

V. Internal Hydrogen-atom abstraction in Acetals and Ethers

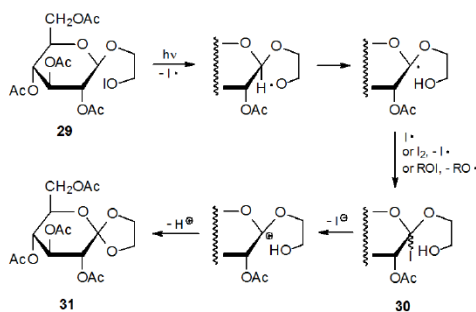
A. Abstraction by Alkoxy Radicals

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.

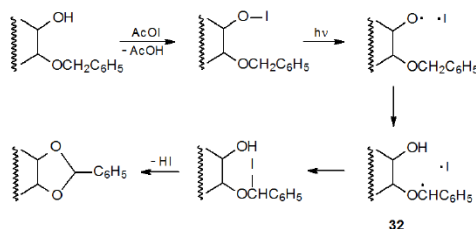
Scheme 10



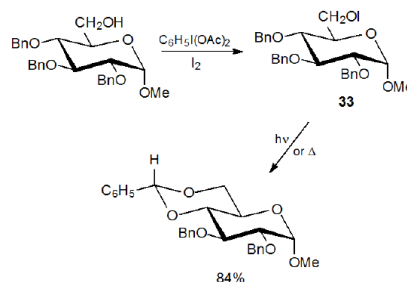
2. Abstraction From an Ether

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 ¹³C NMR spectroscopy. Such direct observation of a hypoiodite is rare.

Scheme 11



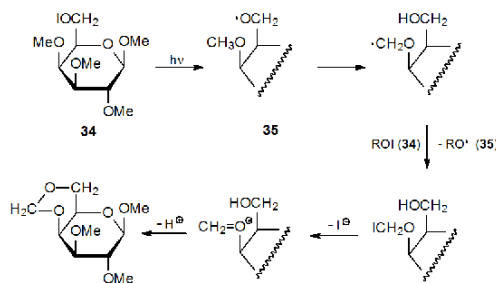
Scheme 12



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.

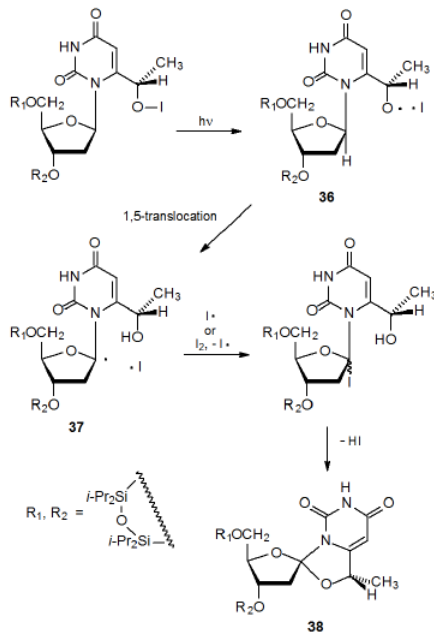
Scheme 13



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}

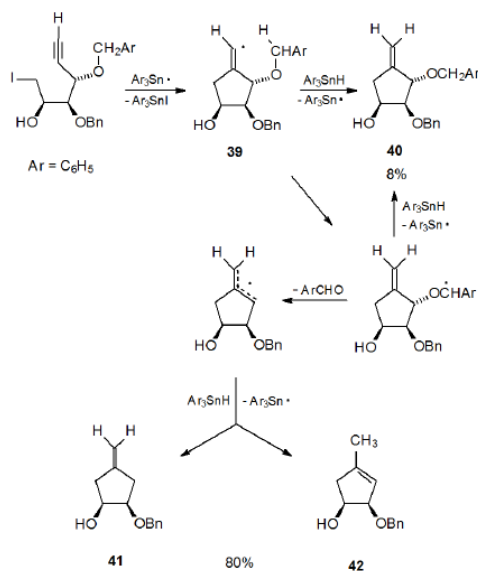
Scheme 14



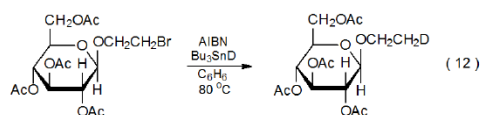
B. Abstraction by Carbon-Centered Radicals

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 primary²⁷ 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 (C₆H₅)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 Bu₃SnH is more rapid than internal 1,4- or 1,5-HAT.³¹



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