8.5: ALPHA BROMINATION OF CARBOXYLIC ACIDS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the Hell-Volhard-Zelinskii reaction.
2. identify the product formed from the reaction of a given carboxylic acid with bromine and phosphorus tribromide.
3. identify the carboxylic acid, the reagents, or both, needed to synthesize a given α-bromo carboxylic acid.
4. outline the stereochemical implications of the fact that the Hell-Volhard-Zelinskii reaction proceeds through the formation of an acid bromide enol.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Hell-Volhard-Zelinskii reaction

STUDY NOTES

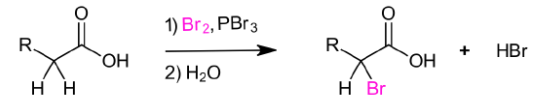
The reagents for the Hell-Volhard-Zelinskii reaction are given as bromine and phosphorus tribromide. In some questions, you may observe that only bromine and phosphorus are listed as reagents. Really there is no difference, as phosphorus tribromide would be formed *in situ* by the combination of bromine and red phosphorus:

$$3\,BR_2 + 2\,P \rightarrow 2\,PBr_3$$

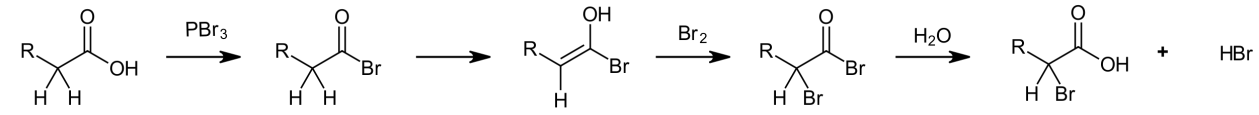
Excess bromine is required to ensure that enough reagent is available for the reaction with the enol.

HELL-VOLHARD-ZELINSKII REACTION

Although the α-bromination of some carbonyl compounds, such as aldehydes and ketones, can be accomplished with Br_2 under acidic conditions, the reaction will generally not occur with carboxylic acids, esters, and amides. Carboxylic acids do not enolize to a sufficient extent since the carboxylic acid proton is preferably removed before an α-hydrogen. However, carboxylic acids, can be brominated in the α-position with a mixture of Br_2 and phosphorus tribromide (PBr_3) in what is called the Hell-Volhard-Zelinskii reaction.

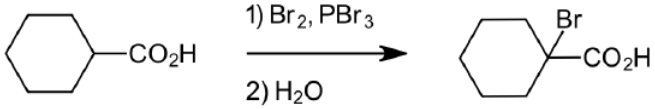


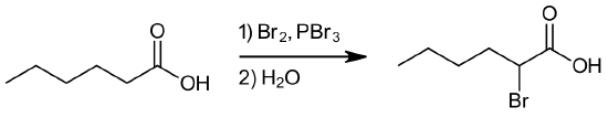
MECHANISM



This reaction is the combination of three separate reaction mechanisms all of which have been previously discussed. The mechanism starts with the reaction of the carboxylic acid with PBr_3 to form an acid bromide and HBr. Formation of an acid bromide is vital to this reaction because they lack the acidic carboxylic acid proton and can enolize much more readily making α-bromination possible. Next, HBr catalyzes the tautomerization of the acid bromide into its enol tautomer, acid bromide enol, which subsequently reacts with Br_2 to give α-bromination. Lastly, the product undergoes nucleophilic acyl substitution which cause the hydrolysis of the acid bromide to reform the carboxylic acid and the HBr catalyst. Because an enol intermediate is formed, this reaction will form a racemic mixture at the α-carbon.

EXAMPLES

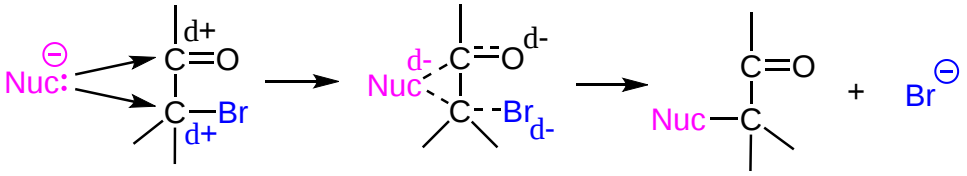




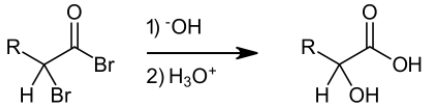
(Racemic)

FURTHER REACTIONS OF *A*-BROMO CARBOXYLIC ACIDS

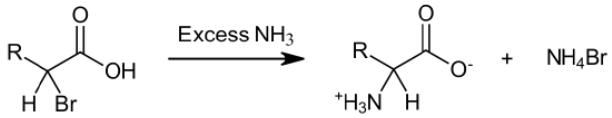
α-Bromo carboxylic acids are extremely useful synthetic intermediates because the halogen is highly reactive towards S_N2 reactions. Having the electrophilic carbon of the carbonyl adjacent to the electrophilic *α*-carbon attached to the bromine allows an incoming nucleophile to share its charge between the two. This stabilizes the transition state of the S_N2 reaction, lowering the energy of activation, and increasing reaction rates. Primary *α*-Halogenated carbonyls have S_N2 reaction rates which are much greater than the corresponding primary aliphatic halogens.



Because bromides are capable of reacting with a wide variety of nucleophiles, *α*-bromo carboxylic acids serve as important intermediates. Reaction of *α*-bromo carboxylic acids with an aqueous basic solution followed by an acidic work-up produces *α*-hydroxy carboxylic acids. Reaction of *α*-bromo carboxylic acids with an excess of ammonia provides *α*-amination, which provides a possible route to amino acids.

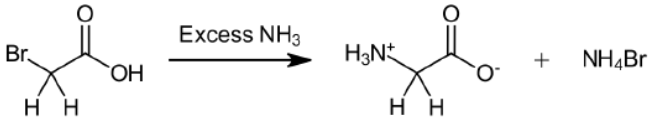


α-Bromo Carboxylic Acid **α-Hydroxy Carboxylic Acid**



α-Amino Carboxylic Acid

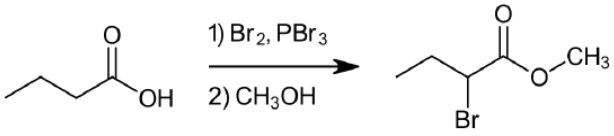
EXAMPLE



Bromoacetic acid **Glycine**

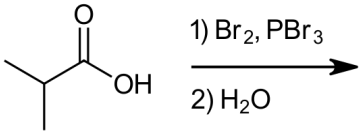
EXERCISES

1) Explain why the following reaction occurs.

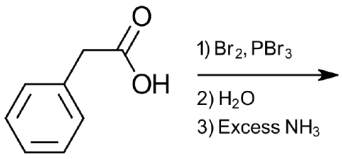


2) Draw the products of the following reactions:

a)

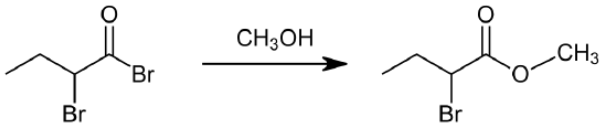


b)



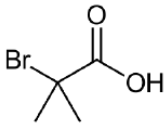
SOLUTIONS

1) The first step represents the beginning of the Hell-Volhard-Zelinskii reaction which provides a-bromination and creates and acid bromide intermediate. The second step adds methanol which reacts with the acid bromide to produce an ester.



2)

a)



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