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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).

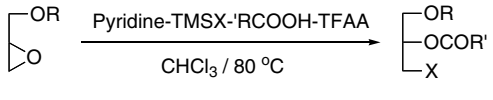
Although these preliminary results were most encouraging, the poor availability of acyl halides derived from long-chain fatty acids (especially the corresponding bromides and iodides), would make the scope of this reaction rather narrow. To alleviate this problem, we turned our attention to mixed carboxylic 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.

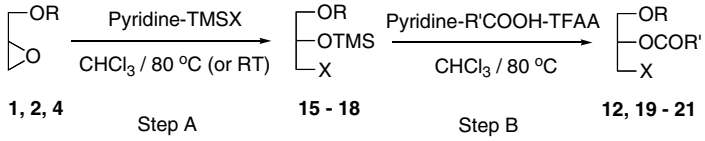


1 - 4 **5 - 14**

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)	—

Table 2.



Step A) Molar ratio of (**1, 2, 4**) : pyridine : TMSX = 1.0 : 6.0 : 1.5
Step B) Molar ratio of (**15-18**) : pyridine : R'COOH : TFAA = 1.0 : 6.0 : 6.0 : 1.5

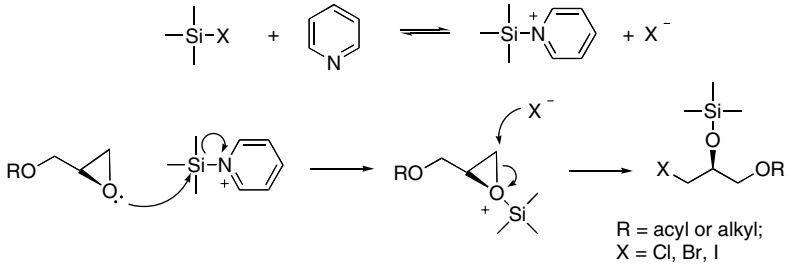
Run	Substrate	R	TMS or R′	X	Reaction time (h)	Product (yield in %)	Optical rotation in $CHCl_3$ $[\alpha]_D^{20}/c$
Step A							
1	**1**, *S*(+)	$C_{17}H_{33}CO$	TMS	Cl	7	**15** (92)	+1.7/10.7
2	**2**, *R*(−)	$C_{17}H_{33}CO$	TMS	Br	0.5	**16** (96)	−1.9/10.1
3	**1**, *S*(+)	$C_{17}H_{33}CO$	TMS	I	0.1/at RT	**17** (97)	+2.4/13.6
4	**4**, *rac*	$C_{16}H_{33}$	TMS	Cl	7	**18** (89)	—
Step B							
1	**15**, 1,2-*sn*	$C_{17}H_{33}CO$	$C_{17}H_{33}$	Cl	7	**19** (85)	+1.9/7.4
2	**16**, 2,3-*sn*	$C_{17}H_{33}CO$	CH_3	Br	6	**20** (83)	−3.1/10.8
3	**17**, 1,2-*sn*	$C_{17}H_{33}CO$	$C_{15}H_{31}$	I	3	**21** (95)	+3.6/11.3
4	**18**, *rac*	$C_{16}H_{33}$	CH_3	Cl	6	**12** (81)	—

to the reaction with the silyl halides (Table 2, Step A). It was found that the exclusive products of these reactions were the corresponding silyl halohydrins **15**–**18**, which were formed practically quantitatively. For trimethylsilyl iodide, the reactions went to completion within a few minutes at RT, while for the other halide derivatives, the reaction times were longer and required slightly elevated temperatures (see Table 2).

The exclusive formation of 2-*O*-silyl derivatives **15**–**18** with defined stereochemistry (e.g., **15**–**17**) suggested that the oxirane ring opening in **1**, **2**, and **4** with TMSX occurred via nucleophilic attack of the halide anion on the primary carbon center with simultaneous formation of the silyl ether bond, as shown in Scheme 1. The absence of bis-halogenated by-products indicated a critical role for pyridine in this reaction, which can be due both to releasing of a halide nucleophile from TMSX and generation of a highly electrophilic species, the *N*-silylpyridinium cation. Since the latter is expected to act as a powerful electrophilic catalyst, the opening of the oxirane ring, and silylation of the incipient 2-hydroxyl function are likely to be a synchronous process, that should occur without scrambling of the adjacent acyl moiety. At the mechanistic level, the transformation depicted in Scheme 1 indicates retention of configuration at C-2.

Next, the isolated silyl ethers **15**–**18** were treated in chloroform containing pyridine (6.0 equiv) with a mixture of a carboxylic acid (6.0 equiv) and TFAA (1.5 equiv), similarly as described for the one-pot synthesis of halohydrin derivatives **5**–**14** (see Table 1). The results in Table 2 (Step B), show that replacement of the silyl group by an acyl residue occurred smoothly affording the target compounds (**12** and **19**–**21**) regioselectively, and in consistently high isolated yields (81–95%). For these reactions, no significant differences in rates were observed for the various substrates.

The above data for Step A and Step B (Table 2) suggested that the conversion of glycidyl esters and ethers into the corresponding 2-*O*-acylated halohydrin derivatives in a one-pot reaction, apparently involves two consecutive steps: (i) generation of the corresponding 2-*O*-silylated vicinal halohydrins, and (ii) displacement of the trimethylsilyl residue by the respective acyl moiety with retention of configuration.[28] In the second step, a critical role is played by TFAA and pyridine, that most likely involves pyridine-mediated formation of a carboxylic-trifluoroacetic mixed anhydride, and its further activation by the pyridine present. These are consistent with the facts, that pyridine was an indispensable reaction component for the replacement of the silyl group by the acyl moiety, and that other carboxylic anhydrides



Scheme 1.

(including acetic acid anhydride) were unable to effect the above replacement even in pyridine.

In conclusion, we have developed a novel, simple, and efficient strategy for the synthesis of 2-*O*-acylated halohydrin derivatives. It consists of a regioselective and stereospecific opening of an oxirane system of glycidyl esters or ethers using trimethylsilyl halides, a carboxylic acid, and TFAA in the presence of pyridine. Although, this is apparently a two-step process, consisting of the formation of the corresponding 2-*O*-trimethylsilyl intermediate, followed by replacement of the silyl group by an acyl moiety, the favorable kinetics of the steps involved made it possible to carry out this transformation as a five-component-one-pot reaction. The reactions are clean, make use of commercially available reactants, and are easily scaled up. The approach seems to be rather general, and the acylating system used, CA-TFAA-pyridine, can be useful on its own for direct conversion of trimethylsilyl protected alcohols into carboxylic esters under mild conditions, without exposing a free hydroxyl group.

2. Typical procedure for the conversion of glycidyl derivatives 1–4 into 2-*O*-acylated vicinal halohydrins 5–14 (Table 1)

To a solution of glycidyl derivatives **1**–**4** (1.00 mmol) in alcohol-free chloroform (3.0 mL) were added pyridine (0.484 mL, 6.00 mmol), a trimethylsilyl halide (1.50 mmol), and a mixture of the corresponding carboxylic acid (6.00 mmol) with trifluoroacetic anhydride (0.209 ml, 1.50 mmol), prepared in the same solvent (3.0 mL). The reaction mixture was kept under argon, in a pressure-proof glass ampoule at 80 °C (bath temperature) for 3–17 h and then passed through a chloroform-filled aluminum oxide pad (~5 g). The support was washed with the same solvent (~150 mL) and after evaporation of organic solvents, the residue was purified by flash silica gel column chromatography (mobile phase for **5**, **7**, **9**, **11**, **12**, and **14**: pentane–toluene–EtOAc, 40:50:10, v/v/v; mobile phase for **6**, **8**, **10**, and **13**: toluene) to give the target haloesters **5**–**14** (purity >99%, ^{1}H NMR spectroscopy).

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.2006.02.050.

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