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Regioselective and stereospecific opening of an oxirane system mediated by trifluoroacetic acid and halide anions. A new direct approach to C3-vicinal halohydrins

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Abstract—Glycidol derivatives bearing ester, ether or silyl functionality upon treatment with trifluoroacetic acid (TFA) in the presence of a halide anion (e.g., Bu_4NX; X = Cl, Br or I) at room temperature undergo regioselective and stereospecific opening of the oxirane ring to produce the corresponding C3-vicinal haloalkanols in practically quantitative yields.

1. Introduction

Vicinal halohydrins are important synthetic intermediates that provide access to a vast array of biologically important compounds[1,2] including lipids[3] and halogenated marine natural products.[4] Halohydrins are also substrates for a particular class of enzymes, halohydrin dehalogenases,[5] that are of interest to both organic synthesis[6] (e.g., chiral resolution of racemic synthons[7]) and bioremediation of the environment (e.g., removal of pollutants from soil, ground-water or waste-water[5,8]).

Since addition of hypohalous acids and hypohalites to olefins[9] usually shows low regioselectivity, a much more attractive approach to vicinal halohydrins seemed to be opening of oxirane systems with various nucleophiles.[10] Unfortunately, regioselective and stereospecific incorporation of a halogen atom, even into a relatively simple three-carbon system (e.g., glycerol), turned out to be a rather difficult task. Although acid catalysis in the ring opening of epoxides is well established[11] and kinetic investigations have been carried out for the reactions of various epoxides with halide ions,[12] the methods for converting oxiranes into halohydrins by electrophilic cleavage with hydrohalic acids[13] are limited due to competing rearrangements, low regioselectivity and side reactions with other acid-sensitive functional groups.[11,14]

At present, the most convenient method for the preparation of vicinal halohydrins is opening of the oxirane system with metal halides (e.g., LiX/HOAc[15] or LiX/Amberlyst 15 acid resin,[16] X = Cl, Br or I). The major limitation of this approach is, however, that it involves lithium alkoxide as an intermediate and thus the method is, in principle, incompatible with the presence of hydrolytically susceptible functionalities (e.g., esters). In addition, regioselectivity of the reaction becomes rather poor in the absence of a vicinal ether bond which apparently serves as a supplementary coordination centre (besides the epoxide function) for the lithium cation.[2,16,17]

Recently, ring-cleavage of epoxides with organosilicon halides via trapping of the incipient hydroxyl function in the form of a silyl ether with simultaneous production of the corresponding halohydrin intermediate, followed by removal of the *O*-silyl fragment, was advocated to delineate a milder and less arduous route to vicinal halohydrins with specified configuration.[18] Unfortunately, such a two-step tactic cannot reduce synthetic problems since halosilylating fission of oxiranes is not always regioselective and varies widely depending upon steric factors in the substrates.[18,19] Furthermore, removal of even relatively labile trimethylsilyl and *tert*-butyldimethylsilyl ethers requires conditions that either preclude

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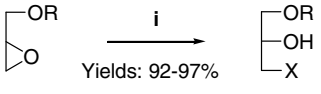
access to compounds with acid-,[18] base-,[20] or oxidation/reduction sensitive functionalities,[21] or are known to trigger side reactions (e.g., acyl migration, racemization, etc.) after exposure of a free hydroxyl group adjacent to an acyl substituent.[20,22]

Other methods for halohydrin synthesis suffer from various drawbacks, for example, (i) costly[23] or poorly available reagents;[18,24] (ii) erratic regiochemistry and yields depending on the halogen introduced;[2,15,16] (iii) requirements for a polar solvent which often creates solubility problems;[15,16] (iv) lack of enantioselectivity.[25]

Searching for a general and convenient method that would circumvent the aforementioned shortcomings during vicinal halohydrin synthesis, we embarked on an investigation of acid-catalyzed opening of oxiranes of glycidol derivatives. In this Letter we report on an efficient and highly stereo- and regiocontrolled conversion of glycidols having proximate ester (e.g., **1**, **2**), ether (e.g., **3**), or silyloxy fragments (e.g., **4**, **5**) into the corresponding C3-vicinal chloro- (e.g., **6**, **10**), bromo- (e.g., **7**, **9**) and iodohydrins (e.g., **8**, **11**, **12**) mediated by trifluoroacetic acid (TFA) in the presence of quaternary ammonium halides (Scheme 1).[26] Since these direct transformations can be carried out quantitatively under mild conditions, and the products can be isolated by simple solid-phase filtration, this may constitute a novel strategy for the synthesis of configurationally homogeneous vicinal halohydrins and related compounds.

The scope and generality of this straightforward protocol to vicinal halohydrins **6**–**12** was assessed by subjecting representative glycidol derivatives bearing acyl (**1** or **2**), alkyl ether (**3**) or silyl ether residues (**4** or **5**) to the ring-opening as shown in Scheme 1. After evaluation, the best results were achieved when a solution of substrates **1**–**5** with Bu_4NX (3.0 equiv) in chloroform at room temperature was treated with TFA (1.5 equiv) for 5 min–1 h. ^1H and ^{13}C NMR spectra of the isolated products revealed that in all instances the conversion to target haloalkanols **6**–**12** was practically quantitative and entirely chemo- and regioselective (>99%).



1 - 5 **6 - 12**

1 = *S*-(+), R = $C_{17}H_{33}CO$
2 = *rac*, R = C_6H_5CO
3 = *rac*, R = $C_{16}H_{33}$
4 = *S*-(+), R = TBDMS
5 = *R*-(+), R = TIPS

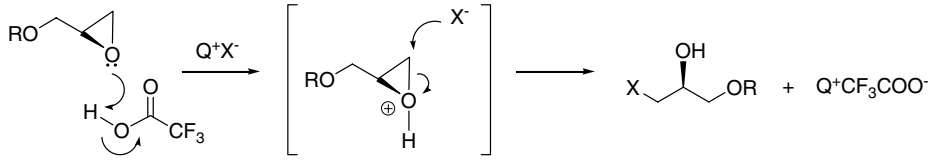
6 = 3-halo-*sn*, R = $C_{17}H_{33}CO$, X = Cl
7 = 3-halo-*sn*, R = $C_{17}H_{33}CO$, X = Br
8 = 3-halo-*sn*, R = $C_{17}H_{33}CO$, X = I
9 = *rac*, R = C_6H_5CO, X = Br
10 = *rac*, R = $C_{16}H_{33}$, X = Cl
11 = 3-halo-*sn*, R = TBDMS, X = I
12 = 1-halo-*sn*, R = TIPS, X = I

Scheme 1. Reagents and conditions: (i) F_3CCOOH (1.5 equiv)/Bu_4NX (3.0 equiv), $CHCl_3$, rt/5 min–1 h.

It was found that the rates of the reactions were not appreciably influenced by electronic or steric factors in the terminal substituents present in **1**–**5** (e.g., aliphatic- or aromatic acyl vs alkyl- or sterically hindered silyl ether) but they were sensitive to the nature of the incoming halogen, increasing rapidly from chloride to iodide (e.g., reaction time for **1**/Bu_4NCl and **1**/Bu_4NI were 1 h and 5 min, respectively). The observed dependence of rates as a function of halide is in agreement with early studies by Brönsted et al.[12] When TFA was replaced with acetic acid, the reaction was sluggish (e.g., **1**/Bu_4NI/CH_3COOH; ca. 36 h for the completion) but was completely regioselective and stereospecific. Organic bases, when used in equimolar proportions with TFA, significantly slowed the epoxide cleavage (e.g., 5 h for **1**/Bu_4NI/TFA/pyridine vs 5 min for **1**/Bu_4NI/TFA), but this did not affect regioselectivity and the quantitative character of the transformations. Pyridine and tetra-*n*-butylammonium halides (used either separately or in combination) showed no reactivity towards the epoxide functions of the glycidol derivatives studied.

On the other hand, opening of the oxirane ring of glycidyl oleate (**1**, but racemic) with TFA in chloroform afforded a mixture of 1-oleoyl-3-trifluoroacetyl-*rac*-glycerol and its isomeric 2-oleoyl-3-trifluoroacetyl-*rac*-derivative in a ratio of 3:1 (room temperature, 4 h; ^1H NMR).

The above data are consistent with the mechanism shown in Scheme 2, which involves initial protonation of the epoxide oxygen atom by trifluoroacetic acid to form an intermediate of type **A**, followed by nucleophilic attack of halide on the primary carbon centre. This is apparently the rate-determining step of the process but one cannot exclude another possibility that both steps (i.e., protonation and halogenation) might be synchronous. The electrophilic and nucleophilic catalysis provided by this particular reagent combination facilitates the cleavage of the epoxide function and rationalizes the observed regioselective production of vicinal halohydrins without scrambling of the adjacent acyl moiety, if present. As no bond breaking takes place at the stereogenic secondary carbon atom, the transformation is stereospecific and occurs with retention of configuration. This, and the lack of an intramolecular acyl migration, are in agreement with the above mechanism.



A

R = acyl, alkyl or silyl; $Q^+ = Bu_4N^+$; X = Cl, Br or I

Scheme 2.

In conclusion, we have developed a novel, simple and efficient synthetic strategy to vicinal chloro-, bromo- and iodohydrins (e.g., **6**–**12**) which is based on direct regiocontrolled opening of the oxirane system of glycidol derivatives (e.g., **1**–**5**) by means of a TFA–Bu_4NX reagent system. The method seems to be rather general and tolerates the presence of the most commonly employed in organic synthesis silyl protections (e.g., TBDMS and TIPS), makes use of commercially available reactants, and can easily be scaled up.

2. General procedure for the synthesis of vicinal halohydrins 6–12

To a solution of glycidyl substrate **1**–**5** (1.00 mmol) and tetra-*n*-butylammonium halide (3.00 mmol) in alcohol-free chloroform (10.0 mL), trifluoroacetic acid (0.115 mL, 1.50 mmol) was added and the reaction system was kept under argon at room temperature for 5 min–1 h. The solution was passed through a silica gel pad (~5 g) prepared in chloroform and the support was washed with the same solvent (~100 mL). The eluent was removed under reduced pressure and target halohydrin **6**–**12** was isolated in pure state by flash column chromatography (silica gel; mobile phase for **6**–**10**: pentane–toluene–EtOAc = 40:50:10, v/v/v; mobile phase for **11**, **12**: toluene/ethyl acetate = 98:2, v/v). Compounds **6**–**12** were characterized by ^1H and ^{13}C NMR spectroscopy, and their purity (>99%) assessed by ^1H NMR. For additional experimental details and characterization of the representative compounds, see Supplementary data.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.083.

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