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Efficient, highly regioselective, and stereospecific conversion of glycidol systems into C2-*O*-acylated vicinal halohydrins

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Abstract—Glycidyl esters and ethers undergo a regioselective and stereospecific opening of the oxirane ring upon treatment in chloroform in the presence of pyridine with trimethylsilyl halide (TMSX, X = Cl, Br, or I) and a mixture of carboxylic acid (CA)–trifluoroacetic anhydride (TFAA), to produce the corresponding C2-*O*-acylated vicinal halohydrins in high yields.

1. Introduction

Vicinal halohydrins are important and versatile synthons in organic synthesis, finding numerous applications, for example, in functional group transformations[1] or for introduction of a chiral unit with defined stereochemistry during the synthesis of biologically active compounds[2,3] (e.g., various lipid mediators,[4,5] halogenated natural products,[6] and others[7]). In addition, halohydrins are substrates for a special class of enzymes, halohydrin dehalogenases,[8] that are of importance in organic synthesis[7] and in bioremediation of the environment (e.g., for the removal of pollutants from soil, ground water, or waste water[8,9]).

While recent progress in oxirane chemistry[10,11] has resulted in the development of efficient methods for the preparation of vicinal haloalkanols,[3,12,13] relatively little attention has been paid to the direct conversion of 2,3-epoxy alcohol derivatives into vicinal haloesters, although the latter are superior intermediates in the synthesis of structurally defined bioconjugates[4,5,14] of interest in membranology,[15] enzymology,[16] gene therapy,[17] and drug design.[18]

In contrast to simple haloalkanols, which can be conveniently prepared by cleavage of oxirane derivatives with metal halides under acidic conditions,[11,13] preparation of the corresponding halohydrin esters always poses synthetic problems. The existing protocols, involving electrophilic cleavage of the terminal oxirane unit with acyl chlorides (alone,[19] or in combination with CrO_2Cl_2,[20] $CoCl_2$,[21] Bu_2SnCl_2/Ph_3P,[22] hexaalkylguanidinium chloride[23]) or related haloacylating systems (e.g., $TiCl_4$/EtOAc/imidazole[24]), provide only limited access to rather poorly reactive chlorohydrin esters,[5] and the methods are usually incompatible with oxidation-/Lewis acid-sensitive substrates.

Opening of the epoxide ring to produce the appropriate halohydrin intermediate, followed by its in situ acylation, delineates another viable route to vicinal haloesters. Unfortunately, the sole literature precedent reports a SnX_2-promoted fission of 2,3-epoxy ethers with trimethylsilyl halide (TMSX), that after acylation, affords 2-acetyl-3-halohydrins in rather erratic yields and with mediocre regioselectivity.[25] Attempted extension of this protocol to the preparation of chloroester derivatives form the corresponding glycidyl esters, resulted in extensive (~80%) acyl migration.[25]

One should also note that none of the aforementioned methodologies for halohydrin synthesis based on opening of an oxirane system, can be considered as general in terms of compatibility with the functional groups present in the substrates (ethers vs esters) and the kind of halogen that can be introduced during opening of the epoxide function.

Keywords: Glycidol; Trimethylsilyl halides; Trifluoroacetic anhydride; Carboxylic acids; Vicinal haloesters.

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We report here that treatment of glycidyl esters and ethers in chloroform in the presence of pyridine with trimethylsilyl halides, and a mixture of carboxylic acid (CA) with trifluoroacetic anhydride (TFAA), provides a convenient entry to configurationally pure 2-*O*-acylated vicinal chloro-, bromo-, and iodohydrin derivatives. These one-pot transformations are completely regioselective, stereospecific, and afford the desired halohydrin derivatives in high yields.

For the initial experiments, as a representative substrate, a racemic glycidyl oleate (compound **1** in Table 1, but racemic), bearing an acyl function predisposed to migration, was chosen. It was found that in aprotic solvents (e.g., CH_2Cl_2 or $CHCl_3$) treatment of glycidyl oleate **1** with acetyl bromide (3.0 equiv) at room temperature for 12–24 h, produced complex reaction mixtures consisting of the starting material (~30%), 1,3-dibromo-2-oleoyl glycerol (~20%), 1-oleoyl-2-acetyl-3-bromoglycerol (~35%), and its isomeric 1-acetyl-2-oleoyl-derivative (~15%) (TLC, ^1H and ^{13}C NMR analyses). Replacement of acetyl bromide by trimethylsilyl bromide (TMSBr, 3.0 equiv) led under the same conditions to practically quantitative formation of 1,3-dibromo-2-oleoyl glycerol (isolated in 91% yield).

Analysis of the chemical structures of the by-products indicated that the initially formed bromohydrin intermediates probably underwent a competing acyl migration (triggered, most likely, by intramolecular addition to the adjacent carbonyl function to form a tetrahedral intermediate), which led to compounds with the oleoyl group at the C-2 position. To remedy this problem, we tried to carry out the reactions in the presence of pyridine to increase trapping efficiency of the incipient hydroxyl function in the form of acetate or a silyl ether. Indeed, the course of the reaction was dramatically changed when the oxirane ring opening was carried out in the presence of a small amount of pyridine. In this instance, treatment of glycidyl oleate with either TMSBr (3.0 equiv) or acetyl bromide (3.0 equiv) in chloroform containing pyridine (6.0 equiv) at 80 °C (pressure tube) for 0.5–3 h resulted in highly regioselective formation of the expected 1-oleoyl-2-*O*-trimethylsilyl-3-bromoglycerol (compound **16** in Table 2, but racemic) or its 1-oleoyl-2-acetyl derivative (compound **7** in Table 1, but racemic) (isolated in >90% yields; purity >99% as judged by ^1H and ^{13}C NMR spectroscopy).

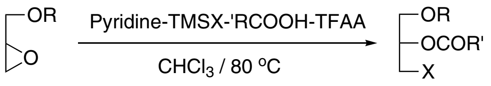
Although these preliminary results were most encouraging, the poor availability of acyl halides derived from long-chain fatty acids (especially the corresponding bromides and iodides), would make the scope of this reaction rather narrow. To alleviate this problem, we turned our attention to mixed carboxylic anhydrides as alternatives to acyl halide acylating agents,[26] that have recently been advocated for acylolytic cleavage of some acetal systems.[26,27] These, in combination with trimethylsilyl halides (TMSX, X = Cl, Br, or I) were expected to provide a convenient reagent system for the synthesis of 2-*O*-acyl-halohydrin derivatives.

After evaluation of various reaction conditions, the best results were obtained when a solution of the glycidyl derivatives **1**–**4**, pyridine (6.0 equiv), and TMSX (1.5 equiv) in chloroform was treated in a tightly stoppered pressure flask at 80 °C for 3–17 h with a mixture of the requisite carboxylic acid (6.0 equiv; acetic or oleic acid) and trifluoroacetic anhydride (TFAA, 1.5 equiv) (Table 1). ^1H and ^{13}C NMR spectra of the isolated products showed that the conversion of **1**–**4** to the target haloesters **5**–**14** was practically quantitative and entirely chemo- and regio-selective (>99%), in all the examples investigated.

The reaction times of the investigated transformations were fairly independent of the chemical nature of substrates **1**–**4** (aliphatic vs aromatic esters, or ethers vs esters) and varied only as a function of the chalcogen atom present in the silylating agent.

To clarify some mechanistic aspects of the formation of 2-*O*-acylated halohydrins in this five-component-one-pot reaction, first oxiranes **1**, **2**, and **4** were subjected

Table 1.



1 - 4 **5 - 14**

Molar ratio of (1 - **4**) : pyridine : TMSX : 'RCOOH : TFAA = 1.0 : 6.0 : 1.5 : 6.0 : 1.5

Run	Epoxide	R	R′	X	Reaction time (h)	Product (yield in %)	Optical rotation in $CHCl_3$ $[\alpha]_D^{20}/c$
1	**1**, *S*(+)	$C_{17}H_{33}CO$	CH_3	Cl	14	**5** (80)	+1.3/9.5
2	**2**, *R*(−)	$C_{17}H_{33}CO$	$C_{17}H_{33}$	Cl	17	**6** (83)	−1.8/8.0
3	**1**, *S*(+)	$C_{17}H_{33}CO$	CH_3	Br	6	**7** (91)	+3.1/9.0
4	**2**, *R*(−)	$C_{17}H_{33}CO$	$C_{17}H_{33}$	Br	7	**8** (93)	−2.9/11.2
5	**1**, *S*(+)	$C_{17}H_{33}CO$	CH_3	I	4	**9** (93)	+3.9/9.7
6	**2**, *R*(−)	$C_{17}H_{33}CO$	$C_{15}H_{31}$	I	3	**10** (96)	−3.6/10.3
7	**3**, *rac*	C_6H_5CO	CH_3	Br	6	**11** (85)	—
8	**4**, *rac*	$C_{16}H_{33}$	CH_3	Cl	15	**12** (87)	—
9	**4**, *rac*	$C_{16}H_{33}$	$C_{17}H_{35}$	Br	6	**13** (93)	—
10	**4**, *rac*	$C_{16}H_{33}$	CH_3	I	4	**14** (93)	—