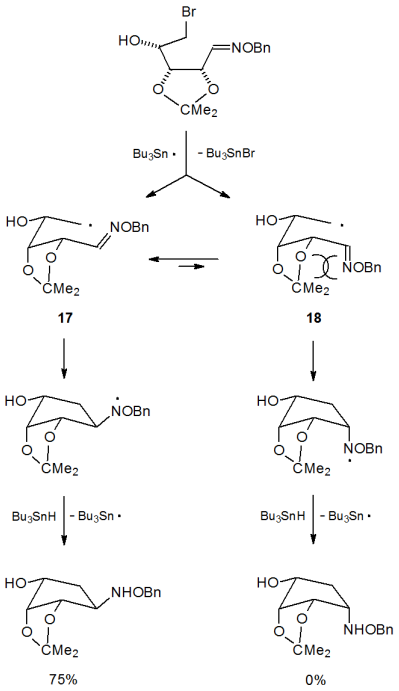
Scheme 4



One difference between the substrates **6** and **11** is that **6** has a benzyloxy group at C-2 (Scheme 3), and **11** has an acetamido group at this position (Scheme 4). The possibility exists that hydrogen bonding involving the acetamido group stabilizes the transition state **16** to the point that the reaction pathway containing this boat-like structure (**16**) becomes the lowest energy one (Scheme 4).

An *O*-isopropylidene group that is close to the reactive centers in a cyclization reaction has a pronounced effect of stereoselectivity.[17–24] This effect is illustrated by the reaction shown in Scheme 5, where the sole product has the NHOBn substituent on the side of the newly formed ring that is opposite to the *O*-isopropylidene group.[18] In this reaction the chair-like conformation (**17**) of the intermediate radical is greatly favored over its boat-like counterpart (**18**) due, in large measure, to destabilizing steric interactions that involve the *O*-isopropylidene group.

Scheme 5



3. Radical Forming Reactions

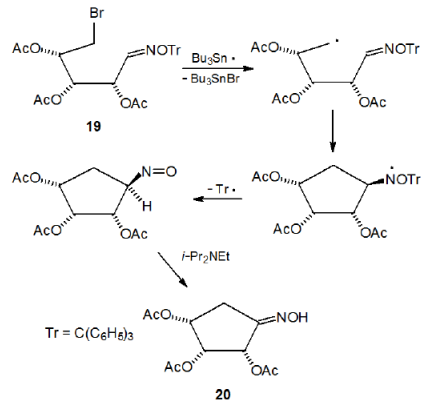
Carbohydrate radicals that add internally to carbon–nitrogen double bonds come from a variety of sources. Such radicals often form by reaction of *O*-thiocarbonyl compounds[6,8–11,20,21,23] or bromides[15–19] with tri-*n*-butyltin hydride. Reactions of Bu_3SnH with

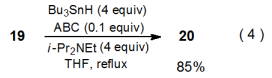
carbonyl compounds[12] and dithioacetals[13] represent two less common ways for generating radicals that then undergo ring formation. The necessary radicals also can be formed by electron-transfer reaction.

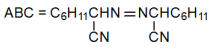
4. Preserving the Double Bond

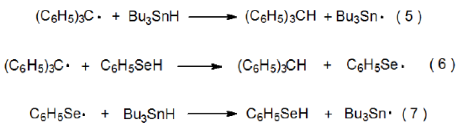
Normally, the double bond in an oxime ether is converted into a single bond during ring formation, but when an *O*-trityl oxime undergoes cyclization, the carbon–nitrogen double bond is preserved in the product. A proposed mechanism for this type of reaction is shown in Scheme 6, and the preferred reagents, all of which are critical to the success of the reaction, are given in eq 4.[24] Slow addition of Bu_3SnH and the initiator ABC also are necessary for synthetically useful reaction. The persistent radical $(C_6H_5)_3C\cdot$ hinders chain propagation by its slow reaction with Bu_3SnH; consequently, to avoid buildup of $(C_6H_5)_3C\cdot$, diphenyl diselenide, a convenient precursor for the very reactive hydrogen-atom transfer C_6H_5SeH, can be added to the reaction mixture. This addition replaces a slow reaction (eq 5) with two rapid ones (eq 6 and eq 7).[24] Although the carbohydrates that have been studied thus far give good product yields without addition of diphenyl diselenide, other compounds do not; consequently, the selenide inclusion in the reaction mixture is now part of the recommended procedure.

Scheme 6



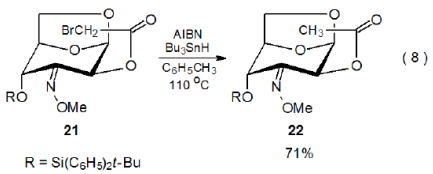


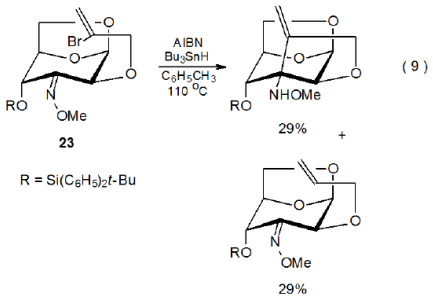




5. Enhanced Reactivity of Vinylic Radicals

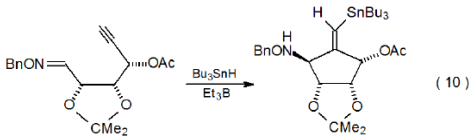
Attempted cyclization of the radical generated from the bromide **21** produces only the simple-reduction product **22** (eq 8), but reaction of the related vinylic bromide **23** gives both a cyclic product and a simple-reduction product (eq 9).[25] One factor that may contribute to the difference in ability of compounds **21** and **23** to undergo radical cyclization is the considerable reactivity of vinylic radicals. This reactivity may be sufficient to cause new ring formation during reaction of **23**.





(9)

In addition to halogen-atom abstraction, vinylic radicals also form by reaction of a tin-centered radical with a compound containing a carbon–carbon triple bond.[26–30] When a radical formed in this way adds internally to a carbon–nitrogen double bond, it produces a cyclic, tin-containing product (eq 10).[26] The triple bond in such reactions usually is a terminal one, but internal bonds, particularly those in conjugation with radical-stabilizing groups, also undergo reaction.[30]

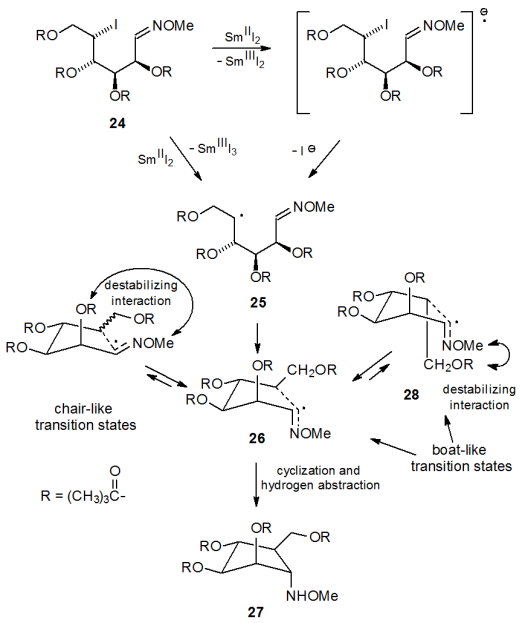


(10)

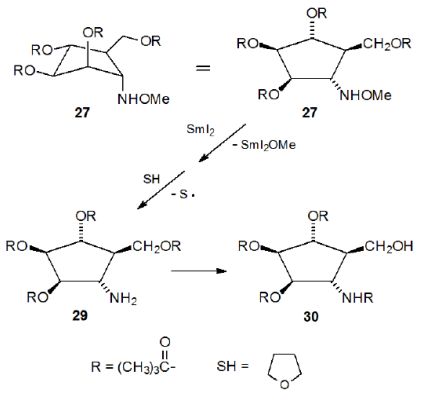
C. Electron-Transfer Reaction

Electron transfer provides another means for generating a ring-forming radical from an oxime ether. The electron donor in such reactions typically is samarium(II) iodide and the electron acceptor often is an oxime ether containing a halogen atom. A typical reaction is shown in Scheme 7,[31] where dissociative electron transfer involving the carbon–iodine bond in **24** leads to formation of the carbon-centered radical **25**. Cyclization and hydrogen-atom abstraction complete this reaction by forming the cyclopentylamine derivative **27** in a process that passes through the boat-like transition state **26**. Although chair-like transition states typically are favored in cyclization reactions, in this case chair-like structures have destabilizing interaction between C-1 and C-2 substituents; furthermore, the other boat-like transition state (**28**) has reduced stability due to the interaction between the C-1 and C-6 substituents (Scheme 7). If excess SmI_2 is present during reaction, dissociative electron transfer breaks the N–O bond in **27** to produce, after hydrogen-atom abstraction, the corresponding cyclopentylamine **29** (Scheme 8). Nonradical migration of the acyl group from oxygen to nitrogen then forms the final product (**30**).[31] (Samarium(II) iodide also cleaves N–O bonds that are not formed from reaction of oxime ethers.[32])

Scheme 7

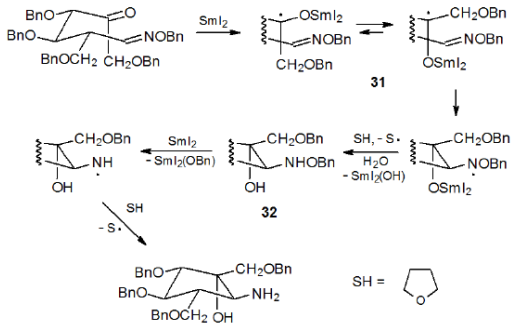


Scheme 8



Electron transfer to an aldehydo or keto group in a oxime ether also can be the initial step in ring formation.[33–38] When SmI_2 is the electron-donor, the first reactive intermediate is a samarium ketyl formed by one-electron reduction of the carbonyl group.[1] In the reaction shown in Scheme 9, the carbon atom on which the radical in the samarium ketyl **31** is centered adds internally to the carbon–nitrogen double bond leading to the cyclic product **32.** When excess SmI_2 is present, electron transfer to **32** causes N–O bond cleavage and ultimate replacement of the *O*-benzyl group attached to nitrogen with a hydrogen atom (Scheme 9).[36] Similar cyclization has been observed when the tri-*n*-butyltin radical reacts with a oxime ether containing an aldehydo or keto group.[39]

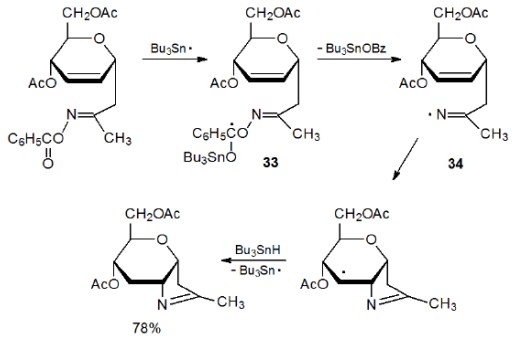
Scheme 9



D. Oxime Esters as Radical Sources

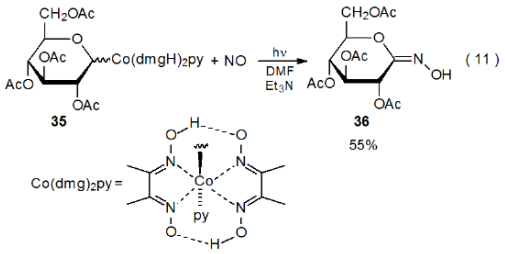
The signature event of the cyclization reactions discussed thus far is a carbon-centered radical adding to a carbon–nitrogen double bond in an oxime ether. The majority of ring-forming reactions involving oxime derivatives take place in this way, but a change occurs in the reaction shown in Scheme 10, where the adding radical (**34**) is generated from an *O*-benzoyloxime.[40] In general, adding $Bu_3Sn\cdot$ to an *O*-benzoyl group is an inauspicious beginning for a radical reaction because such addition reverses rapidly, nearly always before any other reaction can occur. Further reaction is possible in this case (Scheme 10) due primarily to rapid fragmentation of the weak N-O bond in the initially formed radical **33**.[40]

Scheme 10



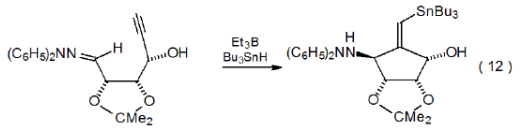
E. Oxime Synthesis

Oximes can be the products of radical reaction.[41,42] When the cobalt-containing, D-glucopyranosyl derivative **35** is photolyzed, the radical produced adds to a molecule of nitric oxide to give a nitroso compound. This compound then tautomerizes to form the corresponding oxime **36** (eq 11).[41]

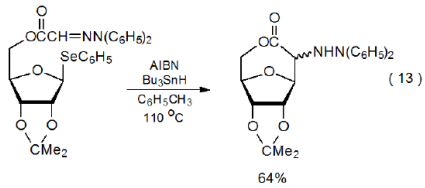


III. Hydrazones and Imines

Radical reactions of carbohydrate hydrazones[2,43–46] are less common than those of oxime ethers; reactions of imines[43] are still more rare. The reported reactions of hydrazones, such as that shown in eq 12,[43] all involve radical cyclization. The substrates in most of these reactions are esters derived from (2,2-diphenylhydrazono)acetic acid (eq 13).[44,45]

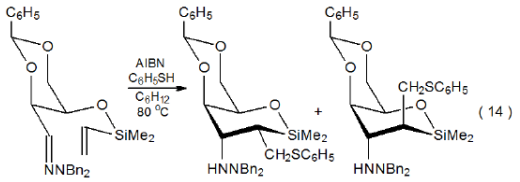


(12)



(13)

The reaction shown in eq 14 pictures a highly stereoselective cyclization involving a carbohydrate hydrazone.[46] Stereoselectivity in this reaction is determined by the preferred conformation (**37**, Figure 1) of the intermediate produced by a phenylthiyl radical adding to the carbon–carbon double bond in the substrate. Conformation **37** has the carbon–nitrogen bond *anti* to the adjacent carbon–oxygen bond. The conformation **38**, expected to be more stable because it has more pseudoequatorial substituents, is destabilized by dipole-dipole interactions arising from a gauche relation between the neighboring C=N and C–O bonds.[46]



(14)

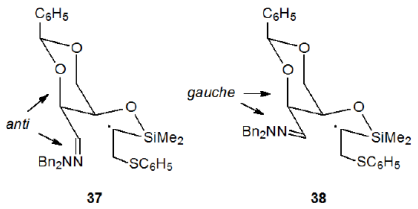
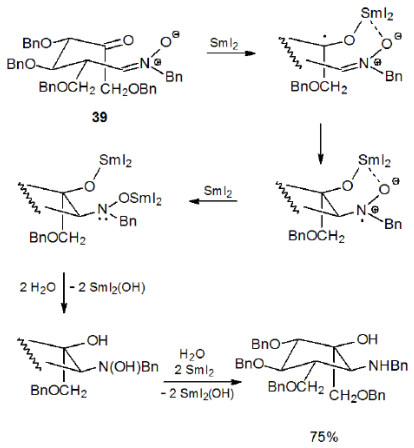


Figure 1. *Anti* and *gauche* conformations of a radical about to form a new ring

IV. Ketonitrones

The ketonitrone **39** undergoes radical cyclization when treated with excess SmI_2 (Scheme 11).[47] This reaction is similar to that shown in Scheme 9 for a related ketooxime. Both reactions depend upon electron transfer from SmI_2, and each produces a new five-membered ring. These reactions are stereoselective but their selectivity is controlled in different ways. In the reaction of the ketonitrone, samarium remains coordinated with the oxygen atoms in the two developing substituent groups during reaction. This coordination insures the stereoselective formation of a cyclopentane ring in which the OH and N(OH)Bn groups are cis-related (Scheme 11). Since similar coordination does not occur during ketooxime reaction (Scheme 9), the emerging OH and NHOBn groups are not held on the same side of the ring; in fact, due to the steric size of the groups attached to the bonding carbon atoms in the radical **31**, OH and NHOBn groups become trans-related in the product **32**.

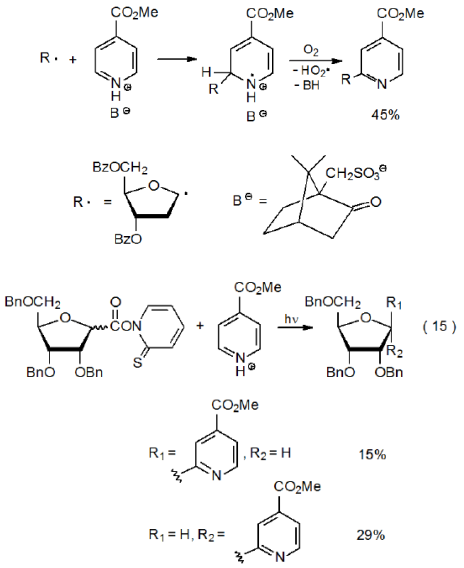
Scheme 11



V. Protonated Heteroaromatics

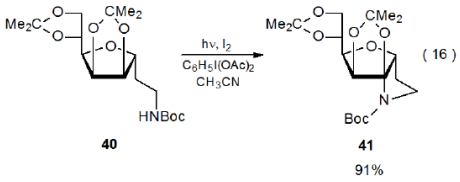
Pyranos-1-yl and furanos-1-yl radicals add to protonated heteroaromatics to produce *C*-nucleoside derivatives.[48–54] A proposed mechanism for this type of reaction is given in Scheme 12.[50] Protonation dramatically increases the rate of addition of a carbon-centered radical to a heteroaromatic compound; in fact, the rate is so fast that it is not necessary to conduct the reaction in an inert atmosphere. Not only does reaction take place in the presence of molecular oxygen but oxygen is a likely participant in the rearomatization stage of this process (Scheme 12). In reactions of this type the initially formed radical (R·) usually is generated by photolysis of an *O*-acyl-*N*-hydroxy-2-thiopyridone (eq 15).[48] (Reactions of *O*-acyl-*N*-hydroxy-2-thiopyridones are discussed in Chapter 13.)

Scheme 12



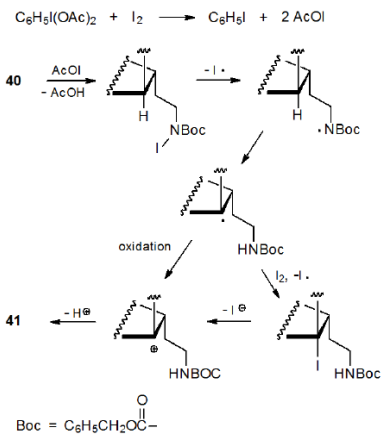
VI. Protected Amines

The benzyloxycarbonyl protected amine **40** reacts with (diacetoxyiodo)benzene–iodine to give a product (**41**) that contains a new ring system (eq 16).[55] The proposed mechanism for this reaction (Scheme 13) involves internal hydrogen-atom abstraction by a nitrogen-centered radical. Similar internal hydrogen-atom abstraction takes place when a nitrogen-centered radical is generated from a sulfonamidate.[56] Such reactions are reminiscent of the hydrogen-atom abstraction by alkoxy radicals described in Chapter 6.



40 **41** 91%

Scheme 13



VII. Summary

Carbon-centered radicals add to carbon–nitrogen double bonds in oxime ethers, hydrazones, ketonitrones, and protonated heteroaromatics. These reactions are regiospecific with addition occurring to the carbon atom in the double bond. The majority of such reactions involve oxime ethers and usually result in formation of a new ring. These cyclization reactions often are quite stereoselective. This is particularly true if an *O*-isopropylidene group is near the reactive center, in which case the nitrogen-containing substituent and the *O*-isopropylidene group in the product are on opposite sides of the new ring. Radical addition to protonated heteroaromatics is different from addition to other compounds containing carbon–nitrogen multiple bonds because addition is always followed by hydrogen-atom abstraction that rearomatizes the ring.

CHAPTER OVERVIEW

18: Compounds with Carbon–Carbon Multiple Bonds I: Addition Reactions

Earlier chapters in this book describe radical formation from reaction of various carbohydrate derivatives. Among the reactions of these radicals is addition to unsaturated compounds. The current chapter builds on earlier ones in that the discussion of radical addition reactions continues, but the focus in the present chapter is less on how radicals are formed and more on the process of their addition to compounds with carbon–carbon multiple bonds.

Topic hierarchy

II. Defining Characteristics of Radical Addition Reactions

III. Chain Reactions

IV. Nonchain Reactions: Radical Formation by Electron Transfer

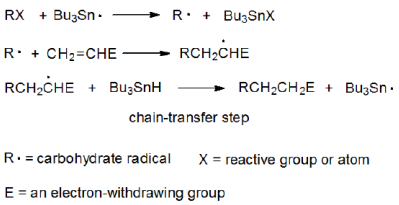
V. Summary

II. Defining Characteristics of Radical Addition Reactions

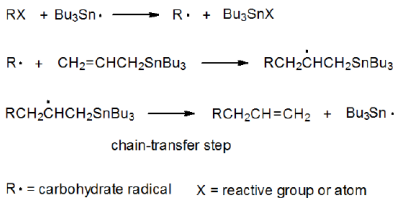
A. Reaction Mechanisms

Radical addition can take place by either chain or nonchain reaction. For each of these there are two variations on the basic reaction mechanism. For chain reactions (Schemes 1 and 2) each variation has a different type of chain-transfer step. For nonchain reactions both mechanisms involve electron transfer. They differ in that the transfer is either from (Scheme 3) or to (Scheme 4) an organometallic complex.

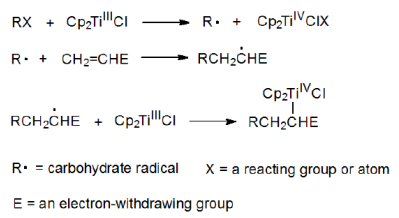
Scheme 1



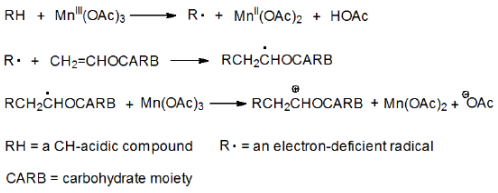
Scheme 2



Scheme 3



Scheme 4



1. Chain Reactions

Both mechanisms for radical addition by chain reaction have a propagation phase that begins with group or atom abstraction (Schemes 1 and 2). In each of these mechanisms $Bu_3Sn\cdot$ is shown as the abstracting radical, although other radicals [e.g., $(Me_3Si)_3Si\cdot$] are capable of filling this role. The defining difference between these two mechanisms is the chain-transfer step. In the reaction shown in Scheme 1 it is bimolecular, and in that in Scheme 2 it is unimolecular.

a. Bimolecular Chain Transfer

The distinguishing feature of a chain reaction that takes place by bimolecular chain-transfer is an elementary reaction between a radical and a nonradical that ends one propagation sequence and creates the radical that begins a new sequence. In the reaction shown in Scheme 1, chain transfer occurs when the adduct radical abstracts a hydrogen atom from Bu_3SnH to form the addition product RCH_2CH_2E and generate the chain-carrying radical $Bu_3Sn\cdot$.

b. Unimolecular Chain Transfer

Unimolecular chain transfer describes a reaction in which the chain-transfer step in a propagation sequence is an elementary reaction with a single reactant. The propagation steps for a typical, unimolecular, chain-transfer reaction are shown in Scheme 2, where the transfer step is a β-fragmentation that produces an unsaturated compound and a chain-carrying radical.

2. Nonchain Reactions

Schemes 3 and 4 each describe a mechanism for a reaction that has no repeating cycle. In the first of these (Scheme 3) the carbohydrate radical R· forms by electron transfer from a transition-metal complex (Cp_2TiCl) to a carbohydrate derivative. (Cp_2TiCl is one of several transition-metal complexes known to function as an electron donor in this type of reaction.) Radical reaction ends when a second molecule of Cp_2TiCl combines with an adduct radical to produce an unstable, carbometallic product. Products of this type undergo rapid, nonradical reaction (e.g., elimination of the elements of Cp_2TiClH to form a double bond).

In the second type of nonchain reaction (Scheme 4) radical formation occurs when the transition-metal complex donates an electron to a CH-acidic compound. The radical phase of the reaction ends with a second electron transfer, one that produces a carbocation. This cation undergoes rapid, nonradical reaction, such as capture by a molecule of solvent.

B. Selectivity in Addition Reactions

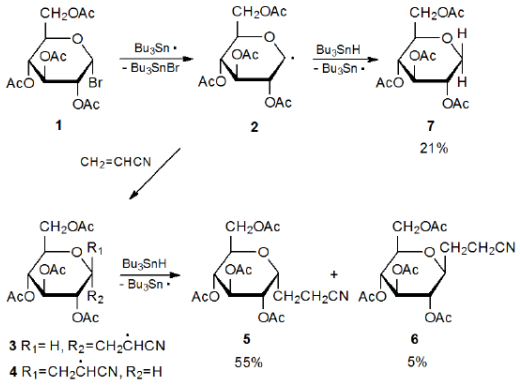
1. Chemoselectivity

Chemoselectivity is of consequence at two stages in a radical addition reaction. The first is in the radical forming step, where selectivity is determined by the reactivity of the functional groups present in a molecule of substrate. Forming the desired radical is accomplished at this stage by insuring that the radical precursor has the most reactive substituent attached to the carbon atom where the radical center is to be located. The next place at which selectivity potentially is of significance is during radical addition to the multiple bond. Chemoselectivity is meaningful at this time if there are two or more multiple bonds to which addition can occur.

2. Regioselectivity

Most radical addition reactions involving carbohydrates are regiospecific. Addition occurs exclusively at the less substituted carbon atom in a multiple bond. The way in which the pyranos-1-yl radical **2** adds to acrylonitrile is typical (Scheme 5).[1,2] The reactions in Tables 1 and 2 document a similar regiospecificity in the addition of **2** to other unsaturated compounds. The data in Tables 3-5 show that reactions of other pyranos-1-yl radicals exhibit similar reactivity. (All of these tables are located at the end of this chapter.)

Scheme 5



Both steric and polar effects have a role in determining regiospecificity in addition reactions. Steric effects become progressively more important as the effective size of the substituents near a multiple bond in an unsaturated compound increases and as the effective size of the adding radical increases. Polar effects exert themselves whenever a nucleophilic radical adds to an electron-deficient multiple bond, or an electrophilic radical adds to an electron-rich multiple bond. The extent of the influence of each effect depends upon the point at which the transition state is reached as a reaction progresses. For example, because addition of a nucleophilic radical to an electron-deficient multiple bond (the most common type of addition reaction) is exothermic, such a reaction should have an early (reactant-like) transition state[11] with minimal, new bond formation. When there is little new bond formation at the transition state, there is a diminished opportunity for steric interactions to affect regioselectivity. The situation with

polar effects is different because, as described in the next paragraph, they can exert considerable regioselective control in a reaction that has an early transition state.

For a reaction with an early transition state the molecular orbitals in the reactants do not change greatly by the time the transition state is reached. In such a situation frontier-orbital interactions are helpful not only in understanding why a reaction takes place but also in explaining reaction regioselectivity. Briefly, reaction occurs readily because the SOMO of the carbohydrate radical and the LUMO of the unsaturated reactant are energetically close enough for significant stabilizing interaction between the two at the transition state (Figure 1).[12,13] The extent of early bonding between a radical and the carbon atoms in a reacting multiple bond is a function of the magnitude of the atomic orbital coefficient at each carbon atom in the LUMO of the unsaturated reactant. Attaching an electron-withdrawing or electron-donating substituent to a multiple bond causes these coefficients to be quite unequal, a situation that leads to regiospecific reaction. For a polarized multiple bond such as that found in an α,β-unsaturated nitrile or carbonyl compound, regiospecific addition to the β-carbon atom reflects the greater magnitude of the atomic orbital coefficient at this atom in the LUMO when compared to the magnitude of the coefficient at the α carbon atom (Figure 1).

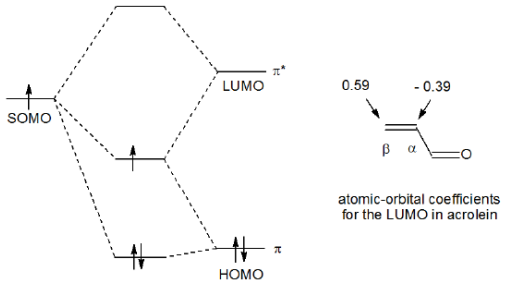


Figure 1. Frontier orbital interactions for addition of an unsubstituted, carbon-centered radical to an electron-deficient double bond

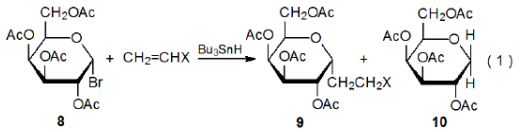
3. Stereoselectivity

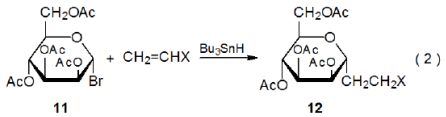
As described in the next several sections, stereoselectivity in radical addition reactions is determined by a combination of steric and stereoelectronic effects. The stereoelectronic effect of primary importance is the kinetic anomeric effect. Steric effects that have an impact on reaction stereoselectivity have various names, but they all depend on steric interactions favoring a particular approach of an unsaturated compound or a hydrogen-atom transfer to a radical center.

a. The Kinetic Anomeric Effect

The reaction between the pyranos-1-yl radical **2** and an unsaturated compound with an electron-deficient double bond is highly stereoselective (Scheme 5). Preferential reaction on the α face of the pyranoid ring in **2** is due, in large part, to the kinetic anomeric effect (discussed in Chapter 11 of Volume I). Stereoselectivity in the addition reactions of **2** also is affected by reaction conditions. The information in Table 1 includes several sets of conditions suitable for highly stereoselective reaction with little, competing simple reduction.

The selectivity observed in reactions of **2** extends to other D-hexopyranos-1-yl radicals. Reactions of the D-galacto- and D-manno-pyranosyl bromides **8** (eq 1) and **11** (eq 2), respectively, are at least as stereoselective as those of the corresponding D-gluco-pyranosyl bromide **1**. The data in Tables 3 and 4 confirm that reactions of **8** and **11** occur preferentially on the α face of the pyranoid ring.

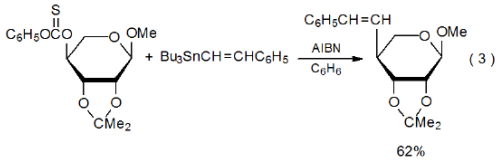




b. Steric Effects

(1). Group Shielding

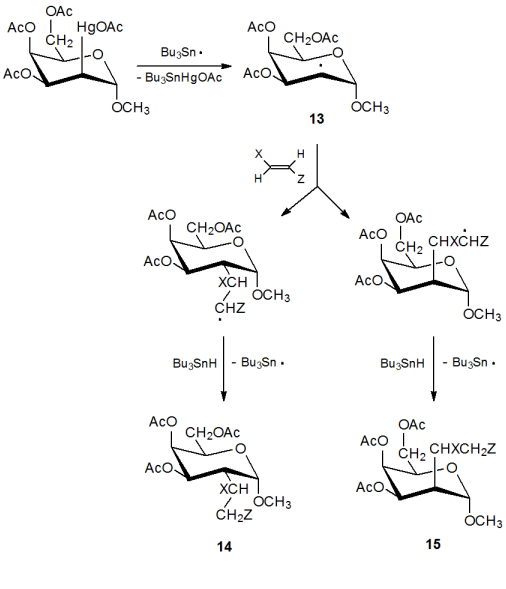
Group shielding causes preferential addition to the less-hindered face of a ring system. In the reaction shown in eq 3 the 2,3-*O*-isopropylidene group shields the α face of the radical centered at C-4 in the pyranoid ring from approach by the unsaturated reactant.[14]



(2). Size of the Unsaturated Reactant

The reaction shown in Scheme 6 illustrates the combined effect of steric size of the unsaturated reactant and group shielding of a radical by ring substituents.[15] In this reaction the amount of addition to the better shielded, β face of the pyranoid ring in the radical **13** decreases as the effective size of the unsaturated reactant increases. The data in Scheme 6 show that, even in a reaction with an early transition state, steric effects can have a significant role in determining reaction stereoselectivity if these effects are large enough.

Scheme 6

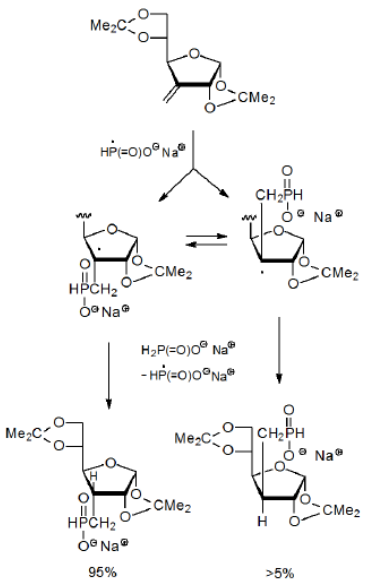


	14 + 15	14/15
X = H, Z = CN	67%	67/33
X = H, Z = CO_2CH_3	55%	71/29
X = Z = CN	55%	90/10
X = Z = CO_2CH_3	50%	97/3

(3). Size of the Hydrogen-atom transfer

Sometimes a reaction forms the less stable of two possible stereoisomers due to restricted approach of a hydrogen-atom transfer to a radical center in the product-forming step. In the reaction shown in Scheme 7, for example, the less hindered approach of sodium hypophosphite to the β face of the furanoid ring produces the less stable stereoisomer in greater the 95% yield.[16]

Scheme 7



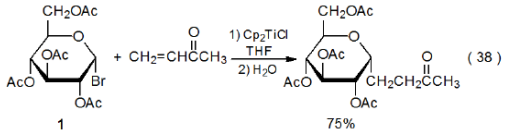
III. Chain Reactions

Radical addition that takes place by chain reaction naturally divides into three categories. These three are reactions in which (a) a carbohydrate radical adds to an unsaturated noncarbohydrate, (b) a noncarbohydrate radical adds to an unsaturated carbohydrate, and (c) both reaction participants are carbohydrates. Each group can be further divided into mechanistic type, a distinction based upon whether a reaction has a bimolecular or a unimolecular chain-transfer step.

IV. Nonchain Reactions: Radical Formation by Electron Transfer

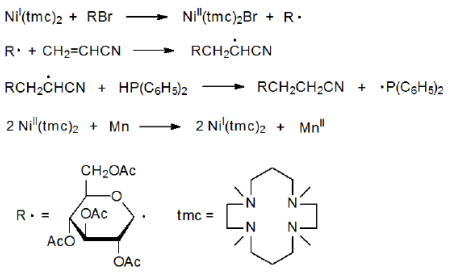
A. Transition-Metal Complexes as Electron Donors

As is indicated in Scheme 3, radical formation in a nonchain reaction often occurs by dissociative electron transfer from a transition-metal complex (e.g., Cp_2TiCl) to a halogenated carbohydrate. An example of such a reaction is shown in eq 38, where electron donation by Cp_2TiCl enables a pyranos-1-yl radical to be formed from the glycosyl bromide **1**; this radical then adds to methyl vinyl ketone.[181] Other reactions of this type, all of which are nonchain and involve pyranos-1-yl radicals generated from glycosyl bromides, are listed in Table 6.

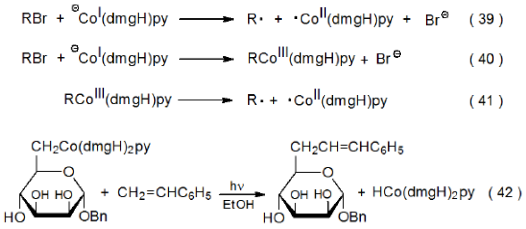


Although the reactions shown in Table 6 are nonchain in nature and, thus, do not require the typical addition of a catalytic amount of an initiator, they can be made catalytic in the transition-metal complex, if the metal ion in the complex is returned to its original oxidation state quickly after electron transfer. An example of a reaction taking place by such a process is found in Scheme 27, where Ni(I) is proposed to be continuously formed by reaction of Ni(II) with manganese metal.[25]

Scheme 27

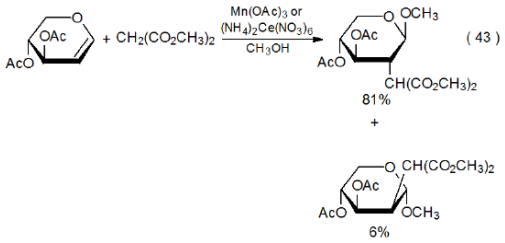


Cobalt is another transition metal capable of forming carbohydrate radicals by electron transfer.[183–187] An overall reaction showing electron donation by a cobalt complex is given in eq 39, but the transfer actually takes place in two, distinct steps (equations 40 and 41). Because many cobalt complexes of carbohydrates are stable enough to be isolated, the radical forming step for reactions of such compounds is carbon–cobalt bond homolysis (eq 41). Eq 42 describes a reaction in which a pyranos-1-yl radical, produced by C–Co bond homolysis, adds to a molecule of styrene.[184]



B. Transition-Metal Complexes as Electron Acceptors

Reaction of a CH-acidic compound such as $CH_2(CO_2CH_3)_2$ with $(NH_4)_2Ce(NO_3)_6$ [or $Mn(OAc)_3$] transfers an electron to the transition-metal complex to produce $\cdot CH(CO_2CH_3)_2$, an electron-deficient radical (Scheme 4).[188–192] This radical then adds to an electron-rich double bond, such as that found in a typical glycal (eq 43).[189] A similar glycal addition takes place with the electrophilic radical $CH_3NO_2\cdot$, which is formed by electron transfer from $CH_3NO_2^-$ to $(NH_4)_2Ce(NO_3)_6$.[193]



(43)

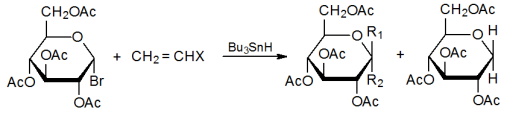
V. Summary

Radical addition to compounds with carbon–carbon multiple bonds can take place by several reaction mechanisms. The most common of these is a chain reaction that is characterized by a bimolecular, chain-transfer step. This type of reaction governs addition to unsaturated compounds of radicals centered on various carbon atoms in pyranoid and furanoid rings. These reactions are regiospecific and often highly stereoselective. Since most carbon-centered radicals, including those derived from carbohydrates, are nucleophilic, successful addition requires an electron-withdrawing substituent attached to one of the carbon atoms of the multiple bond. The primary limitation placed on this type of addition reaction is that it is in competition with a hydrogen-atom abstraction reaction that causes simple reduction of the carbohydrate derivative.

Addition reactions also can occur by unimolecular chain-transfer. This type of reaction also takes place with radicals centered on various carbon atoms in pyranoid and furanoid rings. Most of these reactions involve addition of a carbohydrate radical to an allylic or vinylic stannane followed by loss of a tin-containing substituent. An advantage to this type of reaction is that competition with simple reduction can be largely avoided. A disadvantage is that 1,3-tin migration can occur in allylic stannanes; such migration places a synthetic limitation on the usefulness of the reaction.

Although the unsaturated compound in a typical addition reaction is a noncarbohydrate, addition also occurs to unsaturated carbohydrates. The carbon–carbon double bond in such reactions usually is part of an enol ether or an α,β-unsaturated ketone or lactone and the product is often a *C*-disaccharide.

Most addition reactions to carbon–carbon triple bonds involve a tri-*n*-butyltin radical adding to a triple bond in a carbohydrate. The structures of the carbohydrates are such that the vinylic radicals produced often undergo a cyclization reaction.



$R_1 = H, R_2 = CH_2CH_2CN$ **5**

$R_1 = CH_2CH_2CN, R_1 = H$ **6**

initiator	solvent	temp(°C)	product yields (%)			ref
X = CN			**5**	**6**	**7**	
hν	Et_2O	35	55	5	21	1
AIBN, hν	*t*-BuOH	35	79	T	6	3, 4
AIBN	C_6H_6	78	32	2	18	5, 6
V-70 (1.2eq)	Et_2O	25	68	ND	T	5, 6
V-70 (0.1eq)	Et_2O	25	41	ND	27	5, 6
Et_3B	Et_2O	25	18	ND	T	5, 6
X = CO_2CH_3						
hν			41	4	4	5, 6
V-70			59	ND	T	5, 6
V-70	Et_2O	25	30	ND	T	5, 6
X = $C(=O)CH_3$						
AIBN	C_6H_6		80	40	24	7
X = $P(=O)(OEt)_2$						
AIBN, hν	*t*-BuOH	35	70	ND	ND	3, 4
X = $P(=O)(OMe)_2$						
hν	Et_2O	35	44	3	a	9

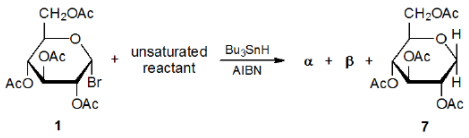
T = trace

ND = not detected

[a]present but yield not reported

V-70 = $CH_3OCC(CH_3)(CH_3)CH_2CN{=}NCCH_2C(CH_3)(CH_3)COCH_3$ (CN groups)

Table 1. Addition reactions of the D-glucopyranosyl bromide **1**

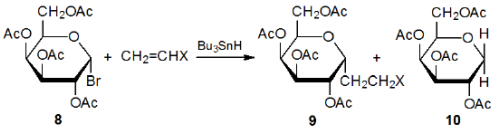


unsaturated reactant	solvent	product yields (%)			ref
		α	β	7	
$MeCO_2CH=CHCO_2Me$	C_6H_6	21	9	26	7
$CH_2=C(CO_2Bn)NHC(=O)OBn$	$C_6H_5CH_3$	61	ND	ND	8
$CH_2=C(CO_2Et)_2$	$C_6H_5CH_3$	99	ND	ND	10

α = adduct from α-face addition β = adduct from β-face addition

ND = not detected

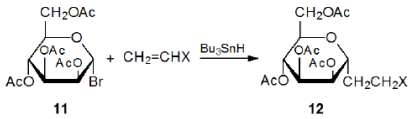
Table 2. Addition reactions of the D-glucopyranosyl bromide **1**



X	conditions	product yield(%)		ref
		9	**10**	
CN	V-70[a]	67	14	5, 6
CN	hν	70	ND	1
CO_2CH_3	V-70[a]	30	14	6
$P(=O)(OEt)_2$	hν/AIBN	76	ND	3, 4
$P(=O)(OEt)_2$	hν	20	T	9

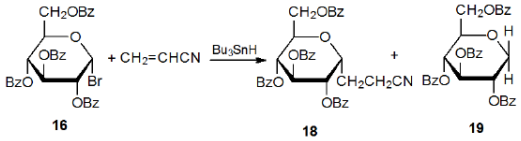
[a]The structure of V-70 is given in Table 1.

Table 3. Addition reactions of the D-galactopyranosyl bromide **8**



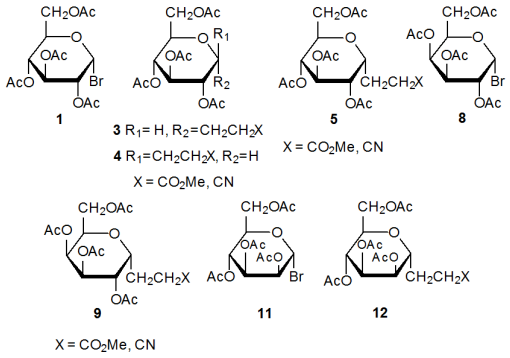
X	conditions	% yield of **12**	ref
CN	hν/Et_2O	65	1
$P(O)(OEt)_2$	hν/AIBN	68	3, 4
$P(O)(OEt)_2$	hν/Et_2O	38	9

Table 4. Addition reactions of the D-mannopyranosyl bromide **11**



initiator	solvent	temp (°C)	product yield(%)		ref
			18	**19**	
hν	Et_2O	25	69	27	5, 6
AIBN	C_6H_6	78	36	52	5, 6
AIBN	Et_2O	35	16	75	5, 6
hν	Et_2O	35	28	63	5, 6

Table 5. Addition reactions of the bromide **16** to acrylonitrile



starting materials	reagents and conditions	product yield (%)					ref
		3	**4**	**5**	**9**	**12**	
1 + CH_2=CHCN	Ni^{2+}/Mn/THF	76	ND	ND	--	--	25
1 + CH_2=$CHCO_2$Me	Ni^{2+}/Mn/THF	69	ND	ND	--	--	25
1 + CH_2=CHCN	Cp_2TiCl/THF	62	ND	ND	--	--	181
1 + CH_2=$CHCO_2$Me	Cp_2TiCl/THF	55	ND	a	--	--	181
1 + CH_2=$CHCO_2$Me	Cp_2TiCl/THF	75	ND	ND	--	--	181
1 + CH_2=CHCN	$FeCp_2(CO)_4$/THF	50	7	ND	--	--	182
8 + CH_2=$CHCO_2$Me	Ni^{2+}/Mn/THF	--	--	--	69	--	25
8 + CH_2=CHCN	Cp_2TiCl/THF	--	--	--	52	--	181
8 + CH_2=CHCN	$FeCp_2(CO)_4$/THF	--	--	--	53	--	182
11 + CH_2=CHCN	Ni^{2+}/Mn/THF	--	--	--	--	49	25
11 + CH_2=$CHCO_2$Me	Ni^{2+}/Mn/THF	--	--	--	--	62	25

[a]present but yield not reported ND = not detected

Table 6. Addition reactions promoted by transition-metal complexes

CHAPTER OVERVIEW

19: Compounds With Carbon–Carbon Multiple Bonds II: Cyclization Reactions

The structural requirements for a molecule destined to undergo radical cyclization are that it contain a substituent from which a radical (almost always a carbon-centered one) can be generated and that it have a properly positioned multiple bond. Carbohydrates that meet these requirements include unsaturated iodides, bromides, thionocarbonates, cyclic thionocarbonates, xanthates, and phenyl selenides. Ring formation in the reactions of these compounds usually is regiospecific and often highly stereoselective.

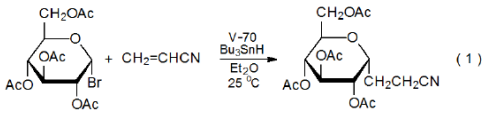
Topic hierarchy

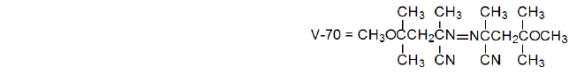
II. Ease of Reaction between a Carbon-Centered Radical and a Multiple Bond
III. Reaction Selectivity
IV. Unsaturated Carbohydrates That Undergo Radical Cyclization
V. An Organization for Carbohydrates That Undergo Radical Cyclization
VI. Summary

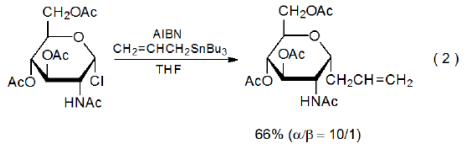
II. Ease of Reaction between a Carbon-Centered Radical and a Multiple Bond

Once structural requirements have been met, successful radical cyclization depends on reaction rates. The basic question is “Will ring formation occur before competing reactions intervene?” The answer to this question depends upon the nature of the radical center and multiple bond and on the separation between these two. The ability of a radical to add to a multiple bond to form a new ring will be addressed first; then, the effect of the separation between the radical center and the multiple bond will be considered.

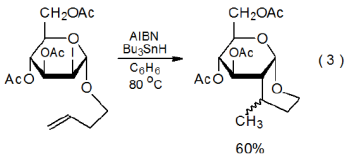
A beginning point for discussing reactivity between a radical center and a multiple bond during internal addition is to recall some of the findings in Chapter 18 about addition reactions that are not internal. Such reactions take place rapidly when a radical is nucleophilic (as are most carbon-centered radicals) and a multiple bond is electron-deficient. This description fits the reaction shown in eq 1.[1,2] If a multiple bond is not electron-deficient, radical addition normally is too slow to compete with hydrogen-atom abstraction; however, minimizing or eliminating effective hydrogen-atom transfers from a reaction mixture can enable addition to occur even when the multiple bond is not electron-deficient. An example of this type of reaction is shown in eq 2, where Bu_3SnH is not present in the reaction mixture even though $Bu_3Sn\cdot$ is there and acts as the chain-carrying radical.[3,4]







Addition of a radical to a multiple bond is potentially much faster when the reaction is intramolecular. If a radical center and a multiple bond in a molecule are positioned so that they frequently come within bonding distance, the rate of internal addition increases to the point that even for a multiple bond that is not electron-deficient, cyclization competes effectively with hydrogen-atom abstraction. In the reaction shown in eq 3, internal addition to a double bond that is not electron-deficient takes place even in the presence of Bu_3SnH.[5]



III. Reaction Selectivity

Chemoselectivity, regioselectivity, and stereoselectivity are defining characteristics of radical reactions. Nowhere are they more important (particularly the latter two) than when a new ring is being formed. Understandably then when regioselectivity and stereoselectivity were broached in Chapters 10 and 11, discussion often turned to cyclization reactions. Some of the ideas and topics from these chapters are revisited here but now with an exclusive focus on their importance to new ring formation.

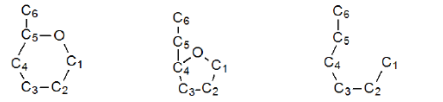
Chapters 10 and 11 of Volume I - pdf

IV. Unsaturated Carbohydrates That Undergo Radical Cyclization

The unsaturated carbohydrates that undergo radical cyclization are an eclectic mixture of compounds in which the reactive multiple bond in each typically is electron-deficient. Reduced electron density in the multiple bond can be caused either by conjugation of this bond with a carbonyl group or by having an electronegative substituent attached to it. Ring formation still can occur when a double or triple bond is not electron-deficient, but as described earlier in this Chapter (Section II), in such a situation cyclization is slower and less able to compete with other radical reactions.

V. An Organization for Carbohydrates That Undergo Radical Cyclization

It is useful in organizing radical cyclization reactions to divide them into groups that have common features. One method for doing this places radicals of similar structure together. Where carbohydrates are concerned, such a plan can be based on the location of the radical center and the multiple bond. A radical center can exist on an atom that is part of the molecular framework (Figure 1) or part of a substituent group. The same possibilities exist for the multiple bond. Cyclization reactions of carbohydrates then naturally divide into the four basic types shown in Figure 2. (A short-hand terminology describing these four types has been proposed[45] and is included in Figure 2.) This division provides the basis for constructing Tables 1-4. In addition to these four tables, two smaller ones are included in recognition of the importance of radical cyclization reactions in the synthesis of nucleosides (Table 5) and carbon-linked disaccharides (Table 6.)



The framework in a typical sugar has one of the three structural types shown above. (A hexose is used as an example.) A framework radical is one centered on a numbered carbon atom, and a framework multiple bond is one involving at least one of these atoms.

Figure 1. Possible carbohydrate frameworks

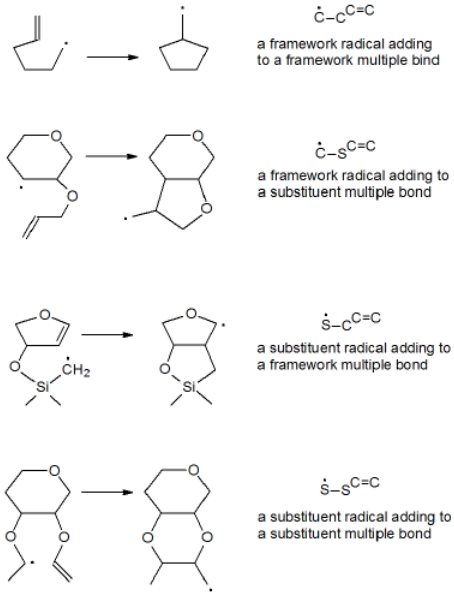


Figure 2. Possible types of cyclization reaction for carbohydrate derivatives

Table 1. Framework Radical Reacting With a Framework Multiple Bond

radical forming substituent	type of multiple bond	number of atoms in the new ring	references
I	$-CH=CHCH_2O-$	5	164, 182
I	$CH_2=CHCH(-)-O-$	5	54, 55
I	$CH_2=CHCH(-)-O-$	6	168
I	$CH_2=CHCH(-)-O-$	7	61, 168
I	$-CH=CHCH(-)-O-$	5	49
I	$-CH=CHCO_2R$	5	60, 64, 68, 69, 85, 92, 164
I	$-CH=CHCO_2Et$	6	91, 92
I	$-CH=CHCO_2Me$	7	61
I	$HC\equiv CCH(-)-O-$	5	171, 172, 185
I	$HC\equiv CCH(-)-O-$	6	186
I	$HC\equiv CCH(-)-O-$	7	61
I	$C_6H_5C\equiv CCH(-)-O-$	6	171, 174
I	$C_6H_5C\equiv CCH(-)-O-$	7	61
I	$Me_2SiC\equiv CC(-)-O-$	5	172
I	$-C\equiv CCO_2Me$	5	172
Br	$-C(-)=CHCO_2R$	5	62, 66, 67, 69, 70, 84, 91, 93
Br	$-CH=CHCO_2Me$	5	87, 89
Br	$-CH(-)-CH=CH-C(-N-)CO$	5	166
MeSC(=S)O–	$CH_2=CHCH_2-$	5	208, 210
MeSC(=S)O–	$CH_2=CCH(-)-O-$	6	22
MeSC(=S)O–	$CH_2=CHCH=CH-$	5	207
MeSC(=S)O–	$-CH=CH-O-$	5	210

Table 1. Framework Radical Reacting With a Framework Multiple Bond (Continued)

radical forming substituent	type of multiple bond	number of atoms in the new ring	references
MeSC(=S)O–	–CH=CHCO$_2$Me	5	210
C$_6$H$_5$OC(=S)O–	CH$_2$=CCH–O–	5	22, 201
C$_6$H$_5$OC(=S)O–	CH$_2$=CCH–O–	6	22, 201
C$_6$H$_5$OC(=S)O–	HC≡CCH–O–	5	178, 181
C$_6$H$_5$OC(=S)O–	HC≡CCH–O–	6	179, 180, 219
C$_6$H$_5$OC(=S)O–	C$_6$H$_5$C≡CCH–	6	175, 176
ImC(=S)O–	CH$_2$=CHCH–O–	5	51, 160, 213
ImC(=S)O–	–OCH=CH–	5	51, 160, 213
ImC(=S)O–	HC≡CCH–O–	5	181
	–CH=CHCO$_2$Me	5	57, 63, 65, 83
	–CH=CHCO$_2$R	5	70, 89
	–CH=CHCO$_2$Me	6	88
	HC≡CCH$_2$–	5	202
	–CH=CCO$_2$*t*-Bu	6	86
	–CH=CHCH=CH$_2$	5	207
C$_6$H$_5$S–	CH$_2$=CHCH–O–	5	158
C$_6$H$_5$S–	CH$_2$=CHCH$_2$–	6	158

Table 1. Framework Radical Reacting With a Framework Multiple Bond (Continued)

radical forming substituent	type of multiple bond	number of atoms in the new ring	references
C$_6$H$_5$S–	–C≡CCH–O–	5	158
MeOC$_6$H$_4$Te–	–CH=CHCO$_2$Et	5	77
H$_2$C=C–	–CH=CHCO$_2$R	5	75, 76
HC≡C–	–CH=CHCH–O–	6	166
HC≡C–	CH$_2$=CHCO–	6	22
HC≡C–	CH$_2$=CHCH–O–	6	196, 201
HC≡C–	–CH=CHCO$_2$Me	7	61

Table 2. Framework Radical Reacting With a Substituent Multiple Bond

radical forming substituent	type of multiple bond	number of atoms in the new ring	references
I	$CH_2{=}C(\mathrm{CH}){-}O{-}$	5	5, 136, 144, 189
I	$CH_2{=}C(\mathrm{CH}){-}O{-}$	6	206
I	$CH_2{=}CHCH_2O{-}$	6	5, 152
I	$CH_2{=}CHCH_2{-}$	6	204
I	$Me_3SiCH{=}C(\mathrm{CH}){-}O{-}$	5	189
I	$CH_2{=}C(\mathrm{SiO})$	5	114
I	$(CH_3)_3CCH{=}CHCH_2O{-}$	5	9
I	$C_6H_5CH{=}CHCH_2O{-}$	5	9, 144, 169, 170
I	$-CH{=}CHCO_2Et$	4	27
I	$-CH{=}CHCO_2Et$	5	91
I	$-CH{=}CHCO_2Et$	6	60, 91
I	$-CH{=}CHCO_2Et$	5 + 6	82
I	$-CH{=}CHCO_2-$	5	112
I	$-CH{=}CHC(=O)NH-$	6	96, 97, 99, 100
I	$-CH{=}CHC(\mathrm{CH}){=}CHC(=O)NH-$	5	107
I	$HC{\equiv}CCH_2O{-}$	5	5, 152
I	$C_6H_5C{\equiv}CCH_2{-}$	6	152
I	$Me_3SiC{\equiv}C(\mathrm{CH}){-}O{-}$	5	177, 189
I	$-C{\equiv}CCH_2O{-}$	5	152
Br	$CH_2{=}CHCH_2O{-}$	5	143, 144, 145, 149
Br	$CH_2{=}CHCH_2{-}$	6	203, 206, 209
Br	$CH_2{=}CHC(Me)_2O{-}$	5	148
Br	$CH_2{=}C(\mathrm{SiO})$	5 + 6	123

Table 2. Framework Radical Reacting With a Substituent Multiple Bond (Continued)

radical forming substituent	type of multiple bond	number of atoms in the new ring	references
Br	$-CH=\underset{\displaystyle CO_2-}{\overset{|}{C}}H-$	5	143
Br	$-CH=CHCO_2Et$	5	27
Br	$-CH=CHCO_2R$	6	27, 203
Br	$-CH=CHCO_2Et$	7	27
Br	$-\underset{\displaystyle CHCO_2Me}{\overset{|}{C}}=CH-$	5	84
Br	$HC\equiv CCH_2O-$	5	143, 148, 151
Br	$HC\equiv CCH_2-$	6	143, 151
Br	$-C\equiv CCH_2O-$	5	143
Br	$-C\equiv CCHO$	5	109
Br	$-CH=\underset{\displaystyle CHC(=O)NH-}{\overset{|}{C}}-CH=CH-$	5	102-106, 108
Br	$-CH=\underset{\displaystyle CC(=O)NH-}{\overset{|}{C}}-CH=$	6	99
C_6H_5Se	$CH_2=\underset{\displaystyle SiO-}{\overset{|}{C}}H-$	5 + 6	11, 12, 113-116
C_6H_5Se	$CH_2=\underset{\displaystyle SiO-}{\overset{|}{C}}H-$	5	115, 116, 119
C_6H_5Se	$CH_2=\underset{\displaystyle SiO-}{\overset{|}{C}}H-$	6	13, 28, 118
C_6H_5Se	$CH_2=\underset{\displaystyle SiO-}{\overset{|}{C}}H-$	8	36
C_6H_5Se	$CH_2=CHCH_2\underset{\displaystyle SiO-}{\overset{|}{C}}H-$	7	24, 28, 29
C_6H_5Se	$CH_2=CHCH_2\underset{\displaystyle SiO-}{\overset{|}{C}}H-$	9	36
C_6H_5Se	$CH_2=\underset{\displaystyle CH-O-}{\overset{|}{C}}H-$	5	161
C_6H_5Se	$CH_2=CHCH_2O-$	6	140, 157
C_6H_5Se	$-\underset{\displaystyle CHCH_2O-}{\overset{|}{C}}=$	5	139, 140
C_6H_5Se	$CH_2=CHCH_2O-$	5	58, 134, 135, 138, 139, 146, 157
C_6H_5Se	$-\underset{\displaystyle CHCH_2NH-}{\overset{|}{C}}=$	5	10

Table 2. Framework Radical Reacting With a Substituent Multiple Bond (Continued)

radical forming substituent	type of multiple bond	number of atoms in the new ring	references
C_6H_5Se	$CH_2{=}CHCH_2NH-$	5	10, 167
C_6H_5Se	$-CH{=}CHCO_2-$	6	140
C_6H_5Se	$-CH{=}CHC(=O)N-$	6	95
C_6H_5Se	$Me_3SiC{\equiv}C\overset{\vert}{S}i-$	5	121
C_6H_5Se	$Me_3SiC{\equiv}CCH_2O-$	5	134
C_6H_5Se	$HC{\equiv}CCH_2O-$	5	58, 134, 135, 138, 139, 146, 157
C_6H_5Se	$RC{\equiv}CCH_2O-$	7	173
$CH_3SC(=O)O$	$CH_2{=}CHCH_2O-$	5	141, 142
$CH_3SC(=O)O$	$CH_2{=}CH\overset{\vert}{C}H-O-$	5	165
$CH_3SC(=O)O$	$HC{\equiv}CCH_2O-$	5	149, 150, 154, 155
$C_6H_5OC(=S)O$	$CH_2{=}CHCH_2O-$	5	157
$C_6H_5OC(=S)O$	$CH_2{=}CH\overset{\vert}{C}{=}N-$	6	220
ImC(=S)O	$-CH{=}CHCO_2-$	5	72, 73, 74
$ArSO_2$	$CH_2{=}CH\overset{\vert}{S}iO-$	5	117
$C_6H_5SO_2$	$CH_2{=}CHCH_2O-$	5	137
$ArSO_2$	$RC{\equiv}C\overset{\vert}{S}iO-$	5	117
$C{\equiv}CH$	$-OCH{=}CHCO_2Et$	5	199
$C{\equiv}CH$	$-OCH{=}CHCO_2Et$	6	199
$C{\equiv}CH$	$-OCH{=}CHCO_2Et$	7	199
$C{\equiv}CH$	$-OCH{=}CHCO_2Et$	8	199
NO_2	$HC{\equiv}CCH_2O-$	5	153
C(=O)H	$-CH{=}C\overset{\vert}{C}C(=O)NH-$	6	101

Table 3. Substituent Radical Reacting With a Framework Multiple Bond

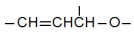
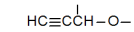
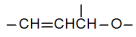
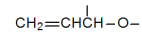
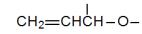
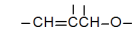
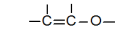
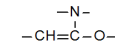
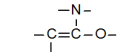
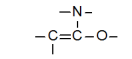
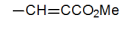
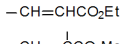
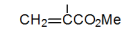
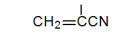
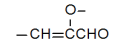
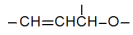
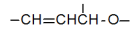
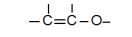
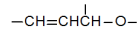
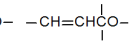
radical forming substituent	type of multiple bond	number of atoms in the new ring	references
I		5	21, 6, 7,109, 159
I		6	6, 7
I		5	185
Br		5	21, 81, 109,124-127, 129,132, 159, 163
Br		6 + 7	184
Br		8	37
Br		6	130
Br		5	124, 133, 183, 211, 212, 214, 218
Br		6	23
Br		5 + 6	23, 215, 217
Br		5	23, 216
Br		5	71
Br		6	7
Br		9	94
Br		9	94
Br		5	109
Cl		5	152, 162
–C≡CH		5	21, 190-193, 195
–C≡CH		5	192, 214
–CH_2C≡CH		5	195
$C_6H_5C(=S)O$–		5	221

Table 4. Substituent Radical Reacting With a Substituent Multiple Bond

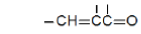
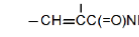
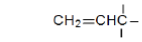
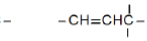
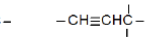
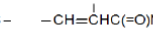
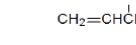
radical forming substituent	type of multiple bond	number of atoms in the new ring	references
I		5	110, 111
I	CH_2=CH–	5	111
I		5	98
I	–CH=CHCO_2–	10	44
Br	CH_2=CHCH_2O–	11	45
Br		6	111, 205
Br	HC≡CCH_2O–	5	156
HC≡C–	CH_2=CHCH_2O–	5 + 6	194
HC≡C–		5	197, 198
HC≡C–		5	197
HC≡C–	$(CH_3)_2$C=CHCH_2O–	5 + 6	194
HC≡C–		6	200
	CH_2=CH	6	147

Table 5. Nucleoside Synthesis

radical forming substituent	type of multiple bond	number of atoms in the new ring	references
Br	–CH=CHCO_2Et	5	80
C_6H_5Se	–CH=CHCO_2Me	5	50
$C_6H_5OC(=S)O$	–CH=CHCO_2Et	5	79

Table 6. Carbon-Linked Saccharides

radical forming substituent	type of multiple bond	number of atoms in the new ring	references
I	$-CH=C(I)CH-O-$	5	9
I	$CH_2=C(I)CO-$	8	33
I	$CF_2=C(I)CO-$	8	31
C_6H_5Se	$CH_2=C(SeC_6H_5)CH-O-$	7	30
C_6H_5Se	$CH_2=C(SeC_6H_5)CH-O-$	8	31, 32, 35, 38, 43
C_6H_5Se	$CH_2=C(SeC_6H_5)CH-O-$	9	38-41, 43, 46
C_6H_5Se	$CH_2=C(SeC_6H_5)CH-O-$	11	38
C_6H_5Se	$CH_2=C(SeC_6H_5)CO-$	8	33, 34
$C_6H_5SO_2$	$CH_2=C(SO_2C_6H_5)CH-O-$	9	42
$C_6H_4NSO_2$	$-SiC(SO_2C_6H_4N)\equiv CCH-O-$	5	117

VI. Summary

Forming a new ring by internal addition of a carbon-centered radical to a multiple bond is a powerful tool in carbohydrate synthesis. Regioselectivity and stereoselectivity are vital aspects of this type of reaction. Being able to predict regioselectivity is critical because a cyclization reaction potentially can form rings of two sizes. Since the newly formed ring nearly always has an additional chiral center (sometimes two), understanding stereoselectivity is essential in predicting stereochemistry in the cyclic product.

Compounds with five-membered rings are the ones most often produced by radical cyclization. Reactions that form five-membered rings are capable of generating six-membered rings also, but rarely do so because the transition state leading to the larger ring has greater ring strain. Compounds with six-membered rings are the major products when cyclization is capable of forming either six- or seven-membered rings consisting only of second row elements. Larger rings (seven or more members) are created when a radical center and a distant multiple bond are linked by a tether, usually one containing a silicon–oxygen bond.

The stereoselectivity of reactions that produce five- and six-membered rings usually can be rationalized by assuming that the reaction passes through a chair-like transition state. The lowest energy transition state for such a reaction has as many substituents as possible in pseudoequatorial positions. A variety of factors (pseudo-1,3-diaxial interaction, allylic strain, hydrogen bonding, conformation of an existing ring) affect transition-state energy and can, on occasion, cause a boat-like transition state to be more stable than a chair-like one.

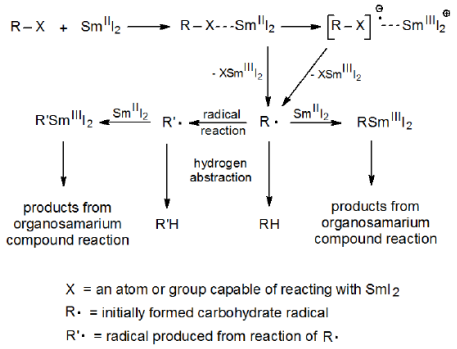
Various types of unsaturated carbohydrates, often α,β-unsaturated esters, undergo radical cyclization. Also prominent among reactive compounds are those in which the radical-forming part of the molecule and the portion containing the multiple bond are connected by a silicon–oxygen tether. A third group of compounds that cyclize readily includes allyl and propargyl ethers and related compounds.

CHAPTER OVERVIEW

20: Reactions of Samarium(II) Iodide With Carbohydrate Derivatives

Samarium(II) iodide (SmI_2) reacts with a variety of carbohydrate derivatives (including halides, sulfones, aldehydes, ketones, α-acyloxy esters, and α-acyloxy lactones) to generate carbon-centered radicals by nonchain, electron-transfer reaction.[1–9] These radicals undergo reactions that include hydrogen-atom abstraction and ring formation, and they combine with SmI_2 to produce organosamarium compounds (Scheme 1). Organosamarium compounds are quite reactive and easily undergo elimination and protonation reactions, as well as addition to aldehydes and ketones.

Scheme 1



X = an atom or group capable of reacting with SmI_2
R• = initially formed carbohydrate radical
R'• = radical produced from reaction of R•

Topic hierarchy

II. Radical Formation
III. Formation of Organosamarium Compounds
IV. Reactions of Organosamarium Compounds
V. Cyclization Reactions
VI. Radical Addition and Hydrogen-Atom Abstraction
VII. Comparison of Reactions of Chromium(II) Reagents With Those of Samarium(II) Iodide
VIII. Summary

II. Radical Formation

A. Reaction Mechanism

Radical formation begins when SmI_2 coordinates with a substituent in a carbohydrate derivative (Scheme 1), that is, when a carbohydrate derivative replaces a solvent molecule within the coordination sphere of samarium(II) iodide. Within this new complex an electron is transferred from SmI_2 to the carbohydrate derivative to produce a radical anion. This radical anion dissociates rapidly to give a carbohydrate radical and an anion complexed with SmI_2. It is possible in some instances that the radical anion never actually forms; instead, the bond between the carbohydrate and the functional group breaks during electron transfer.[3] [Section II.C.3 of Chapter 3 in Volume I contains additional information about samarium(II) iodide and the complexes it forms.]

B. Effect of HMPA

Reaction with SmI_2 typically is conducted in tetrahydrofuran (THF). Adding the cosolvent hexamethylphosphoramide (HMPA) to the reaction mixture dramatically increases the rate constant for samarium(II) iodide reaction.[10,11] Since the redox potential (E^o) of Sm^{2+}/Sm^{3+} increases from -1.33 V to -2.05 V with the addition of four equiv of HMPA to a THF solution of SmI_2,[12] the rate enhancement brought about by added HMPA can be attributed to the substantially increased ability of SmI_2 to donate an electron. (Addition of HMPA beyond four equivalents does not further increase reaction rates.[10])

One explanation for the effect of HMPA on the reactivity of SmI_2 is based on the energies of the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals pictured in Figure 1.[13] (In the reaction represented in this diagram it is assumed that the substrate is a phenyl sulfone.) When HMPA complexes with SmI_2, it raises the HOMO energy of the resulting complex and, in so doing, reduces the energy required for electron transfer to the σ* orbital (LUMO) of the sulfone (Figure 1). This energy reduction translates into a larger rate constant for reaction. HMPA also increases the rate of reaction of SmI_2 with halogenated compounds by elongating the carbon–halogen bond.[11b]

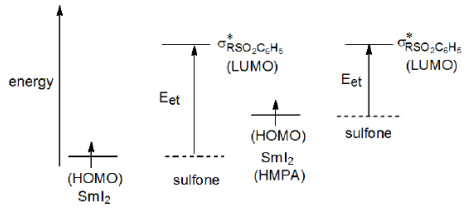
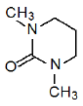


Figure1. Effect of HMPA on the HOMO energy of SmI_2

Radical formation by reaction of samarium(II) iodide with carbohydrate derivatives has been conducted under a variety of conditions.[14–18] In addition to HMPA, other additives used are DMPU (**1**),[14] ethylene glycol,[19] and visible light.[17] Alternative conditions also include reaction with HMPA in the presence of a proton donor[14–18] or a catalytic amount of nickel(II) halide.[9,17] Motivation for trying new reaction conditions comes from the possibilities of gaining greater understanding of the reaction mechanism, improving product yields, developing greater stereoselectivity, and finding a promoter for SmI_2 reaction that is safer than HMPA.



1
DMPU

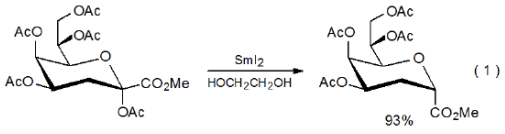
III. Formation of Organosamarium Compounds

At some point after its formation a carbohydrate radical will combine with a molecule of SmI_2 to produce an organosamarium compound. The radical combining with SmI_2 sometimes is the one initially formed and other times is one produced by reaction of the initially formed radical. Because carbon-centered radicals react rapidly with SmI_2 ($k = 7.0 \times 10^6\ M^{-1}s^{-1}$ for reaction of the 5-hexenyl radical with SmI_2 at 25 ^oC in the presence of five equiv of HMPA),[10] only a limited number of radical reactions are fast enough to take place before an organosamarium compound forms. (Even those that are fast enough produce new radicals that are destined to be captured by SmI_2.) Organosamarium compounds are quite reactive and, consequently, rarely isolated. Evidence for their existence takes the form of characteristic reactions (e.g., proton transfer, β elimination, and addition to a carbonyl compound). To understand the outcome of reactions begun by transfer of an electron from SmI_2 to a carbohydrate derivative, it is necessary to be familiar with the reactions of organosamarium compounds.

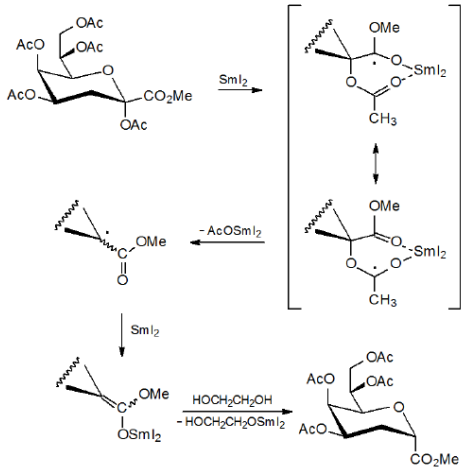
IV. Reactions of Organosamarium Compounds

A. Protonation

Accepting a proton from a suitable donor is a characteristic reaction of an organosamarium compound.[19–28] Lactones with α substituents[19–23] and esters that are similarly substituted[22,25] are common substrates in this type of reaction. Equation 1 describes a typical example.[22] A mechanism for the reaction shown in eq 1 is proposed in Scheme 2. Tosylates[26] and sulfones[27] also form organosamarium compounds that readily protonate.



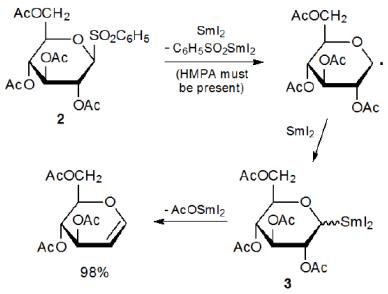
Scheme 2



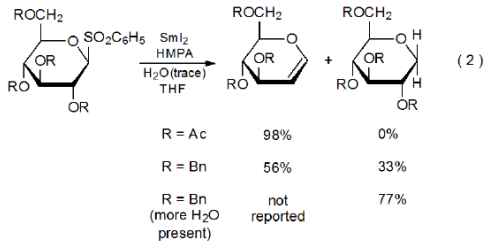
B. β Elimination

Another characteristic reaction of organosamarium compounds is eliminating a samarium-containing group along with a substituent on a neighboring carbon atom to form a compound with a carbon–carbon double bond.[19,20,27,29–32] An example of a reaction in which this happens is shown in Scheme 3, where the glycosyl phenyl sulfone **2** reacts with SmI_2 to give the organosamarium intermediate **3**, from which β elimination produces the corresponding glycal.[27]

Scheme 3



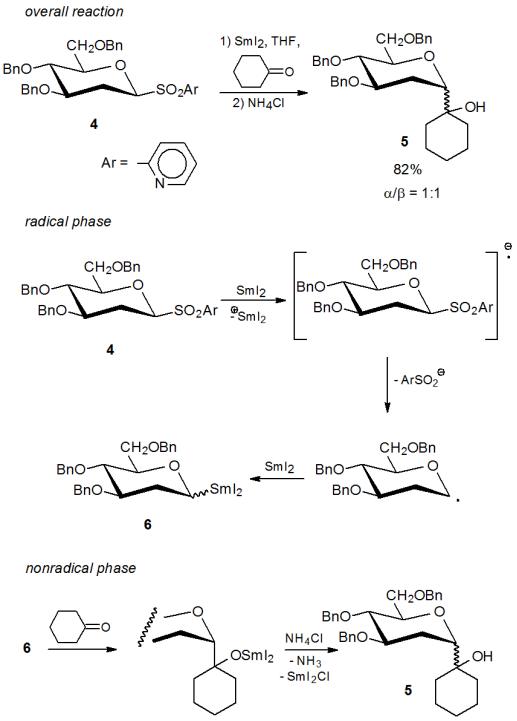
In the reactions of glycosyl phenyl sulfones with SmI_2 the amount of glycal formed depends upon how well the departing, C-2 substituent supports a negative charge. In the reaction shown in eq 2 the compound with the *O*-acetyl group at C-2 gives a far higher yield of glycal than does the substrate with the *O*-benzyl group in the 2-position.[27,32] The primary process competing with glycal formation in this reaction is proton transfer to the organosamarium intermediate from the trace amount of water present in the reaction mixture. For the substrate with the *O*-acetyl group, proton transfer from water is too slow to be of consequence, but for that with the *O*-benzyl group proton transfer is significant and becomes the major reaction pathway when greater than trace amounts of water are present (eq 2).



C. Addition to a Carbonyl Compound

Scheme 4 describes a reaction between samarium(II) iodide and a carbohydrate with an arylsulfonyl group to give an organosamarium compound that then adds to cyclohexanone.[33] Addition to aldehydes and ketones is another characteristic reaction of an organosamarium intermediate. In Scheme 4 the overall reaction is given first, and then a mechanism for the radical and nonradical phases of the reaction is proposed.

Scheme 4



1. The Samarium-Barbier Reaction

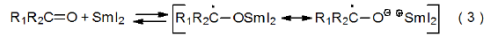
Because in the reaction shown in Scheme 4 the sulfone **4** and cyclohexanone both are present in the reaction mixture from the outset, the reaction is described as a Barbier-type[2] or samarium-Barbier[3,34] reaction. The mechanism pictured in Scheme 4 is a widely accepted one for this type of process.[1–9,34–37] The carbohydrate reactant frequently is a glycosyl sulfone,[28-30,32,33,37-43] but it also can be a glycosyl halide[31,32,37,44-46] or phosphate.[47] Possibilities for the carbonyl compound include ketones,[2,28,32,39,42,43,46] aldehydes,[2,28–30,32,38–46,] and lactones.[45, 48–50] Usually the carbonyl compound is a simple organic molecule, but sometimes the carbonyl group is part of the more complex structure found in a carbohydrate.[38–40,42–44]

2. The Samarium-Grignard Reaction

The defining characteristic of the samarium-Barbier reaction is that all of the reactants are present in the reaction mixture at the outset. If an intermediate organosamarium compound is sufficiently stable, it can be formed prior to adding the carbonyl compound. When reaction takes place using such a procedure, it is described as a Grignard-type or samarium-Grignard reaction.[3,34] Many organosamarium compounds are not stable enough to undergo reaction in this way; in particular, the reaction shown in Scheme 4 is only successful when run under samarium-Barbier conditions.[33]

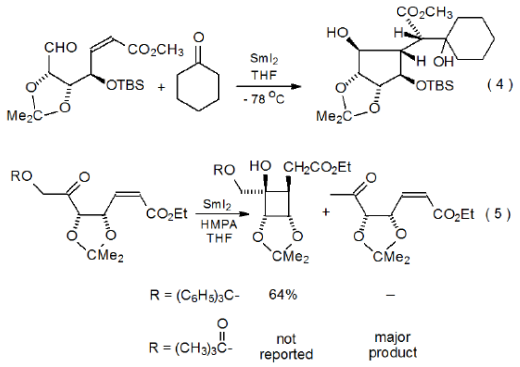
D. Formation and Reaction of Samarium Ketyls

Reaction of samarium(II) iodide with aldehydes and ketones produces ketyl radical anions, sometimes referred to as samarium ketyls (eq 3). These intermediates, each of which has considerable radical character on the former carbonyl carbon atom, form reversibly and have longer lifetimes than typical radical anions and most carbon-centered radicals.

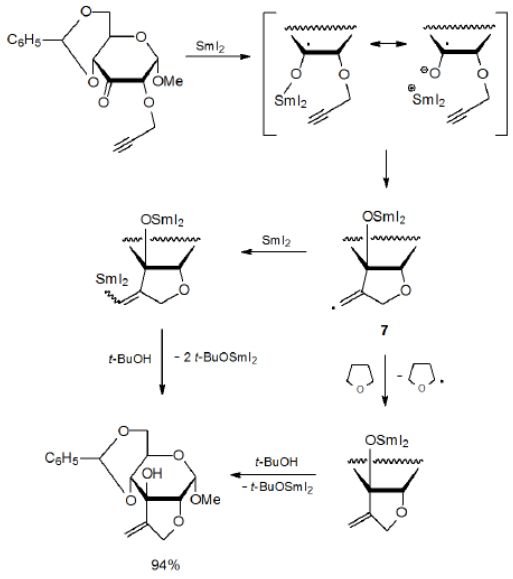


1. Internal Addition to a Carbon–Carbon Multiple Bond

A samarium ketyl that contains a properly positioned multiple bond readily forms a new ring system.[51–62] Examples indicating the range of reactivity of these ketyl intermediates are found in the reactions shown in equations 4 and 5 and Scheme 5. In the reaction pictured in eq 4, an unsaturated aldehyde forms a samarium ketyl that cyclizes and then reacts with cyclohexanone.[60] Eq 5 describes the reaction of an unsaturated carbonyl compound that has a substituent on the carbon atom α to the carbonyl group. If the substituent is a poor leaving group [e.g., $(C_6H_5)_3CO$], ring formation takes place, but when a better leaving group [e.g., $(CH_3)_3CCO_2$] is present, cyclization is replaced by elimination of the corresponding anion [e.g., $(CH_3)_3CCO_2^-$] followed by hydrogen-atom abstraction.[62] The highly stereoselective cyclization shown in Scheme 5 is an internal addition of a samarium ketyl to a triple bond.[51] The resulting cyclic intermediate (**7**) either can react with another molecule of samarium(II) iodide or, since **7** is a highly reactive radical, abstract a hydrogen atom from the solvent (THF). Either reaction can be part of a two-step sequence leading to the final product (Scheme 5).



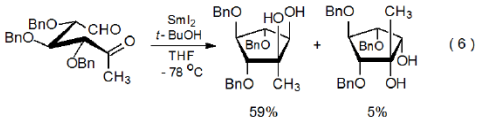
Scheme 5



2. Internal Addition to a Carbon–Oxygen Double Bond (Pinacol Formation)

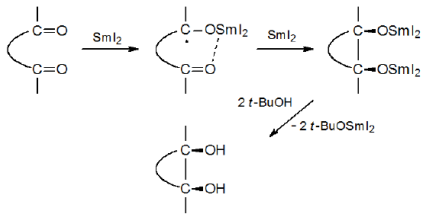
Reaction of samarium(II) iodide with a compound that has 1,4-,[63] 1,5-,[64–68] or 1,6-[69–77] related aldehydo or keto groups produces a samarium ketyl that then forms a cyclic pinacol. A typical example of such a reaction is shown in eq 6,[64] and a general mechanism

for pinacol formation is proposed in Scheme 6.[78] Based on this proposal, one would expect that the two hydroxyl groups in a pinacol should be found on the same side of the newly formed ring system because during reaction the oxygen atoms in these two groups interact simultaneously with a single samarium ion. Further, one also would anticipate that reaction should place the hydroxyl groups stereoselectively on the less-hindered face of the new ring. Both of these expectations are realized not only in the reaction shown in eq 6 but in other, similar reactions, where the major products always are *cis* diols formed by minimizing steric interactions during ring construction.[63,65–77]



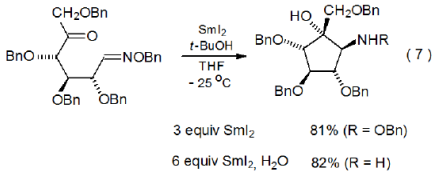
(6)

Scheme 6



3. Internal Addition to a Carbon–Nitrogen Double Bond

Reaction analogous to pinacol formation occurs when one of the carbonyl groups in a reactant molecule is replaced by a group with a C–N double bond (eq 7[79]).[79–83] A significant stereochemical difference between this type of reaction and pinacol formation is that the hydroxyl and substituted amino groups produced during cyclization are on opposite faces of the newly formed ring. This result indicates that complexation between the carbonyl groups and the samarium ion during pinacol formation has no analogous interaction in reactions of keto-oximes.



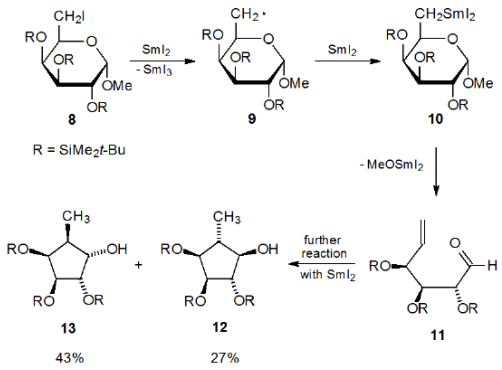
(7)

Sometimes the cyclization of a keto-oxime produces an amine rather than a substituted amine (eq 7).[79,84] This occurs when samarium(II) iodide, in excess of that needed for cyclization, transfers an electron to the N–O bond in the cyclic product leading to replacement of the amine substituent with a hydrogen atom. This reaction is accelerated by addition of water to the reaction mixture.

4. Ring-Contraction Reactions

Scheme 7 describes a reaction in which a samarium ketyl is involved in ring contraction. This process begins with electron transfer from SmI_2 to the carbohydrate iodide **8** to generate the radical **9**.[85] Reaction of **9** with a second molecule of SmI_2 produces the organosamarium compound **10**. Elimination of the elements of $MeOSmI_2$ from **10** causes the pyranoid ring to open to give the unsaturated aldehyde **11**, which reacts with SmI_2 to form a samarium ketyl that then cyclizes to give the substituted cyclopentanes **12** and **13**. Similar ring contractions occur when 6-aldehydo hexopyranosyl derivatives react with SmI_2.[86,87]

Scheme 7

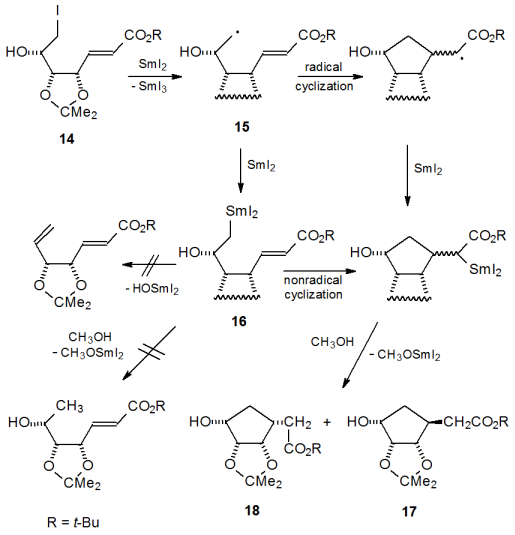


V. Cyclization Reactions

A. Substrates for Radical Cyclization

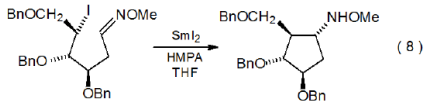
Radicals capable of cyclization can be generated from reaction of SmI_2 with unsaturated carbohydrate sulfones[13,27,88–91] or halides.[14–18,92,93] Internal addition is possible to either a C–C[14–18] (Scheme 8)[14] or C–N[92,93] (eq 8)[92] double bond. Glycosyl phenyl sulfones are often the starting materials of choice for forming pyranos-1-yl radicals because not only are such sulfones more stable[32] than the corresponding iodides and bromides, but they also produce radicals readily upon reaction with SmI_2 in the presence of HMPA (Scheme 3). HMPA is critical to phenyl sulfone reactivity because in the absence of this cosolvent these sulfones are unreactive.[13,91]

Scheme 8



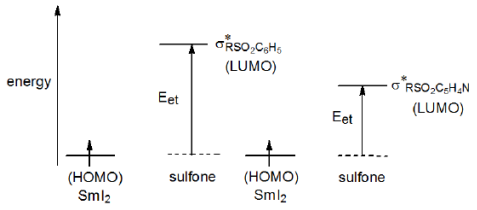
reaction conditions

SmI_2, MeOH, THF, HMPA	**17/18** = 78/1
SmI_2, MeOH, THF	**17/18** = 1/2.4
Bu_3SnH, AIBN, C_6H_6	**17/18** = 1/2.6



(8)

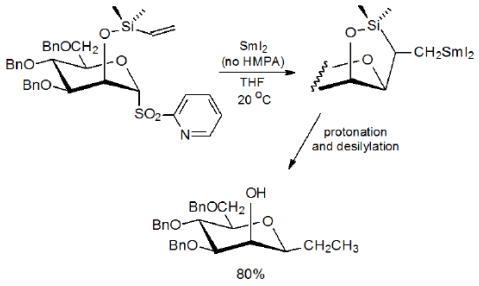
In contrast to phenyl sulfones, HMPA is not required for reaction of 2-pyridyl sulfones. This contrasting behavior is attributed to the effect of the 2-pyridyl group on sulfone MO energy levels. Because the LUMO energy of a 2-pyridyl sulfone is lower than that of a phenyl sulfone, transfer of an electron to the 2-pyridyl derivative occurs more easily (Figure 2); as a result, reaction can take place without HMPA being present (Scheme 9).[13,91]



E_{et} = minimum energy needed for electron transfer

Figure 2. Difference in LUMO (σ^*) energy levels between phenyl and 2-pyridyl sulfones

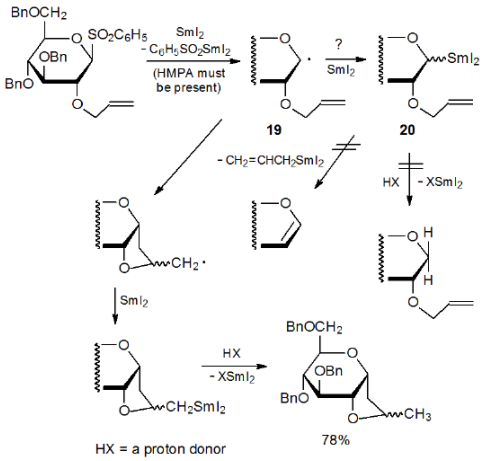
Scheme 9



B. Radical Cyclization Versus Cyclization of an Organosamarium Compound

When single-electron transfer takes place from SmI_2 to a substrate molecule, it often is not clear whether the reactive species is a radical, an organosamarium compound, or even an anion.[94] In the reaction shown in Scheme 10, for example, radical cyclization and organosamarium compound formation are both possible from the radical **19**.[27] Since neither protonation nor β elimination, characteristic reactions of an organosamarium intermediate, is observed, the indication is that the radical **19** undergoes cyclization before formation of the organosamarium compound **20** can take place.

Scheme 10



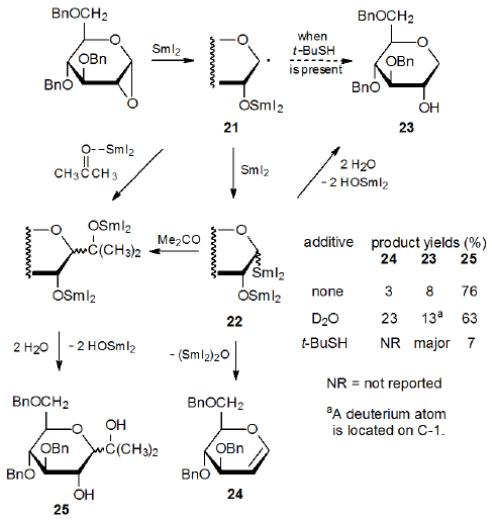
The reaction pictured in Scheme 8[14] is similar to the one shown in Scheme 10 in that ring formation occurs without the simple reduction or β elimination that characterize organosamarium intermediates. In this reaction (Scheme 8) stereoselectivity is highly dependent on the reaction conditions. For the AIBN initiated reaction of **14** with tri-*n*-butyltin hydride, there is little doubt that radical cyclization is taking place. The similarity in product ratios between this reaction and that caused by SmI_2 (in the absence of HMPA) supports the idea that both reactions involve radical cyclization.

There is a dramatic change in stereoselectivity when HMPA is added to the reaction shown in Scheme 8.[14] This change has been attributed to an HMPA-complexed samarium ion becoming associated with the carbonyl group in **15**. The size of this group is believed to be sufficient to create severe steric interaction with the isopropylidene group, an interaction that forces these two groups to opposite faces of the newly formed ring.[14] It is also possible, however, that the large change in stereoselectivity signals a new reaction mechanism. Cyclization may occur from the organosamarium intermediate **16**. For this to happen, however, it would require **16** to be formed faster than internal radical addition to an activated double bond. It also would require cyclization of the organosamarium compound to be faster than protonation or β elimination from **16**. The available information does not provide a definitive, mechanistic choice for this reaction, that is, the radical cyclization shown in Scheme 8 when HMPA is present.[14]

VI. Radical Addition and Hydrogen-Atom Abstraction

The reaction shown in Scheme 11 describes the formation of the *C*-glycoside **25** by addition of the oxygen-stabilized radical **21** or the organosamarium compound **22** (or both) to a molecule of acetone.[95] There is evidence for participation of both of these intermediates at some stage in this reaction. Conducting the reaction in the presence of *t*-BuSH quenches the addition process and dramatically increases the yield of the reduction product **23.** Such a change would be expected from hydrogen-atom abstraction by the radical **21**. In the absence of *t*-BuSH, formation of **23** and the elimination product **24** provide evidence for the organosamarium compound **22** also being present in the reaction mixture. Since conducting the reaction in the presence of D_2O decreases the yield of the *C*-glycoside **25** in favor of the reduction and elimination products **23** and **24**, respectively, the organosamarium compound **22** appears to be a likely intermediate in the addition process, but since a large excess of D_2O only modestly reduces the yield of **25**, radical addition remains a possible (perhaps major) pathway to *C*-glycoside formation.

Scheme 11

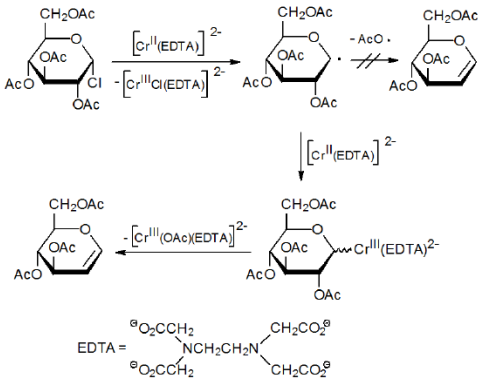


The radical-addition pathway shown in Scheme 11 involves the nucleophilic, carbon-centered radical **21** adding to the carbonyl carbon atom in acetone. The carbonyl carbon atom is rendered quite electron deficient by complexation of acetone with SmI_2. This combination of a reactive radical adding to a double bond with a decidedly electron-deficient atom is found in other reactions promoted by SmI_2.[96,97]

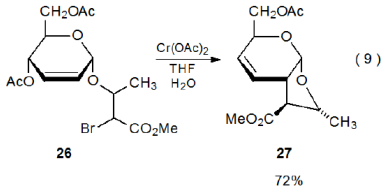
VII. Comparison of Reactions of Chromium(II) Reagents With Those of Samarium(II) Iodide

Chromium(II) reagents participate in radical reactions[98-104] that are similar both mechanistically and in terms of product formation to those occurring when samarium(II) iodide reacts with carbohydrate derivatives. Radical formation from reaction of chromium compounds with carbohydrate derivatives is far less common than radical formation from reaction with samarium(II) iodide. An example of a reaction involving a chromium(II) complex is given in Scheme 12 where $[Cr^{II}(EDTA)]^{2-}$ reacts with a glycosyl halide to produce a pyranos-1-yl radical that then combines with additional $[Cr^{II}(EDTA)]^{2-}$ to generate a glycosylchromium complex.[98,99] This complex undergoes β elimination to give a glycal.

Scheme 12



Radicals generated by chromium(II) reagents also undergo cyclization reactions such as that occurring when the bromide **26** reacts with chromium(II) acetate (eq 9).[103] The presence of a carbon–carbon double bond in the final product (**27**) indicates that a transient organochromium complex forms during this reaction but then reacts to give the unsaturated, bicyclic carbohydrate **27**.



(9)

VIII. Summary

Transfer of an electron from samarium(II) iodide to a carbohydrate with an electron-accepting substituent produces a radical anion. Dissociation of this radical anion generates a carbohydrate radical along with an anion derived from the substituent group. A carbohydrate radical formed in this way reacts rapidly with a second molecule of SmI_2 to produce an organosamarium compound. This organometallic compound can undergo reactions that include addition to a compound containing a carbonyl group, proton capture, and elimination of a samarium-containing leaving group. In order for a radical formed from reaction of a carbohydrate derivative with SmI_2 to avoid immediate reaction with a second molecule of SmI_2, a rapid, radical process must intervene. The one of greatest interest is radical cyclization; thus, a carbohydrate derivative that has a properly placed multiple bond and an electron-accepting substituent reacts with samarium(II) iodide to a form radical that cyclizes. Carbohydrates that contain a pair of properly positioned aldehydo or keto groups cyclize to form pinacols. The intermediate in the cyclization step leading to a pinacol is a radical anion. Organochromium complexes form and react in a manner similar to organosamarium compounds.

CHAPTER OVERVIEW

21: Reactions of Radicals Produced by Electron Transfer to Manganese(III) Acetate & Ammonium Cerium(IV) Nitrate

Manganese(III) acetate and ammonium cerium(IV) nitrate each react with CH-acidic compounds to produce carbon-centered radicals.[1–12] These radicals add preferentially to compounds with electron-rich multiple bonds. The role of a carbohydrate in a reaction of this type is to provide the multiple bond to which addition occurs.

II. Manganese(III) Acetate

III. Ammonium Cerium(IV) Nitrate

IV. Summary

II. Manganese(III) Acetate

Manganese(III) acetate has a more complicated structure than the formula $Mn(OAc)_3$ indicates. It is an oxo-centered trimer of three manganese ions held together by six bridging acetates.[10,13] Three representations for this structure are shown in Figure 1. It is often convenient in discussing reactions of this compound to use one of the abbreviated structures [frequently $Mn(OAc)_3$]

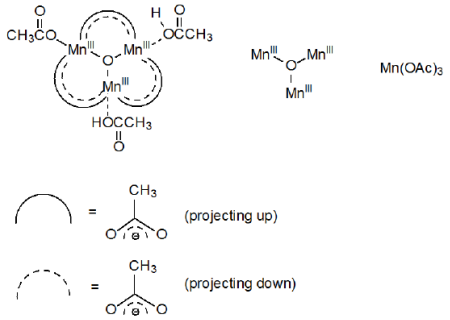


Figure 1. Three representations for maganese(III) acetate

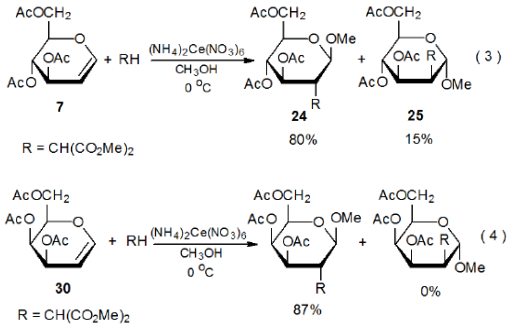
III. Ammonium Cerium(IV) Nitrate

A. Addition of CH-Acidic Compounds to D-Glycals

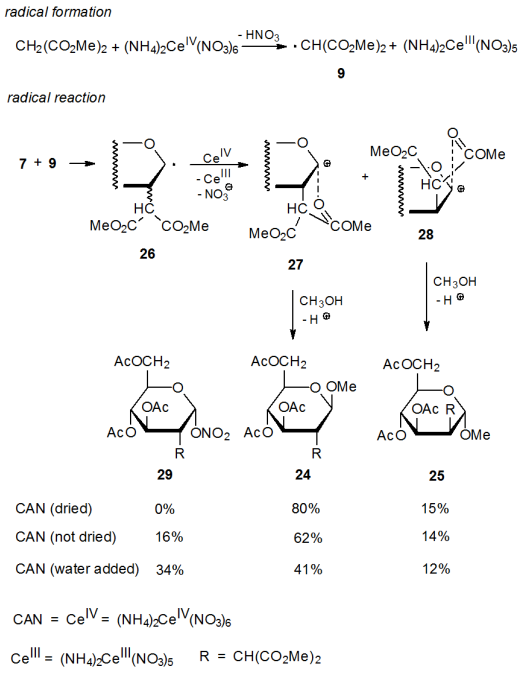
1. Dimethyl Malonate

a. Regioselectivity

In a manner similar to manganese(III) acetate reaction, ammonium cerium(IV) nitrate promotes regioselective addition of CH-acidic compounds to carbohydrates with electron-rich double bonds.[6–9,15,16,19–22] Examples of such reactions are given in equations 3 and 4, and a mechanism for the addition process is proposed in Scheme 7.[6–9] Reactions of glycals with $(NH_4)_2Ce(NO_3)_6$ (eq 3 and eq 4) can be conducted at lower temperatures than those with $Mn(OAc)_3$ (eq 1 and eq 2). These milder conditions completely suppress formation of the Ferrier rearrangement product **8**, a compound formed in the reaction given in eq 1 but absent in that shown in eq 3.



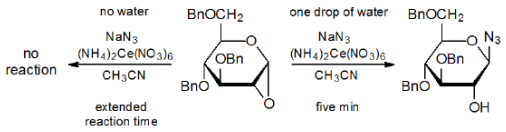
Scheme 7



If water is present, even in small amounts, a new compound (**29**) is produced in the reaction shown in Scheme 7.[22] How is this compound formed? Direct reaction between the cation **27** and the nitrate anion is one possibility, but if this pathway is the correct one, addition of sodium nitrate to the reaction mixture should increase the yield of **29**. It does not.[7] Ligand transfer from $(NH_4)_2Ce(NO_3)_6$ to the radical **26** also is possible,[6,7] but it is difficult to see why such a process should be dependent on the amount of water present in the reaction mixture. Both of these possibilities [reaction of **27** with $NaNO_3$ or ligand transfer from $(NH_4)_2Ce(NO_3)_6$] appear more likely to produce the anomer of **29** rather than **29** itself. The data in Scheme 7 do show that formation of the nitrate **29** comes at the expense of the β-glycoside **24**. Conversion of **24** into **29** could result from reaction of **24**

with the nitric acid produced by interaction of $(NH_4)_2Ce(NO_3)_6$ with water. This possibility is supported by the reaction shown in Scheme 8, where a drop of water apparently reacts with $(NH_4)_2Ce(NO_3)_6$ to create the nitric acid needed for an acid-catalyzed ring opening.[23]

Scheme 8



b. Stereoselectivity

Reaction stereoselectivity improves when $(NH_4)_2Ce(NO_3)_6$ replaces $Mn(OAc)_3$ in the addition of dimethyl malonate to 3,4,6-tri-*O*-acetyl-D-glucal (**7**). The ratio of α-face to β-face addition at C-2 by the malonyl radical changes from 52:14 (eq 1, Scheme 4)[6] to 80:15 (eq 3, Scheme 7).[22] The difference in the temperature of these reactions [95 °C (eq 1) to 0 °C (eq 3)] is a likely cause for this increase in stereoselectivity.

A second, stereoselective step in the reactions shown in Schemes 3 and 7 occurs during solvent capture by intermediate cations. Methanol reacts with the cations **27** and **28** exclusively from the face of the ring opposite to the malonyl group and produces a single stereoisomer in each case (Scheme 7). The capture of acetic acid pictured in Scheme 3 also is stereoselective but less so because each intermediate cation reacts to give a mixture of stereoisomers. Once again, greater reaction stereoselectivity correlates with lower reaction temperature.

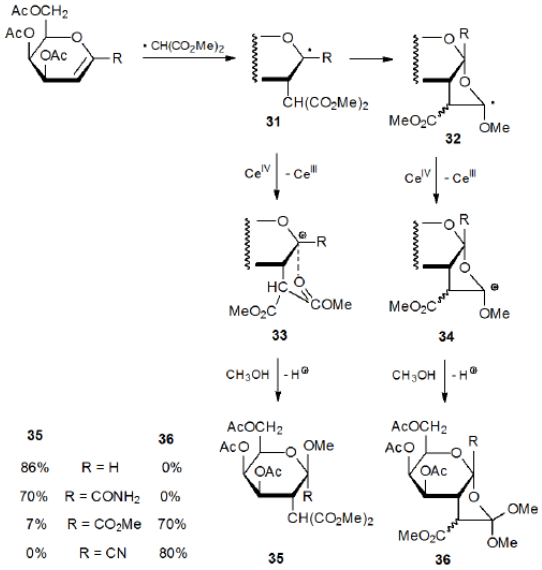
Stereoselectivity in malonyl-radical addition also increases when approach to one face of a ring becomes more difficult due to a change in substrate structure. Such a change occurs when 3,4,6-tri-*O*-acetyl-D-glucal (**7**) (eq 3) is replaced by 3,4,6-tri-*O*-acetyl-D-galactal (**30**) (eq 4).[7] Projection of the C-4 acetoxy group onto the β face of the pyranoid ring in **30** makes this face more congested than the β face of the pyranoid ring in **7**.

c. Reactivity

(1). Effect of C-1 Substituents on Glycal Reactivity Ortho-Ester Formation

The products formed from addition of the malonyl radical **9** to C-1 substituted glycals depend on the structure of the C-1 substituents (Scheme 9).[24] When R is H or C(=O)NH_2, the glycoside **35** forms, but when R is CO_2Me or CN, the products are the orthoesters **36**. An explanation for this difference in reactivity is that when R is highly electron-withdrawing (e.g., CN or CO_2Me), the oxidation potential of the radical **31** is high enough that its conversion to the cation **33** by reaction with $(NH_4)_2Ce(NO_3)_6$ is suppressed (Scheme 9).[24,25] When this suppression occurs, cyclization of **31** produces **32**, a radical that now can be oxidized easily to the corresponding cation (**34**). Reaction of this cation with methanol then gives the orthoesters **36**.

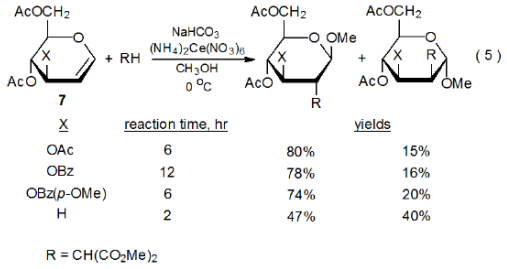
Scheme 9



35		36
86%	R = H	0%
70%	R = $CONH_2$	0%
7%	R = CO_2Me	70%
0%	R = CN	80%

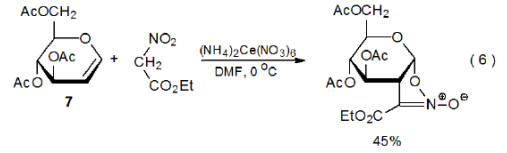
(2). Effect of a C-3 Substituent of Glycal Reactivity

The importance of electron-withdrawing substituents to glycal reactivity also is apparent when different substituents are attached to C-3 (eq 5).[25] The reactions shown in eq 5 confirm the previously mentioned findings (Sections III.A.1.a and III.A.1.b) about regioselectivity (the malonyl radical **9** adds exclusively to C-2) and stereoselectivity (**9** adds preferentially to the face of the pyranoid ring opposite to that containing the C-3 substituent). These reactions also demonstrate the effect of the electron-withdrawing character of a C-3 substituent on reaction rate (eq 5). Since the reactions involve the electrophilic malonyl radical adding to an electron-rich double bond, increasing the electron-withdrawing character of the R group decreases the reaction rate by reducing the electron density in the double bond; thus, an *O*-benzoyl group, which is more electron-withdrawing than an *O*-acetyl group, causes a slower rate of reaction. The reaction rate of an *O*-benzoyl-substituted glycal can be increased by placing an electron-donating methoxy group in the benzene ring. Reaction can be made even faster by eliminating any electron-withdrawing group from C-3 (eq 5).

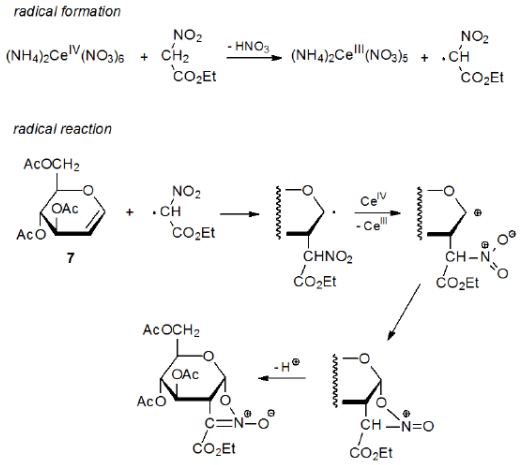


2. Ethyl Nitroacetate

When ethyl nitroacetate reacts with $(NH_4)_2Ce(NO_3)_6$ in the presence of the D-glucal **7** (eq 6),[20] a transformation takes place that is similar in its early stages to the dimethyl malonate reaction shown in eq 3. These two processes follow different pathways once the adduct radical has been oxidized to a cation. In the ethyl nitroacetate reaction, cyclization occurs (Scheme 10) rather than the solvent capture that characterizes reaction with dimethyl malonate (Scheme 7).



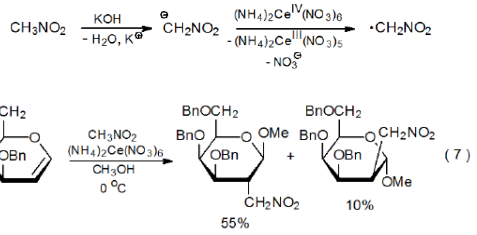
Scheme 10



3. Nitromethane

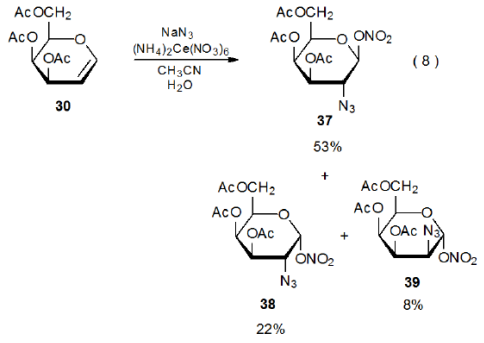
Nitromethane is a CH-acidic compound that reacts with potassium hydroxide to form a nitronate anion. Oxidation of this anion with ammonium cerium(IV) nitrate produces the electrophilic radical $\cdot CH_2NO_2$ (Scheme 11). If a compound with an electron-rich double bond is present in the reaction mixture, radical addition takes place (eq 7).[26]

Scheme 11

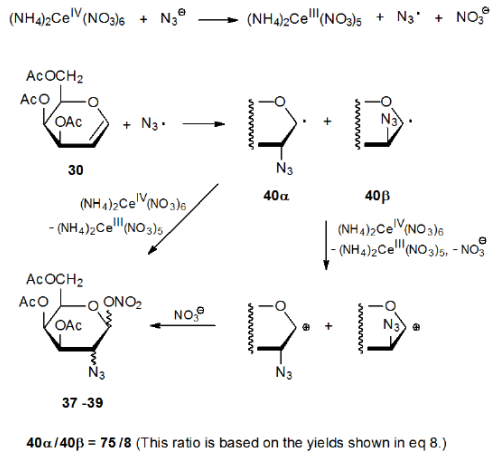


B. Addition of the Azide Radical to a D-Glycal

Reaction of ammonium cerium(IV) nitrate with sodium azide in the presence of the D-galactal **30** produces the diastereomeric azido nitrates **37**-**39** (eq 8).[27] There is convincing evidence that $(NH_4)_2Ce(NO_3)_6$ oxidizes NaN_3 to produce the azide radical (Scheme 12).[28] Highly stereoselective addition of this radical to **30** gives adduct radicals **40α** and **40β**in a ratio of 75:8. The azido nitrates **37**-**39** then form either indirectly by reaction of nitrate ion with the cations produced by oxidation of **40α** and **40β** or directly by ligand transfer from $(NH_4)_2Ce(NO_3)_6$ to these radicals.[29] (Section II.B.2 of Chapter 15 contains more information on azidonitration and additional references to this reaction.)



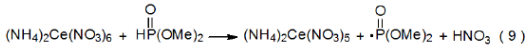
Scheme 12

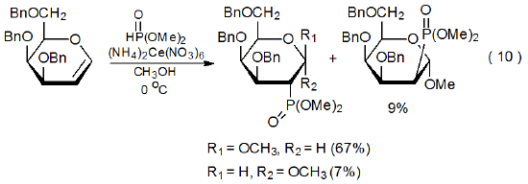


40α/40β = 75/8 (This ratio is based on the yields shown in eq 8.)

C. Addition of a Phosphonyl Radical to a D-Glycal

Dimethyl phosphite reacts with $(NH_4)_2Ce(NO_3)_6$ to produce the phosphorous-centered radical **41** (eq 9).[30] This radical then adds to D-glycals in a regiospecific, highly stereoselective manner (eq 10).





$R_1 = OCH_3$, $R_2 = H$ (67%)

$R_1 = H$, $R_2 = OCH_3$ (7%)

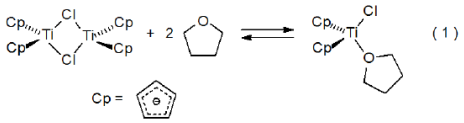
IV. Summary

Manganese(III) acetate and ammonium cerium(IV) nitrate react with CH-acidic compounds to produce carbon-centered radicals that add to carbohydrates with electron-rich double bonds. The resulting adduct radicals usually undergo oxidation to produce cations, each of which captures a nucleophile and then deprotonates to complete the reaction. Most reported reactions of this type involve the malonyl radical adding to an unsaturated carbohydrate. When the carbohydrate is a glycal, this reaction is a regio-specific addition to C-2. Such an addition takes place stereoselectively from the less hindered face of the ring system. Radical addition also occurs to less electron-rich double bonds, but the adduct radical is not oxidized to a cation; instead, it abstracts a hydrogen atom. Manganese(III) acetate also reacts with unsaturated carbohydrates to produce lactones.

CHAPTER OVERVIEW

22: Reactions of Carbohydrate Derivatives With Titanocene(III) Chloride

Titanocene(III) chloride [Cp_2TiCl, bis(cyclopentadienyl)titanium(III) chloride] is an oxygen-sensitive compound that is prepared by reaction of Cp_2TiCl_2 with metals such as zinc, aluminum, or manganese. Cp_2TiCl exists as a dimer in the solid state, but coordinating solvents (e.g., tetrahydrofuran) dissociate the dimer into a reactive monomer (eq 1).[1,2] (Although the monomer is coordinated with a solvent molecule, it usually is represented simply as Cp_2TiCl; more generally, Cp_2TiCl can be looked upon as representing all the Ti(III) species present in a solution of titanocene(III) chloride.[1–3])

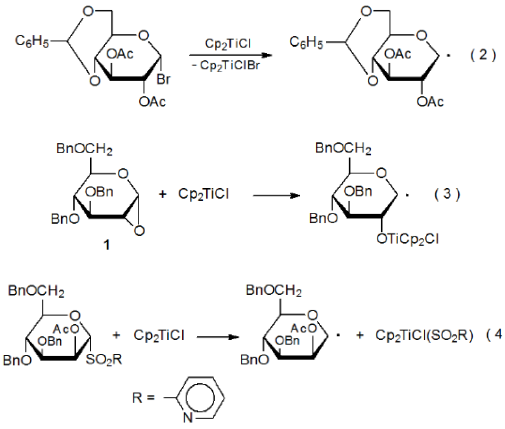


Topic hierarchy

II. Reactions
III. Electron Donation by a Ruthenium Complex
IV. Summary

II. Reactions

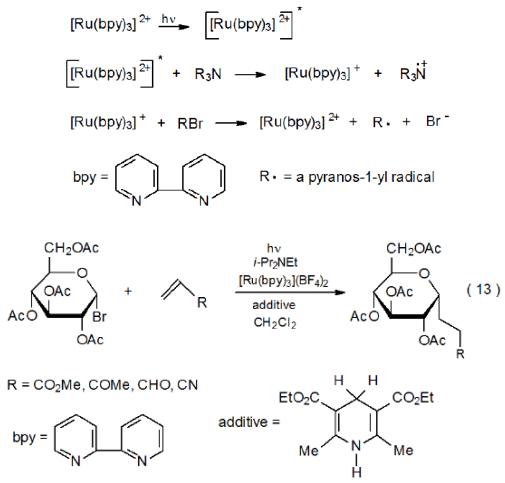
Three types of carbohydrate derivatives form carbon-centered radicals upon reaction with Cp_2TiCl. Halogen-atom abstraction from glycosyl halides produces furanos-1-yl and pyranos-1-yl radicals.[1,4–11] Radicals also can be generated by abstractive ring opening of epoxides.[12–19] Finally, Cp_2TiCl produces pyranos-1-yl radicals when it reacts with glycosyl 2-pyridyl sulfones.[7] An example of the first type of reaction is found in eq 2,[5,6] one of the second type in eq 3,[16] and one of the third in eq 4.[7] These radical-forming reactions have the attractive, chemoselective feature that Cp_2TiCl does not affect acetal, ester, or silyl ether protection.[5,6]



III. Electron Donation by a Ruthenium Complex

Ruthenium is a transition metal that, like titanium, can transfer an electron to a glycosyl halide. Photochemical reaction of $[Ru(bpy)_3]^{2+}$with a tertiary amine produces $[Ru(bpy)_3]^{+}$, a complex that then donates an electron to a glycosyl bromide to form a pyranos-1-yl radical (Scheme 10).[29,30] The radical formed in this way from the bromide **20** is capable of adding to a variety of electron-deficient alkenes (eq 13). The role of the additive in this reaction is to improve product yield by suppressing oligmerization.[29]

Scheme 10



IV. Summary

Titanocene(III) chloride reacts with glycosyl halides and with epoxides to generate carbon-centered radicals. The primary reaction of these radicals is combination with another molecule of Cp_2TiCl. These radicals also can abstract hydrogen atoms from the solvent or other hydrogen-atom transfers in the reaction mixture or undergo radical addition and cyclization reactions. If a radical combines with a second molecule of titanocene(III) chloride, the resulting organotitanium compound typically undergoes a β-elimination reaction. The result of such a reaction usually is formation of a glycal.

CHAPTER OVERVIEW

23: Organocobalt & Organomercury Compounds

I. Organocobalt Compounds
II. Organomercury Compounds
III. Summary

I. Organocobalt Compounds

An organometallic complex that contains a carbon–cobalt bond can function as a radical precursor because such a bond is easily broken homolytically. Facile cleavage occurs because carbon–cobalt bonds are significantly weaker than most covalent bonds:[1,2] in fact, the C–Co bond in coenzyme B_{12} (**1**, Figure 1) is one of the weakest covalent bonds known (BDE = 31.5 kcal mol^{-1}).[3] Enzymatic reaction, mild heating, and photolysis with visible light all cause homolysis of C–Co bonds. Adding to the usefulness of organocobalt complexes as radical precursors is the fact that, despite their considerable reactivity, many of these complexes can be handled in the laboratory.

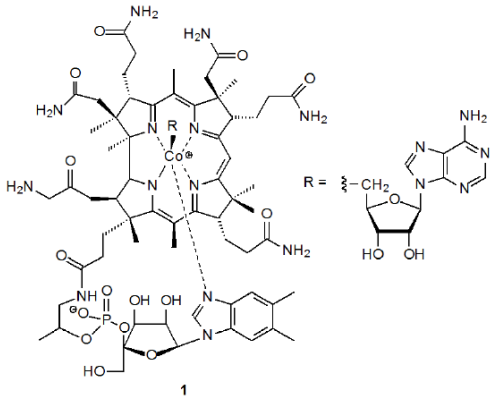
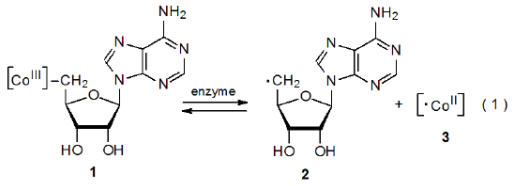


Figure 1. The structure of coenzyme B_{12} (5'-adenosylcobalamin)

Although C–Co bond homolysis takes place at relatively low temperatures, photolysis is the method of choice for radical formation in reactions conducted outside biological settings.[4–9] The reason for this choice is that C–Co bond fragmentation occurs with low-energy (visible) light at temperatures that avoid possible side reactions from even mild heating of complex, cobalt-containing compounds.

Coenzyme B_{12} (**1**, Figure 1) provided the original stimulus for using carbon–cobalt bond homolysis to form carbon-centered radicals.[7–11] The enzyme-induced homolysis of the C–Co bond in **1** produced the 5-deoxyadenosyl radical **2** and the cobalt-containing radical **3** (eq 1). The discovery that carbon-centered radicals could be produced in this way led to interest in finding simpler molecules that would mimic such behavior.



[Co^{III}] and [· Co^{II}] are general formulas for cobalt complexes in different oxidation states. In this reaction these symbols represent the portion of coenzyme B_{12} (see Figure 1) that does not include an adenosyl group.

Among the several types of organocobalt complexes found to be useful in generating carbon-centered radicals, cobaloximes [bis(dimethylglyoximato)cobalt complexes] (Figure 2) are the most widely used in carbohydrate chemistry.[11-15] Many reactions of cobalt-containing carbohydrates and much of the mechanistic information about reactions caused by C–Co bond homolysis come from study of cobaloximes.

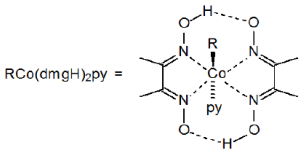
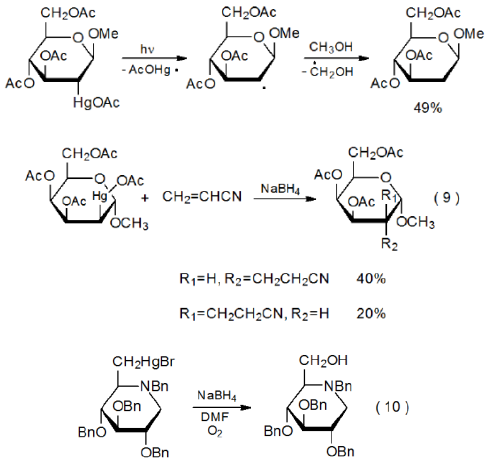


Figure 2. General structure for a cobaloxime derivative

II. Organomercury Compounds

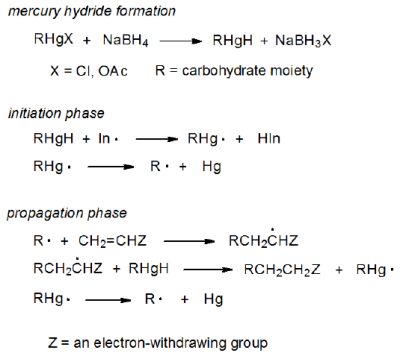
There are similarities between the reactivities of carbon–cobalt and carbon–mercury bonds. Both are strong enough to exist in stable structures that can be isolated and both readily cleave upon heating or photolysis. The result in each case is formation of a metal-centered and a carbon-centered radical. Carbon-centered radicals produced by carbon–mercury bond homolysis undergo typical radical reactions, such as hydrogen-atom abstraction (Scheme 6[27]),[27,28] addition to a multiple bond (eq 9),[29] and combination with molecular oxygen (eq 10[30]).[30,31] Although organomercury compounds can be effective sources of carbon-centered radicals, their use in this role is limited by toxicity and environmental concerns.

Scheme 6



Two basic methods exist for generating radicals from organomercury compounds. The first, photochemical homolysis of a carbon–mercury bond, is illustrated by the reaction shown in Scheme 6.[27] The second is more complicated and consists of initially converting an organomercury compound into the corresponding mercury hydride by reaction with $NaBH_4$ (Scheme 7).[32] The hydride then produces a carbon-centered radical capable of reactions such as the addition to acrylonitrile shown in eq 9.[29] Adventitious initiation is credited with beginning this reaction.

Scheme 7



III. Summary

Organocobalt complexes are sources of free radicals because heating, photolysis, or enzymatic reaction cleaves a carbon–cobalt bond homolytically to produce carbon-centered and cobalt-centered radicals. Cleaving the carbon–cobalt bond in this way changes the oxidation state of cobalt from Co(III) to Co(II). Complexes with cobalt in the Co(II) oxidation state exhibit radical reactivity. Cobalt-containing carbohydrates easily undergo epimerization reactions because the radicals formed by bond fragmentation readily recombine. Carbon-centered radicals produced from organocobalt complexes also undergo the characteristic radical reactions of addition and cyclization.

Organocobalt and organomercury compounds have a similarity in reactivity because each contains a carbon-metal bond that is easily cleaved by heating or photolysis. Carbon-centered radicals produced from organomercury compounds undergo hydrogen-atom abstraction and radical addition reactions. Concern about the toxicity of organomercury compounds reduces their usefulness as radical precursors.

CHAPTER OVERVIEW

24: Redox Couples

The previous four chapters describe electron-transfer reactions between carbohydrate derivatives and transition-metal ions. Some ions [chromium(II), samarium(II), and titanium(III)] are electron donors and others [cobalt(III), cerium(IV), manganese(III), and mercury(II)] are electron acceptors. Another form in which a transition-metal ion can participate in a radical reaction is as a part of a redox couple. (A redox couple is a combination of a transition metal and an ion from a different transition metal that act together in donating electrons to organic compounds.) Redox couples promote the addition of halogenated carbohydrates to electron-deficient double bonds, and they participate in the conversion of glycosyl halides into glycals and simple reduction products.

Topic hierarchy

II. Electron Transfer from a Redox Couple

III. Reactions with Redox Couples

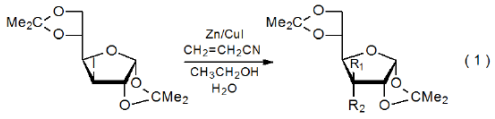
IV. Reaction Mechanism

V. Summary

II. Electron Transfer from a Redox Couple

A. Direct Electron Donation

Electron donation from the metal in a redox couple to a halogenated carbohydrate can occur either directly or indirectly. With direct reaction the role of the metal ion is primarily to prepare the surface of the metal for interaction with the halogenated compound. This is believed to be the purpose of the copper ion in a zinc–copper couple, a reagent that has been described as an active form of zinc metal.[1] Equation 1 pictures an addition reaction in which the adding radical is generated by reaction of a deoxyiodo sugar with a zinc–copper couple (Zn and CuI) suspended in an ethanol-water solution.[2]

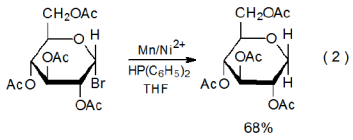


1/2 = 75/25 **1** $R_1 = CH_2CH_2CN$, $R_2 = H$ (56%)

2 $R_1 = H$, $R_2 = CH_2CH_2CN$ (19%)

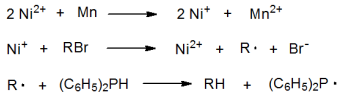
B. Indirect Electron Donation

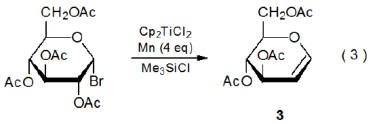
Indirect electron donation from the metal in a redox couple occurs when the metal ion is actively involved in the transfer process.[3–5] An example of this type of participation is shown in eq 2, where Ni(I) is oxidized to Ni(II) during reaction with a halogenated carbohydrate, and Ni(II) then is reduced to Ni(I) by the manganese metal.[3] Since the electrons being transferred to the carbohydrate are coming indirectly from manganese, the nickel ion performs a delivery role in the reaction and the manganese is the stoichiometric reactant (Scheme 1). In reactions of this type the metal ion need be present in only catalytic amounts; for example, in the glycal formation pictured in eq 3, the complex containing the titanium ion is added in as little as 10 mol%.[4]



68%

Scheme 1





3

Cp_2TiCl	yield
0%	0%
10%	59%
20%	62%
40%	77%

III. Reactions with Redox Couples

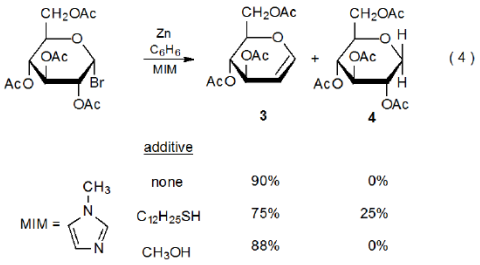
A. Addition Reactions

The total number of reactions of carbohydrate derivatives with redox couples is modest; among these addition reactions are reported more often than any other type.[2,3,5–9] Addition processes often involve a couple formed by combining zinc metal with a copper salt.[2,6,7,9] Such a reactions is illustrated in eq 1, where a zinc–copper couple participates in the addition of a halogenated carbohydrate to a compound with an electron-deficient double bond.

Since reaction between a zinc–copper couple and a carbohydrate is a heterogeneous process that takes place on the surface of finely divided zinc, efficient mixing during reaction is essential. Sonication, which often is used during redox-couple preparation and reaction, is believed to aid electron transfer indirectly by increasing mixing and improving metal-surface cleaning and directly by promoting electron transfer through the influence of ultrasonic waves.[10]

B. Elimination and Hydrogen-atom abstraction Reactions

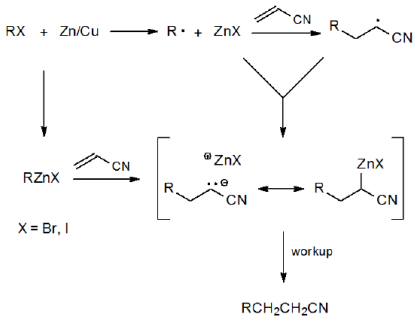
The idea that a copper ion is not directly involved in electron transfer from a zinc–copper couple garners some support from the reaction shown in eq 4, where zinc metal alone is able to act as the electron source in generating a pyranos-1-yl radical.[11] After formation, this radical undergoes further reaction that leads to the D-glucal **3**. Support for the intermediacy of a pyranos-1-yl radical in this reaction comes from conducting reaction in the presence of 1-dodecanethiol ($C_{12}H_{25}SH$), an excellent hydrogen-atom transfer. When this thiol is present, a substantial amount of hydrogen-atom abstraction by the pyranos-1-yl radical takes place to produce the simple-reduction product **4**. Proton transfer (the competing, nonradical possibility) does not appear to be involved in formation of **4** because when methanol replaces 1-dodecanethiol in the reaction mixture, none of this simple-reduction product is formed (eq 4).[11]



IV. Reaction Mechanism

Although the radical mechanism shown in Scheme 1 offers a reasonable explanation for the reactions pictured in eq 2, there is uncertainty in some reactions involving redox couples about whether a free-radical is ever produced. This uncertainty is reflected in the reaction mechanism shown in Scheme 2, which describes two possible pathways for participation of a zinc–copper couple in an addition reaction. One pathway involves radical formation by electron transfer, and the second describes formation of an organo-zinc intermediate. The stereochemical evidence and solvent effects described in the next two sections offer insight into the nature of the reactive species generated by a typical redox couple.

Scheme 2



V. Summary

A redox couple is a combination of a transition metal with an ion from another transition metal. These couples serve as electron donors in addition of halogenated carbohydrates to compounds with electron-deficient double bonds. There is some uncertainty as to whether a free radical or an organometallic compound is the intermediate in this type of reaction. Stereochemical evidence supports the radical pathway, but solvent effects indicate a more complicated situation.

Appendix I: Hydrogen-Atom Donors

Hydrogen-atom donors are widely used in radical reactions because hydrogen-atom abstraction is the final step in most radical chain processes. Donors can have a hydrogen atom bonded to a tin, silicon, sulfur, selenium, boron, phosphorous, or carbon atom. Most reactions involve organotin compounds, usually tri-*n*-butyltin hydride (Bu_3SnH). Some organosilanes, in particular tris(trimethylsilyl) silane [$(Me_3Si)_3SiH$], are effective enough as hydrogen-atom transfers to serve as replacements for organotin hydrides. Most other hydrogen-atom transfers are either so reactive or so unreactive that they typically are used only in special situations.

II. Organotin Hydrides

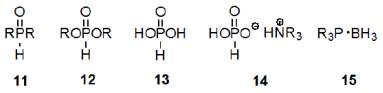
Organotin hydrides are the most frequently employed hydrogen-atom donors in radical reactions of carbohydrates. Clearly, the compound of choice is tri-*n*-butyltin hydride (Section II.A). Phenyl-substituted compounds, such as triphenyltin hydride, can serve in the same role, but they offer no advantage and are rarely used. Polymer-supported (Section II.B) and fluorous (Section II.C) tin hydrides have been used as replacements that avoid some of the difficulties inherent in the use of tri-*n*-butyltin hydride.

III. Organosilanes

Difficulties associated with use of tri-*n*-butyltin hydride have prompted chemists to search for alternative, hydrogen-atom sources, ones that avoid the problems associated with organotin compounds. Most attention has focused on organosilanes, compounds that do not have the toxicity associated with organotin reagents.[4] Initially, the outlook was not promising because simple organosilanes are poor hydrogen-atom transfers when reacting with alkyl radicals and do not support chain reactions under normal conditions.[4] Innovative ideas, however, have overcome these problems.

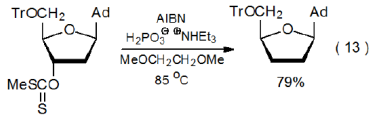
IV. Compounds with Phosphorous–Hydrogen Bonds

The search for less problematic hydrogen-atom transfers for use in the Barton-McCombie reaction has led to compounds with phosphorus–hydrogen bonds. These include dialkylphosphine oxides (**11**), alkyl phosphites (**12**), hypophosphorous acid (**13**), and salts of hypophosphorous acid (**14**) (Figure 2). All of these compounds can function as inexpensive, nontoxic hydrogen-atom transfers that form the chain-carrying radicals needed for reaction and do not produce byproducts difficult to remove.[3,10,57] An example of a reaction in which hydrogen donation is from a P–H bond is shown in eq 13.[58]



R = an alkyl group

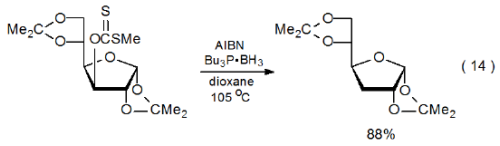
Figure 2. Hydrogen donors with P-H or B-H bonds



Alkyl phosphites (**12**) are excellent hydrogen-atom transfers, but reactions involving these compounds have the disadvantage of not being able to be initiated by 2,2'-azobis(isobutyronitrile); benzoyl peroxide usually is the initiator.[3,10] Reactions in which the hydrogen-atom transfer is a dialkylphosphine oxide (**11**), hypophosphorous acid (**13**), or a salt of hypophosphorous acid (**14**) can be initiated by AIBN.[9,57] Because it is difficult to completely remove water from hypophosphorous acid and its salts, these donors are less attractive choices when moisture sensitive compounds are reacting.[9]

V. Compounds with Boron–Hydrogen Bonds

Phosphine-boranes (**15**) (Figure 2) are a group of compounds that have the ability to react selectively with xanthates in the presence of compounds containing bromine or chlorine (but not iodine).[11] For example, cyclohexyl bromide is recovered without change when it is added to the reaction shown in eq 14; in contrast, tri-*n*-butyltin hydride and most other hydrogen-atom transfers used in radical reactions readily dehalogenate bromides. If this lack of reactivity between alkyl bromides and phosphine-boranes extends to halogenated carbohydrates, it will make possible their chemoselective deoxygenation without dehalogenation.

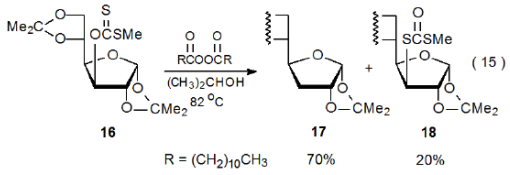


(14)

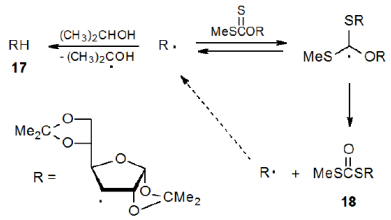
VI. Compounds with Carbon–Hydrogen Bonds

A. 2-Propanol

Few compounds in which a carbon–hydrogen bond must serve as the hydrogen-atom source are reactive enough to function as hydrogen-atom transfers in radical reactions of carbohydrates. The reason for this is that when less reactive donors are used, other reactions become competitive. Even compounds with quite reactive C–H bonds are poor hydrogen-atom transfers when compared to tri-*n*-butyltin hydride or tris(trimethylsilyl)silane. One compound that does have the necessary reactivity, but just barely, is 2-propanol. When reaction of the xanthate **16** is conducted with 2-propanol as the solvent, hydrogen-atom abstraction is in spirited competition with xanthate-dithiocarbonate rearrangement (eq 15).[59] This competition exists because hydrogen-atom abstraction by the carbohydrate radical R· is slow enough that addition of R· to another molecule of the xanthate **16** has a comparable rate (Scheme 5). The adduct radical formed by this addition fragments to give the dithiocarbonate **18** and a carbohydrate radical (R·).

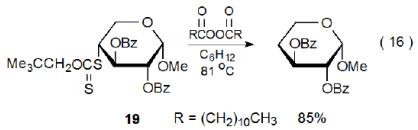


Scheme 5

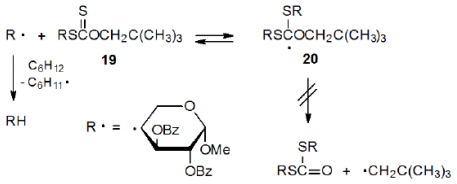


B. Cyclohexane

The xanthate **19** reacts to form the corresponding deoxy sugar in 85% yield (eq 16).[60] In this reaction cyclohexane functions as the hydrogen-atom transfer. Since cyclohexane is not a noticeably better hydrogen-atom transfer than 2-propanol, it is initially surprising that no dithiocarbonate is formed from **19** even though (as described in the previous section) dithiocarbonate formation is significant in reaction of the xanthate **16** (eq 15). The structural difference between the starting materials (**16** and **19**) in these two reactions accounts for their difference in reactivity. Unlike **16**, the xanthate **19** has a sulfur atom directly attached to the carbohydrate portion of the molecule. This means that when the carbohydrate radical R· adds to **19**, the options available to the adduct radical **20** are either regenerating the starting materials or expelling an unstabilized, primary radical (Scheme 6). Not surprisingly, no dithiocarbonate from primary radical expulsion is observed; therefore, the only operative pathway for the radical **20** is reforming of R· and the xanthate **19**. Each regeneration of R· creates a new opportunity for it to abstract a hydrogen atom. With these multiple opportunities even a marginally effective hydrogen-atom transfer eventually is able to react with R· to produce the hydrogen-abstraction product RH.



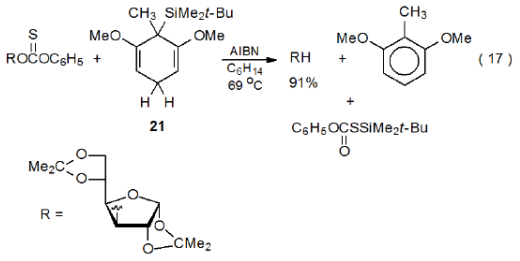
Scheme 6



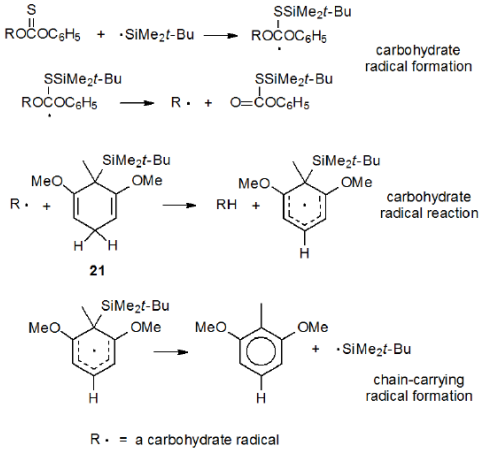
Even though the yield is good, the reaction shown in eq 16 is not an attractive option for deoxy sugar synthesis because it requires reaction of the carbohydrate to replace a C–O bond with a C–S bond before conducting the Barton-McCombie reaction. The additional steps necessary for this conversion add to the effort required for deoxygenation.

C. Silylated Cyclohexadienes

Silylated cyclohexadienes, such as **21**, are effective hydrogen-atom transfers in Barton-McCombie reactions (eq 17).[61] Compound **21** has the advantage of being a solid material that can be easily stored and handled. Although this compound (**21**) is an order of magnitude less reactive than $(Me_3Si)_3SiH$ (**3**), it is able to support chain reactions. The propagation steps in a proposed mechanism for replacement of an *O*-phenoxythiocarbonyl group with a hydrogen atom supplied by **21** are given in Scheme 7.



Scheme 7



VII. Compounds with Sulfur–Hydrogen or Selenium–Hydrogen Bonds

The rate constants for hydrogen-atom abstraction from sulfur–hydrogen and selenium–hydrogen bonds are so rapid [k_{SH} = 1.5 x 10^8 $M^{-1}s^{-1}$ (from C_6H_5SH) and k_{SeH} = 2.1 x 10^9 $M^{-1}s^{-1}$ (from C_6H_5SeH)] that abstraction typically will take place before other radical reactions (e.g., addition, cyclization, and rearrangement) can occur. (Rate constants for hydrogen-atom abstraction from various, hydrogen-atom donors, as well as rate constants for other radical reactions are given in Chapter 8 of Volume I.)

VIII. Summary

Since some tin-containing compounds are toxic and can cause purification problems, procedures have been developed both to minimize the amount of these materials needed for successful reaction and to make their removal easier and more complete. Another solution to toxicity and purification problems created by tin-containing compounds is to replace them with less offensive reagents. An effective replacement is tris(trimethylsilyl)silane. For reactive carbohydrate iodides cyclohexane also can be used.

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Chapter 12: Reactions of *O*-Thiocarbonyl Compounds

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Chapter 18: Compounds with Carbon–Carbon Multiple Bonds I: Addition Reactions

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Chapter 19: Compounds With Carbon–Carbon Multiple Bonds II: Cyclization Reactions

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Chapter 20: Reactions of Samarium(II) Iodide With Carbohydrate Derivatives

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