

Trifluoromethanesulfonic Acid Catalyzed Alkylation of Arenes with Methyl (2*R*)-Glycidate

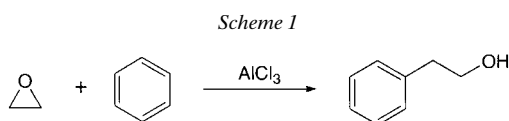
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Dedicated to Professor Rolf Huisgen on the occasion of his 85th birthday with admiration and friendship

Methyl (*R*)-glycidate (= methyl (*R*)-oxiranecarboxylate; **2**) in superacidic trifluoromethanesulfonic acid medium reacts with electron-rich arenes to give α -hydroxy- β -arylpropanoate derivatives **3a–3f** with high stereospecificity. At the same time, the observed high regioselectivity has been attributed to superelectrophilic activation of the glycidate.

Introduction. – *Friedel–Crafts* alkylation and acylation are important methodologies for C,C bond-formation with aromatic compounds [1]. Epoxides are versatile building blocks for the synthesis of many bioactive natural products [2]. They are well-known carbon electrophiles able to react with various nucleophiles, and their ability to undergo regioselective ring opening reactions contributes largely to their synthetic value [3]. The epoxide ring opening with certain nucleophiles, in particular, with arenes, has been reported under acid catalysis [4][5]. For instance, β -phenylethyl alcohol, an important ingredient of artificial rose-oil, is prepared by the condensation of benzene with ethylene oxide in the presence of AlCl₃ catalyst (*Scheme 1*) [6].

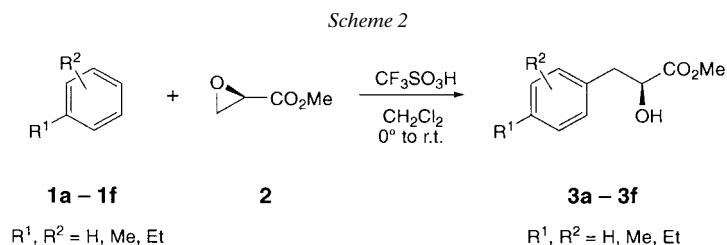


However, the above studies have revealed that these alkylations are often accompanied by various side reactions, such as isomerization, fragmentation, and dealkylation, together with side-skeletal and positional rearrangements and polymerization of oxiranes. Although, the acid-coordinated epoxide complex initially undergoes ring opening to give the most stable ion pair before attacking the arene, isomeric by-products are always observed as well [4c][5]. The stereochemistry of the ring-opening process has been investigated thoroughly. It has been shown that the use of *Lewis* acids or strong protic acids, well-known catalysts of *Friedel–Crafts* reactions, cause partial racemization even under mild reaction conditions [7].

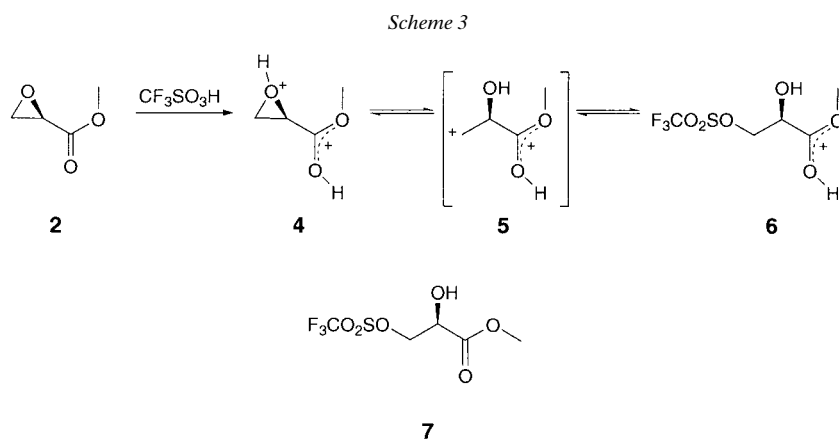
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Rarely, reports have been published on the use of glycidate as an electrophilic reagent in *Friedel–Crafts* chemistry. This is mainly due to the instability of the carboxy group under the reaction conditions [8]. This drawback has prevented the use of glycidates as useful building blocks in *Friedel–Crafts* reactions.

Herein, we describe a convenient synthetic approach for the preparation of α -hydroxy- β -arylpropanoates **3a–3f** in high stereospecificity from methyl (*R*)-glycidate (= methyl (*R*)-oxiranecarboxylate; **2**) and arenes **1a–1f** under superacidic conditions (*Scheme 2*).



Results and Discussion. – We have found that superacidic $\text{CF}_3\text{SO}_3\text{H}$ ($H_0 = -14.1$) serves as a suitable medium to effectively catalyze the regioselective ring opening of the glycidate and to induce the stereospecific *Friedel–Crafts* electrophilic alkylation of several arenes. Although epoxides can undergo ring opening at either of the C-atoms, with the glycidate in superacids, products derived from only one regioselective ring opening is observed²⁾. It appears that the protonation of methyl (*R*)-glycidate (**2**) in $\text{CF}_3\text{SO}_3\text{H}$ results in the dioxonium dication **4** which may be in limited equilibrium with the O,C-diprotonated form (**5**) or the protonated primary sulfonate derivative **6** (*Scheme 3*). This renders the unsubstituted C-atom with significant electropositive



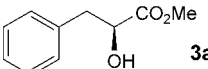
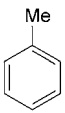
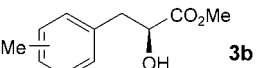
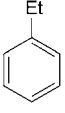
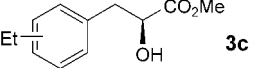
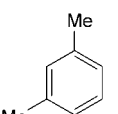
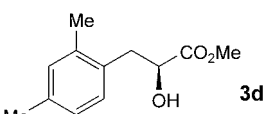
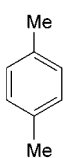
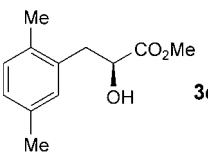
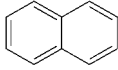
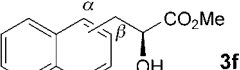
²⁾ The ring opening of dioxonium dication **4** leading to the secondary carbocation would entail the positive charges too proximal resulting in significant charge–charge repulsion.

character. Such superelectrophilic activation [9] is capable of effecting facile, regioselective *Friedel–Crafts* alkylation.

The nature of the reaction depends, furthermore, on the activation of the arene, as seen from the yields obtained from various arenes (*Table*). The reaction works well with electron rich arenes. In the case of benzene, the product yield is only moderate. Although it is not necessary to postulate the limiting dication **5** as the *de facto* intermediate, the intermediacy of ion **6** is reasonable. It is significant to note that the related neutral sulfonate **7** is indeed the main product when the glycidate **2** is allowed to react with $\text{CF}_3\text{SO}_3\text{H}$ in absence of arenes under comparable experimental conditions. It is also the main by-product when the aromatic ring is not sufficiently activated.

To establish the role of methyl 2-hydroxy-3-[(trifluoromethylsulfonyl)oxy] propanoate (**7**) on the reaction pathway, it was itself used as an electrophilic reagent with a

Table. Formation of Friedel–Crafts Products **3a–3f** from Methyl (R)-Glycidate (**2**) and Arenes **1a–1f**

Entry	Arene	Friedel–Crafts Products	Yield [%]	By-products (Yield [%])
a	 1a	 3a	53	7 (30)
b	 1b	 3b	91 (4:4:2) ^a	7 (5)
c	 1c	 3c	75 (5:4:1) ^a	7 (20)
d	 1d	 3d	92	7 (5)
e	 1e	 3e	79	7 (11)
f	 1f	 3f	93 (6:4) ^b	7 (3)

^a) *p/o/m* Ratio. ^b) α/β Ratio.

very active arene, *m*-xylene, as the substrate in *Friedel–Crafts* alkylation under comparable experimental conditions. The reaction mainly gave the expected *Friedel–Crafts* alkylation product **3d** in excellent yield (*Entry d* in the *Table*).

Furthermore, from **7** we never detected any dehydrated cinnamate derivatives despite their greater stability. This can be best rationalized by the electron-withdrawing property of the ester functionality, which destabilizes the α -carbocationic intermediate [10] necessary to produce the alkene by subsequent deprotonation. This is the same reason why the glycidate also undergoes regioselective ring opening under superacidic conditions to provide the alkylation products (*vide infra*). Moreover, since the C,C bond-formation takes place specifically at the CH₂ C-atom, the configuration (*R*) at the stereogenic methine C-atom bearing the ester and the OH functionalities is mostly retained in the products³). This indicates the high stereospecific nature of the alkylation reaction.

Conclusion. – We have developed a useful stereoselective *Friedel–Crafts* alkylation reaction for electron-rich arenes to α -hydroxy- β -aryl propanoates derivatives **3a–3f** in high stereospecificity by activating methyl (*R*)-glycidate (**2**) in superacidic CF₃SO₃H medium. Extension of these reactions to a wide variety of substituted aromatic and heteroaromatic systems is currently underway.

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Experimental Part

General. A freshly opened bottle of CF₃SO₃H (3M) was used as received. All reactions were carried out under a blanket of Ar with the rigid exclusion of moisture from all reagents and glassware. All the compounds were isolated and purified by flash chromatography (FC), with silica gel (*Mallinckodt*, 60–200 Mesh) and dry hexane and AcOEt as eluents. In some cases only one pure isomer was isolated. ¹H-, ¹³C-, and ¹⁹F-NMR spectra were recorded on a 300-MHz superconducting *Varian Unity* NMR spectrometer. High-resolution mass spectra (HR-MS) were measured at the Mass Spectrometry Service Facility of the University of California at Los Angeles. Isomer ratios in different reactions were determined by ¹H-NMR and GC/MS analyses.

General Procedure for the Alkylation. To a soln. of arene (22.5 mmol) and CF₃SO₃H (18.75 mmol, 1.65 ml) in 0.75 ml of CH₂Cl₂, cooled to 0°, a soln. of methyl (*R*)-glycidate (=methyl (*R*)-oxiranecarboxylate 1.875 mmol, 0.195 g) in CH₂Cl₂ (0.75 ml) was added dropwise with a syringe over 4 min. The soln. was stirred vigorously; after the mixture turned pale orange, the cooling bath was removed, and the mixture was brought to r.t. After 15 min, the mixture was poured onto 10 g of ice. The mixture was made slightly basic with NaHCO₃ and extracted with CH₂Cl₂. The org. phase was finally washed with brine and H₂O, and dried (anh. MgSO₄). The residue obtained after concentration under vacuum was purified by column chromatography (CC), and analyzed by NMR and GC/MS.

Methyl (R)-2-hydroxy-3-phenylpropanoate (3a) was purified by FC with hexane/AcOEt 2:1. ¹H-NMR (300 MHz, CDCl₃): 2.97 (*dd*, *J* = 6.9, 13.8, 1 H); 3.14 (*dd*, *J* = 4.2, 13.8, 1 H); 3.72 (*s*, 3 H); 4.47 (*dd*, *J* = 4.2, 6.9, 1 H); 7.20–7.25 (*m*, 1 H); 7.26–7.29 (*m*, 2 H), 7.28–7.34 (*m*, 2 H). ¹³C-NMR (75 MHz, CDCl₃): 40.5; 52.5; 71.2; 126.9; 128.4; 129.4; 136.2; 174.6. CI-HR-MS: 180.0787 (C₁₀H₁₂O₃; calc. 180.0786).

Methyl (R)-2-hydroxy-3-(4-methylphenyl)propanoate (3b) was purified by FC with hexane/AcOEt 2:1. ¹H-NMR (300 MHz, CDCl₃): 2.34 (*s*, 3 H); 3.08 (*dd*, *J* = 4.4, 13.9, 1 H); 3.16 (*dd*, *J* = 2.0, 13.9, 1 H); 3.76 (*s*, 3 H); 4.11 (*dd*, *J* = 2.0, 4.4, 1 H); 7.09–7.11 (*br.*, 4 H). ¹³C-NMR (75 MHz, CDCl₃): 21.0; 40.0; 52.3; 71.3; 129.1; 129.2; 134.9; 136.1; 174.8. EI-HR-MS: 194.0943 (C₁₁H₁₄O₃; calc. 194.0942).

³) The compounds **3a** and **3e** were obtained with 84 and 77.3% ee, respectively, based on Mosher's acid reaction [11] (¹⁹F-NMR and HPLC analysis on a chiral column).

Methyl (R)-3-(4-ethylphenyl)-2-hydroxypropanoate (3c) was purified by FC with hexane/AcOEt 3:1. ¹H-NMR (300 MHz, CDCl₃): 1.22 (t, *J* = 7.5, 3 H); 2.62 (q, *J* = 7.5, 2 H); 3.10 (dd, *J* = 4.5, 14.1, 1 H); 3.19 (dd, *J* = 4.8, 14.1, 1 H); 3.78 (s, 3 H); 4.44 (dd, *J* = 4.5, 4.8, 1 H); 7.13 (br. s, 4 H). ¹³C-NMR (75 MHz, CDCl₃): 15.6; 28.4; 52.4; 71.3; 127.9; 129.3; 130.1; 174.6. EI-HR-MS: 208.1097 (C₁₂H₁₆O₃; calc. 208.1099).

Methyl (R)-3-(2,4-dimethylphenyl)-2-hydroxypropanoate (3d) was purified by FC with hexane/AcOEt 3:1. ¹H-NMR (300 MHz, CDCl₃): 2.27 (s, 3 H); 2.29 (s, 3 H); 2.77 (br., 1 H); 3.75 (s, 3 H); 2.87 (dd, *J* = 8.1, 14.1, 1 H); 3.11 (dd, *J* = 4.5, 14.1, 1 H); 4.37 (dd, *J* = 4.5, 8.1, 1 H); 6.84 (br. d, *J* = 6, 1 H); 6.95 (m, 1 H); 6.70 (br. d, *J* = 7.5, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 19.3; 20.7; 37.3; 52.2; 70.9; 126.4; 129.8; 131.7; 136.3; 137.0; 126.4; 174.8. EI-HR-MS: 208.1099 (C₁₂H₁₆O₃; calc. 208.1099).

Methyl (R)-3-(2,5-dimethylphenyl)-2-hydroxypropanoate (3e) was purified by FC with hexane/AcOEt 3:1. ¹H-NMR (300 MHz, CDCl₃): 2.30 (br. s, 6 H); 2.66 (d, *J* = 6.0, 1 H); 2.88 (dd, *J* = 7.8, 14.4, 1 H); 3.14 (dd, *J* = 4.2, 14.4, 1 H); 3.79 (s, 3 H); 4.42 (ddd, *J* = 4.5, 7.8, 6.0, 1 H); 7.05 (d, *J* = 7.5, 1 H); 6.97 (br., 2 H). ¹³C-NMR (75 MHz, CDCl₃): 19.1; 20.9; 37.9; 52.4; 71.0; 127.7; 130.3; 130.7; 133.5; 134.6; 135.3; 174.9. EI-HR-MS: 208.1098 (C₁₂H₁₆O₃; calc. 208.1099).

Methyl (R)-2-hydroxy-3-(naphthalen-1-yl)propanoate (3fa) and *methyl (R)-2-hydroxy-3-(naphthalen-2-yl)propanoate (3fb)* were purified as mixtures (but not separated) by FC with hexane/AcOEt 3:1. The assignments for the isomers were based on relative intensities. ¹H-NMR (300 MHz, CDCl₃): **3fa**: 3.30 (dd, *J* = 7.8, 14.1, 1 H); 3.64 (dd, *J* = 4.5, 14.1, 1 H); 3.70 (s, 3 H); 4.52 (ddd, *J* = 4.5, 7.8, 1 H); 7.36–7.40 (m, 2 H); 7.38–7.54 (m, 2 H); 7.74–7.81 (m, 1 H); 7.84 (d, *J* = 8.4, 1 H); 8.06 (d, *J* = 8.4, 1 H); **3fb**: 3.09 (dd, *J* = 6.6, 13.8, 1 H); 3.25 (dd, *J* = 4.5, 13.8, 1 H); 3.73 (s, 3 H); 4.50 (dd, *J* = 6.6, 4.5, 1 H); 7.30–7.34 (m, 1 H); 7.38–7.54 (m, 2 H); 7.65 (s, 1 H); 7.74–7.81 (m, 3 H). ¹³C-NMR (75 MHz, CDCl₃): **3fa**: 37.7; 52.4; 71.0; 123.5; 125.5; 125.9; 127.5; 128.7; 132.3; 132.6; 133.3; 174.6; **3fb**: 40.6; 52.4; 71.2; 125.3; 125.5; 125.9; 127.6; 127.7; 127.9; 128.1; 132.6; 132.0; 133.8; 174.4. EI-HR-MS: 230.0946 (C₁₄H₁₄O₃; calc. 230.0942).

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