Regioselective, Haloacylating Cleavage of an Oxirane System Mediated by Trifluoroacetic Anhydride/Trimethylsilyl Halides: An Efficient Entry to 2-Acyl-3-haloglycerols

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Received 7 June 2006

Abstract: Glycidyl esters in the presence of trifluoroacetic anhydride (TFAA) and trimethylsilyl halides (TMSX), undergo a regioselective opening of the oxirane system with a subsequent migration of the acyl group to afford 1-trifluoroacetyl-2-acyl-3-haloglycerols. From these, the corresponding 2-acyl-3-haloglycerols can be obtained quantitatively and in high purity (>99%) without chromatographic purification.

Key words: glycidyl esters, trimethylsilyl halides, trifluoroacetic anhydride, 2-*O*-acylated 1,3-terminal halohydrins, 2-acylglycerol isosters

2-Monoacylglycerols (2-MAG) have been receiving a steadily growing interest as potent and diverse modulators of protective or physiopathological events in living organisms,[1] as endogenous carriers of fatty acids through intestinal mucosa,[2,3] or metabolic precursors to triglycerides with biologically important acyl residues at the 2-position of a glycerol skeleton.[3] Due to their dual function as vehicle molecules for biologic information and physiological effectors per se, isosteric forms of these unique lipid mediators surfaced as synthetic tools providing structural templates for rational design of micromolecular vectors for drug delivery,[4] endocannabinoid ligands mimetics,[5–7] antioxidants,[8] or triglyceride frameworks of significance to human nutrition[9] and membranology.[10] Incorporation of a halogen atom into either the glycerol backbone or fatty acid residues, along with variations of the substitution pattern around the C-2 center of ether and ester analogues of 2-MAG, appeared to be of special interest in developing new therapeutics,[11] or biochemicals,[12] and medicinal diagnostics.[13]

2-Monoacylglycerols alone did not contribute much to the aforementioned applications due to their high susceptibility to acyl migration during synthesis, isolation, and storage,[5,14,15] and also under the experimental conditions of most biological assays.[16] The isomerization process, which is promoted by acids, bases, heat or polar solvents,[17] leads to equilibrium mixtures of acyl glycerols that are difficult to resolve by means of chromatographic techniques and which contain as major, thermodynamic products, the corresponding 1(3)-isomers.[15,16]

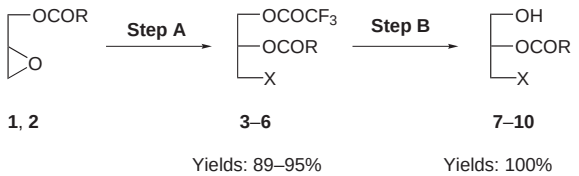
In this context, development of isosteres of 2-MAG for biochemical intervention or as starting materials in a convergent synthesis of various bioconjugates, has become a timely issue relevant to further progress in this field. Since the presence of a free, primary hydroxyl group next to an acyl functionality at the C-2 carbon of glycerol is essential for maintaining bioactivity of 2-MAG,[7] we turned our attention to 2-acyl-3-halo-propanols-1 in view of the close resemblance to 2-acylglycerols and diverse possibilities of their synthetic applications, e.g. in the preparation of 1(3)-asymmetrically derivatized isosteres of 2-MAG, construction of three-functional group models for D/halogen isotope labeling[12,13,15] or as regioisomeric ester analogue building blocks for various natural products[18,19] or anticancer agents.[20]

Although the ring-opening of epoxides to produce vicinal haloalkanols (e.g., by metal halides,[19,21] ammonium halides,[22] hydrohalides,[23] elemental halogens[24]), or to vicinal haloesters (e.g. with acyl chlorides alone,[25] in the presence of CrO_2Cl_2,[26] $CoCl_2$,[27] Bu_2SnCl_2/Ph_3P,[28] or by means of $TiCl_4$/EtOAc/imidazole[29]), seemed a viable methodology for our purpose, this chemistry finds no literature precedents regarding a direct synthesis of 2-acyl-3-haloglycerols from their appropriate oxirane congeners.[30]

As part of our research, we recently proposed a general route to 2-acylglycerols and related prodrug frameworks,[31,32] based on a trifluoroacetic anhydride (TFAA)-assisted fission of the oxirane ring of glycidyl esters with a synchronous migration of the acyl group to the internal C-2 position within the glycerol skeleton. Here, we report that TFAA in the presence of trimethylsilyl halide (TMSX; X = Cl, Br or I), can govern a haloacylating cleavage of the terminal epoxy system with an acyl migration to produce halotrifluoroacetates **3**–**6** (step A, Scheme 1), in practically quantitative yields. Since the subsequent removal of a trifluoroacetyl transient protection can be carried out quantitatively and without final purification (step B, Scheme 1), this two-step reaction sequence offers a novel strategy to regioisomerically homogeneous 1(3)-halogenated isosters of 2-MAG **7**–**10**.

SYNLETT 2006, No. 14, pp 2251–2255
Advanced online publication: 24.08.2006
DOI: 10.1055/s-2006-948206; Art ID: G17206ST

In contrast to our recent findings that carboxylic acid anhydrides in the presence of trimethylsilyl halides (TMSX) and halide anions open the oxirane system in **1** without acyl migration to produce the corresponding 1,2-diacyl-3-haloglycerols,[33] preliminary experiments with equimolar amounts of TFAA and trimethylsilyl chloride showed that this reagent system effected formation of chloroglyceride **3** from **1** with migration of the acyl group. This could provide a convenient entry to the otherwise difficult-to-access 2-acyl-3-haloglycerols of type **7**–**10**.



1 = (*S*)-(+), R = $C_{17}H_{33}$
2 = *rac*, R = $(CH_3)_3C_6H_2$

3, **7** = *rac*, R = $C_{17}H_{33}$, X = Cl
4, **8** = *rac*, R = $C_{17}H_{33}$, X = Br
5, **9** = *rac*, R = $C_{17}H_{33}$, X = I
6, **10** = *rac*, R = $(CH_3)_3C_6H_2$, X = Br

Step A: TFAA (4.0–5.0 equiv), TMSX (1.2–4.0 equiv), CH_2Cl_2, r.t., 2–5 h;
Step B: pyridine (10 equiv), MeOH (250 equiv), CH_2Cl_2–pentane, r.t., 20 min

Scheme 1 *Reagents and conditions*: step A: $(F_3CCO)_2O$ (4.0–5.0 equiv), TMSX (1.2–4.0 equiv), CH_2Cl_2, r.t., 2–5 h; step B: pyridine (10 equiv), MeOH (250 equiv), CH_2Cl_2–pentane, r.t., 20 min.

To assess the scope and generality of this reaction, the TFAA/TMSX-promoted cleavage of selected oxiranes bearing either aliphatic (**1**) or sterically hindered aromatic acyl residues (**2**) was investigated under various experimental conditions (different solvents, ratio of reactants, etc., step A, Scheme 1). ^{1}H NMR and ^{13}C NMR spectral analysis indicated that both amounts of TFAA and TMSX as well as their ratios had profound effect on regioselectivity during attempted preparation of haloglycerols **3**–**6**. The best results were achieved when TFAA and TMSX were mixed together in dichloromethane [for synthesis of chloroglyceride **3**, TMSCl (4.0 equiv)/TFAA (4.0 equiv); for bromoglycerides **4** and **6**, TMSBr (2.0 equiv)/TFAA (4.0 equiv); for iodoglyceride **5**, TMSI (1.2 equiv)/TFAA (5.0 equiv)], added to a cooled solution (–20 °C) of **1** or **2** in the same solvent, and the reaction was left at room temperature for 2–5 hours.[36] This gave quantitatively and in a highly chemo- and regioselective way (>99%, ^{1}H NMR and ^{13}C NMR spectroscopy) products **3**–**6**, which were isolated in 89–95% yields after solid-phase filtration through a short silica gel pad. For such optimized runs, rates of the epoxide opening were not appreciably affected by electronic and steric features of the acyl group present in **1** and **2**. The reactions examined seemed to be rather general as other glycidyl esters (e.g. acetate, arachidonate, 4-nitrobenzoate; results not shown) also underwent quantitative conversion to the same type of trifluoroacetylated haloesters. Lack of optical activity for compounds **3**–**5** obtained from (*S*)-(+) glycidyl (**1**) indicated on racemization occurring during the course of the reaction.

The produced 1-trifluoroacetyl derivative **3**–**6** can be treated as storage forms for the corresponding 2-MAG as their spectral characteristics (^{1}H NMR and ^{13}C NMR spectroscopy) remained unchanged upon keeping under argon at –20 °C for several weeks. On the other hand, compounds **3**–**6** can be conveniently converted into 2-MAG derivatives **7**–**10** by treatment in CH_2Cl_2–pentane with pyridine (10 equiv) and methanol (250 equiv) at room temperature for 20 minutes.[37] The removal of the terminal trifluoroacetyl moiety was quantitative and produced volatile by-products removable with the solvents by simple evaporation under reduced pressure. Thus, this protocol provided positionally homogenous terminal haloalkanols **7**–**10** (purity >99%, ^{1}H NMR and ^{13}C NMR spectroscopy) without any additional purification (step B, Scheme 1).

Since we previously found that treatment of carboxylic acid anhydrides with TMSX (e.g. X = Br or I, 1.0 equiv) at room temperature led to almost instantaneous formation of equimolar amounts of the corresponding acyl halides (ACX) and trimethylsilyl carboxylates (ACOTMS),[34] we carried out additional experiments to elucidate mechanistic contribution of these species in the haloacylating cleavage of the aforementioned oxirane systems.

^{1}H NMR and ^{13}C NMR spectroscopy revealed that acetyl bromide (1.5 equiv) alone effected opening of the oxirane ring of glycidyl oleate **1** with a predominant migration of the oleoyl moiety affording a mixture of 1-acetyl-2-oleoyl- and 1-oleoyl-2-acetyl-3-bromoglycerol in a ratio of 80:20 (CH_2Cl_2, r.t., 72 h, isolated yield as a mixture: ca. 75%). Practically the same results were obtained when TMSBr (1.5 equiv) and acetic anhydride (up to 4 equiv) were used for the reaction. In contrast, treatment of glycidyl **1** with TFAA (4.0 equiv) and TMSBr (2.0 equiv) afforded exclusively 1-trifluoroacetyl-2-oleoyl-3-bromoglycerol (**4**, CH_2Cl_2, r.t., 3 h; isolated yield: ca. 94%). However, when equimolar amounts of TFAA and TMSBr (1.5–4.0 equiv) were used, significant amount of side products [1-oleoyl-2-trifluoroacetyl-3-bromoglycerol (ca. 5–15%) and 2-oleoyl-1,3-dibromoglycerol (ca. 10–20%)], along with the desired compound **4** (ca. 70–80%), were formed.

To secure a clean formation of chloroglyceride **3**, TFAA and TMSCl had to be used in equimolar amounts and in fourfold excess over glycidyl **1**. Attempted synthesis of **3** by reacting **1** with TMSCl (2.0 equiv)/TFAA (4.0 equiv), afforded 1,3-bis(trifluoroacetyl)-2-oleoylglycerol (75%) and only 25% of the desired product **3**. For the synthesis of iodoglyceride **5**, the optimal ratio of TMSI/TFAA that secured complete regioselectivity of the opening of the oxirane ring in **1**, was found to be 1:4.

The above data suggest that fission of oxiranes **1** and **2** is most likely subject to electrophilic catalysis provided by trifluoroacetyl halides (TFAX) generated in situ from

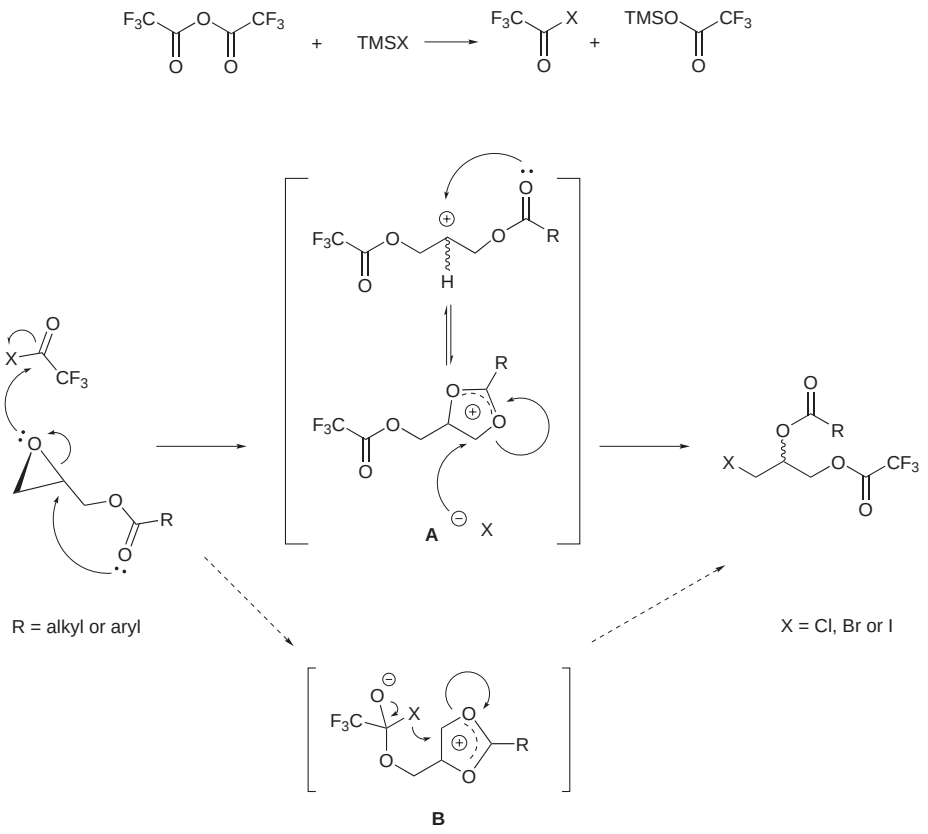
TFAA and TMSX. This involves, most likely, coordination of the electrophile catalyst to the epoxide oxygen with a synchronous intramolecular attack of the vicinal carbonyl group on the secondary carbon atom as depicted in Scheme 2. The combination of electrophile and nucleophile catalysis in these reactions should facilitate opening of the epoxy system to form cyclic acyliumglycerol cation **A** (or **B**), collapsing then to the epimerized 1-trifluoroacetyl-2-acyl-3-haloglycerol by a nucleophilic attack of a halide ion on the primary carbon atom of the dioxolane ring.

Formation of the racemic products in this reaction indicates that acylium cations **A** and **B** are in equilibrium with the corresponding acyclic carbocations, and thus migration of an acyl group which involves this kind of intermediate, is likely to proceed with partial or complete epimerisation.

To explain the observed regiochemistry, one has to assume very low concentration of free halide ions under the reaction conditions,[35] to enable participation of the adjacent carbonyl function as nucleophilic catalyst in the opening of the oxirane ring of **1**. The subsequent coordination of a halide ion by the acylium cation can be an intermolecular (intermediate A) or intramolecular reaction (intermediate B), depending on stability of the tetrahedral intermediate involved. The latter pathway implies also that a nucleophile attacking the acylium cation has to be part of the electrophile catalyst. Thus, if two electrophile catalysts differing in the leaving group (e.g. TFAA vs. TFACl) would compete in opening of the epoxide ring in **1**, two products should be formed – 1,3-bistrifluoroacetyl and 1-trifluoroacetyl-3-chloro derivative. This is consistent with observations that the reactions investigated are very sensitive to the ratio of TFAA and TMSX used. Thus, for the synthesis of chloroglycerides **3**, one has to use TFAA and TMSCl in a ratio of 1:1, otherwise TFAA present in the reaction mixture can compete as electrophilic catalyst with TFACl and give rise to the formation of bistrifluoroacetate derivatives. On the other hand, during synthesis of iodoglyceride **5**, this ratio of TFAA/TMSI can be 4:1, due to apparently higher reactivity of the generated trifluoroacetyl iodide.

In conclusion, we have developed an efficient synthetic strategy based on a novel, chemo- and regioselective opening of the epoxide system of glycidyl esters (e.g. **1**, **2**) to produce 1-trifluoroacetyl-2-acyl-3-halo-*rac*-glycerols (e.g. **3**–**6**) and hence terminal haloalkanols (e.g. **7**–**10**), as prospective isosters of 2-MAG.

The main features of this protocol are: (i) highly regioselective and quantitative generation under mild conditions of trifluoroacetyl-protected haloglycerol intermediates **3**–**6**,which can be either employed as storage forms of or converted into monohalogenated analogues of 2-MAG **7**–**10**; (ii) the produced compounds **7**–**10** are of high purity and their synthesis does not require, potentially detrimental to their chemical integrity, chromatographic processes;



Scheme 2

(iii) the method seems to be general and introduces 2-O-acylated haloglycerols **7**–**10** as versatile three-carbon units useful in the preparation of bis(acylated) vicinal halohydrins or asymmetric triglyceride precursors; (iv) the method makes use of commercially available reactants and preparations can easily be scaled up.

Acknowledgment

Financial support from the Swedish Natural Science Research Council and the Swedish Foundation for Strategic Research is gratefully acknowledged.

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(35) In separate experiments we found that reaction of **1** with TFAA and tetrabutylammonium halides or with TFAA and TMSBr in the presence of pyridine, occurred without acyl migration and involved a nucleophilic opening of the oxirane ring with halide ion, facilitated by electrophilic catalysis exerted by TFAA.

(36) **General Procedure for the Synthesis of 1-Trifluoroacetyl-2-acyl-3-haloglycerols 3–6 (Step A).**
(*S*)-(+)-2-(Oleoyloxymethyl)oxirane (**1**) {$[\alpha]_D^{20}$ +13.89 (*c* 5.66, $CHCl_3$)} and (*rac*)-(±)-2-(2,4,6-trimethylbenzoyloxymethyl)oxirane (**2**) were obtained by direct acylation of chiral or racemic glycidols as described elsewhere.[32] The R_f values refer to mobility on a silica gel plates using the solvent system: pentane–toluene–EtOAc = 40:50:10 (v/v/v).
To a solution of the starting substrate **1**, **2** (1.00 mmol) in CH_2Cl_2 (3.0 mL), a mixture of TFAA (4.00–5.00 mmol) and trimethylsilyl halide (1.20–4.00 mmol), prepared in the same solvent (3.0 mL), was added at –20 °C and the reaction system was kept under argon at r.t. for 2–5 h. Then, CH_2Cl_2 and volatile reaction components were evaporated in vacuo, the residue was taken in toluene (5.0 mL) and passed through a silica gel pad (ca. 5 g) prepared in the same solvent. The support was washed with toluene (ca. 100 mL), fractions containing the target compound were combined, the eluent was removed under reduced pressure, and the rest was kept under high vacuum at r.t. for 2–3 h to afford the rearranged 2-O-acylated halohydrin **3**–**6** (purity >99%, ^{1}H NMR spectroscopy).
1-Trifluoroacetyl-2-oleoyl-3-chloro-*rac*-glycerol (**3**): obtained from **1** (0.338 g, 1.00 mmol), TFAA (0.556 mL, 4.00 mmol) and TMSCl (0.505 mL, 4.00 mmol) for 5 h. Yield: 0.428 g (91%, colorless oil); R_f = 0.68. Anal. Calcd (%) for $C_{23}H_{38}ClF_3O_4$ (470.99): C, 58.65; H, 8.13; Cl, 7.53. Found: C, 58.72; H, 8.10; Cl, 7.51.
1-Trifluoroacetyl-2-oleoyl-3-bromo-*rac*-glycerol (**4**): obtained from **1** (0.338 g, 1.00 mmol), TFAA (0.556 mL, 4.00 mmol) and TMSBr (0.259 mL, 2.00 mmol) for 3 h. Yield: 0.479 g (93%, colorless oil); R_f = 0.67. Anal. Calcd (%) for $C_{23}H_{38}BrF_3O_4$ (515.44): C, 53.59; H, 7.43; Br, 15.50. Found: C, 53.56; H, 7.41; Br, 15.51.
1-Trifluoroacetyl-2-oleoyl-3-iodo-*rac*-glycerol (**5**): obtained from **1** (0.338 g, 1.00 mmol), TFAA (0.695 mL, 5.00 mmol) and TMSI (0.163 mL, 1.20 mmol) for 2 h. Yield: 0.534 g (95%, colorless oil); R_f = 0.66. Anal. Calcd (%) for $C_{23}H_{38}F_3IO_4$ (562.44): C, 49.11; H, 6.81; I, 22.56. Found: C, 49.18; H, 6.78; I, 22.51.
1-Trifluoroacetyl-2-(2,4,6-trimethylbenzoyl)-3-bromo-*rac*-glycerol (**6**): obtained from **2** (0.220 g, 1.00 mmol), TFAA (0.556 mL, 4.00 mmol) and TMSBr (0.259 mL, 2.00 mmol) for 3 h. Yield: 0.353 g (89%, colorless oil); R_f = 0.71. Anal. Calcd (%) for $C_{15}H_{16}BrF_3O_4$ (397.18): C, 45.36; H, 4.06; Br, 20.12. Found: C, 45.41; H, 4.01; Br, 20.18.

(37) **General Procedure for the Synthesis of 2-Acyl-3-haloglycerols 7–10 (Step B).**
To a solution of trifluoroacetyl halohydrin **3**–**6** (1.00 mmol) in pentane–CH_2Cl_2 (3:1, v/v, 5.0 mL), a mixture of pyridine (0.8 mL, 10 mmol) and MeOH (10.1 mL, 250 mmol) in the same solvents (5.0 mL) was added at 0 °C and the reaction system was left at r.t. for 20 min. Solvents were evaporated under reduced pressure (bath temp. 50 °C) and the residue was kept under high vacuum at r.t. for 2–3 h to give the deprotected haloalkanol **7**–**10** (purity >99%, ^{1}H NMR spectroscopy).
2-Oleoyl-3-chloro-*rac*-glycerol (**7**): obtained from **3** (0.471 g, 1.00 mmol). Yield: 0.374 g (100%, colorless oil); R_f = 0.25. Anal. Calcd (%) for $C_{21}H_{39}ClO_3$ (374.98): C, 67.26; H, 10.48; Cl, 9.45. Found: C, 67.22; H, 10.51; Cl, 9.50.
2-Oleoyl-3-bromo-*rac*-glycerol (**8**): obtained from **4** (0.515 g, 1.00 mmol). Yield: 0.419 g (100%, colorless oil); R_f = 0.23. Anal. Calcd (%) for $C_{21}H_{39}BrO_3$ (419.44): C, 60.13; H, 9.37; Br, 19.05. Found: C, 60.08; H, 9.40; Br, 19.00.
2-Oleoyl-3-iodo-*rac*-glycerol (**9**): obtained from **5** (0.562 g, 1.00 mmol). Yield: 0.466 g (100%, yellowish oil); R_f = 0.34. Anal. Calcd (%) for $C_{21}H_{39}IO_3$ (466.44): C, 54.07; H, 8.43; I, 27.21. Found: C, 54.13; H, 8.40; I, 27.24.
2-(2,4,6-Trimethylbenzoyl)-3-bromo-*rac*-glycerol (**10**): obtained from **6** (0.397 g, 1.00 mmol). Yield: 0.300 g (100%, colorless oil); R_f = 0.24. Anal. Calcd (%) for $C_{13}H_{17}BrO_3$ (301.18): C, 51.84; H, 5.69; Br, 26.53. Found: C, 51.79; H, 5.72; Br, 26.57.