Halogenation Reactions of Epoxides

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Abstract: The halogenation of aryl and alkyl epoxides using elemental bromine or iodine has been studied.

Epoxides are among the most important building blocks in synthesis owing to their chemical reactivity¹ and availability in optically active form². The chemistry of epoxides has centered largely on nucleophilic ring opening processes, while reactions with *electrophilic* reagents such as the halogens have received considerably less attention. Halogenations of epoxides in the presence of alkenes are known to produce 2,2'-dibromoethers.³ Similarly, macrocyclic epoxy cycloalkenes have been shown to give diiodo bicyclic furans upon iodination.⁴ In conjunction with ongoing work in our laboratory on electrophilic reactions, we realized the need to study some halogenation reactions of simple epoxides.

Bromination Reactions A selection of alkyl, aryl, and disubstituted epoxides were allowed to react with elemental bromine in various aprotic solvents. The results of these experiments are summarized in Table 1. In each case, cleavage of the epoxide ring occurs and, upon aqueous thiosulfate workup, bromohydrins are produced. The alcohols can be converted to their acetate derivatives for further characterization.⁵ Interestingly, for most of the epoxides studied, only 0.5 molar equivalents of Br_2 is required to complete the reaction. The lone exception is for entry 1, in which bromination of the aromatic ring occurs competitively with epoxide opening. We note that in this case halogenation of the ring takes place exclusively at the para position, and that cleavage of the epoxide occurs more rapidly than for the other substrates. The regioselectivity of these additions appears to be somewhat solvent dependent, as evidenced by the series of brominations listed for entry 1. The reactions generally proceed most cleanly in pentane, CH₂Cl₂, or benzene solution, while those done in THF, nitromethane, or acetonitrile lead to more complex product mixtures and lower yields of bromohydrins. A dramatic rate acceleration is observed for reactions in acetone, but the formation of acetone/bromine by-products makes product purification more tedious.

<u>Lodination Reactions</u> The iodination reactions of epoxides proceed much more slowly than the brominations in most of the solvents studied. In fact, after stirring with <u>three</u> molar equivalents of iodine for several days at room temperature, each of the epoxides is recovered unchanged when benzene, acetonitrile, methylene chloride, or CDCl₃ is used as the solvent. For THF, reactions proceed to only about 30% completion after several days under the same conditions. On the other hand, iodinations occur almost instantaneously when performed in acetone, and require only 0.5 molar equivalents of iodine.



Table 1. Bromination Reactions of Epoxides



Table 2. Iodination Reactions of Epoxides

The results of these iodination reactions are given in Table 2. Interestingly, reactions involving *terminal* epoxides (entries 1-3) give acetonide products in addition to the expected iodoadduct, which is isolated as a single regioisomer in each case. Iodination of styrene oxide (entry 4) gives exclusively the acetal. The acetonides presumably arise from addition of an initial ring-opened alkoxide (or an equivalent species) to acetone, followed by cyclization via displacement of the iodide. Thus, the ratio of iodohydrin:acetonide products reflects the regioselectivity of the addition, in that the iodohydrin arises from iodination at the *primary* center, while the acetonide results from iodination at the *secondary* carbon. As shown for entries 5 and 6, iodinations of internal epoxides do not give the acetonides, probably because the initial secondary alkoxide can not add efficiently to acetone. We also note that for entry 1, the aryl group is not halogenated as had been observed for the brominations.

Representative Procedure for Halogenation Reactions Bromine (0.6 mmol) is added dropwise to a stirred solution of 1-phenoxy-2-epoxypropane (180 mg, 1.2 mmol) in 5 mL of CH₂Cl₂ at room temperature.⁶ The progress of the reaction is monitored by TLC using silica gel plates. Upon complete disappearance of the starting material, the reaction mixture is poured into 5% aqueous Na₂S₂O₃, and the layers are separated. The aqueous layer is further extracted with CH₂Cl₂ (2 x 10 mL), the combined organic layers are dried over MgSO₄, and evaporated to give 358 mg of the crude alcohol. Purification by flash chromatography gives 327 mg (88%) of the bromohydrin as a colorless oil.

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- 5. The purified (or crude) halohydrins are acetylated by dissolving in pyridine (2 mL) and adding Ac₂O (5 eq) to the mixture . After 12 hours, the reaction mixture is diluted with CH₂Cl₂ (10 mL) and the organic layer is washed sequentially with 5% CuSO₄ (3 x 10 mL) and 5% NaHCO₃ (3 x 10 mL). Each of the aqueous layers is back-extracted with CH₂Cl₂ (10 mL), and the combined extracts are dried over MgSO₄ and evaporated. Flash chromatography of the crude mixture gives the haloacetates.
- 6. The same procedure can be followed for the iodination reactions, except that the acetone solution is evaporated prior to thiosulfate workup.

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