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

by **Pablo J. Linares-Palomino**[1]), **G. K. Surya Prakash***, and **George A. Olah***

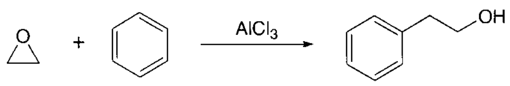
Loker Hydrocarbon Research Institute and Department of Chemistry
University of Southern California, Los Angeles, CA 90089-1661, USA

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 $AlCl_3$ catalyst (*Scheme 1*) [6].

Scheme 1



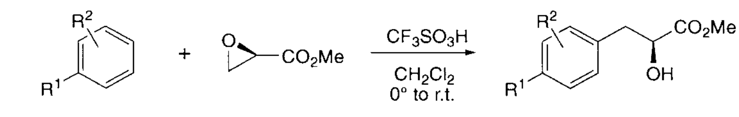
However, the above studies have revealed that these alkylations are often accompanied by various side reactions, such as isomerization, fragmentation, and dealkylation, together with side-skeletal and positional rearrangements and polymerization of oxiranes. Although, the acid-coordinated epoxide complex 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].

[1]) Visiting Scientist from Dpto. Química Inorgánica y Orgánica, Facultad de Ciencias Experimentales, Universidad de Jaén, 23071-Jaén, Spain.

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*).

Scheme 2

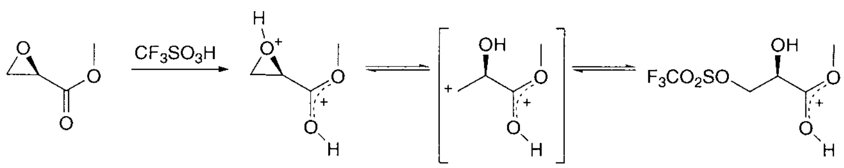


1a – 1f **2** **3a – 3f**

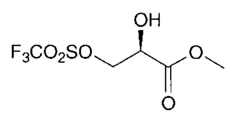
R1, R2 = H, Me, Et   R1, R2 = H, Me, Et

Results and Discussion. – We have found that superacidic CF_3SO_3H ($H_o = -14.1$) 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 observed[2]). It appears that the protonation of methyl (*R*)-glycidate (**2**) in CF_3SO_3H results in the dioxonium dication **4** which may be in limited equlibrium 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

Scheme 3



2 **4** **5** **6**



7

---

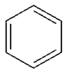
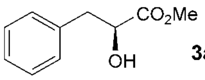
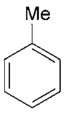
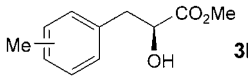
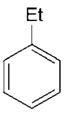
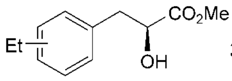
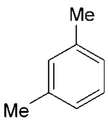
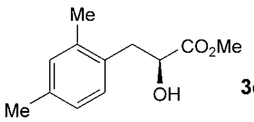
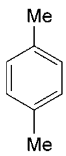
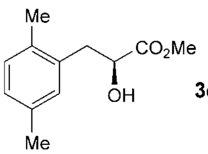
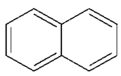
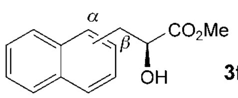
[2]) The ring opening of dionium dication **4** leading to the secondary carbocation would entail the positive charges too proximal resulting in significant charge–charge repulsion.

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 CF_3SO_3H 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 CH_2 C-atom, the configuration (*R*) at the stereogenic methine C-atom bearing the ester and the OH functionalities is mostly retained in the products[3]). 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 CF_3SO_3H medium. Extension of these reactions to a wide variety of substituted aromatic and heteroaromatic systems is currently underway.

We thank the *Loker Hydrocarbon Research Institute* for the financial support. Dr. *T. Mathew* is acknowledged for his help in obtaining some of the mass-spectral data.

Experimental Part

General. A freshly opened bottle of CF_3SO_3H (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. ^{1}H-, ^{13}C-, and ^{19}F-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 ^{1}H-NMR and GC/MS analyses.

General Procedure for the Alkylation. To a soln. of arene (22.5 mmol) and CF_3SO_3H (18.75 mmol, 1.65 ml) in 0.75 ml of CH_2Cl_2, cooled to 0°, a soln. of *methyl* (*R*)-glycidate (=methyl (*R*)-oxiranecarboxylate 1.875 mmol, 0.195 g) in CH_2Cl_2 (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 $NaHCO_3$ and extracted with CH_2Cl_2. The org. phase was finally washed with brine and H_2O, and dried (anh. $MgSO_4$). 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. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 40.5; 52.5; 71.2; 126.9; 128.4; 129.4; 136.2; 174.6. CI-HR-MS: 180.0787 ($C_{10}H_{12}O_3$; calc. 180.0786).

*Methyl (*R*)-2-hydroxy-3-(4-methylphenyl)propanoate* (**3b**) was purified by FC with hexane/AcOEt 2:1. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.0; 40.0; 52.3; 71.3; 129.1; 129.2; 134.9; 136.1; 174.8. EI-HR-MS: 194.0943 ($C_{11}H_{14}O_3$; 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] (^{19}F-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. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.6; 28.4; 52.4; 71.3; 127.9; 129.3; 130.1; 174.6. EI-HR-MS: 208.1097 ($C_{12}H_{16}O_3$; calc. 208.1099).

*Methyl (*R*)-3-(2,4-dimethylphenyl)-2-hydroxypropanoate* (**3d**) was purified by FC with hexane/AcOEt 3:1. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 ($C_{12}H_{16}O_3$; calc. 208.1099).

*Methyl (*R*)-3-(2,5-dimethylphenyl)-2-hydroxypropanoate* (**3e**) was purified by FC with hexane/AcOEt 3:1. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 ($C_{12}H_{16}O_3$; calc. 208.1099).

*Methyl (*R*)-2-hydroxy-3-(naphthalen-1-yl)propanoate* (**3f*α***) *and methyl (*R*)-2-hydroxy-3-(naphthalen-2-yl)propanoate* (**3f*β***) were purified as mixtures (but not separated) by FC with hexane/AcOEt 3:1. The assignments for the isomers were based on relative intensities. ^{1}H-NMR (300 MHz, $CDCl_3$): **3f*α***: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); **3f*β***: 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). ^{13}C-NMR (75 MHz, $CDCl_3$): **3f*α***: 37.7; 52.4; 71.0; 123.5; 125.5; 125.9; 127.5; 128.7; 132.3; 132.6; 133.3; 174.6; **3f*β***: 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 ($C_{14}H_{14}O_3$; calc. 230.0942).

REFERENCES

[1] H. Heaney, in 'Comprehensive Organic Synthesis', Vol. 2, Eds. B. M. Trost, I. Fleming, Pergamon, Oxford, 1991, p. 733, p. 753; G. A. Olah, R. Krishnamurti, G. K. S. Prakash, in 'Comprehensive Organic Synthesis', Vol. 1; Eds. B. M. Trost, I. Fleming, Pergamon, Oxford, 1991, 293; G. A. Olah, 'Friedel–Crafts Chemistry', Wiley-Interscience, New York, 1973.

[2] R. E. Parker, N. S. Isaacs, *Chem. Rev.* **1959**, *59*, 737; C. Bonini, G. Righi, *Synthesis* **1994**, 225.

[3] A. S. Rao, S. K. Paknikar, J. G. Kirtane, *Tetrahedron* **1983**, *39*, 2323; J. Gorzynski Smith, *Synthesis* **1984**, 629.

[4] a) J. F. Norris, J. N. Ingraham, *J. Am. Chem. Soc.* **1938**, *60*, 1421; b) A. F. Barrero, E. J. Alvarez-Manzaneda, P. Linares Palomino, *Tetrahedron* **1994**, *50*, 13239; c) J. S. Yadav, B. V. S. Reddy, S. Abraham, G. Sabitha, *Synlett* **2002**, 1550.

[5] N. Milstein, *J. Heterocycl. Chem.* **1968**, *5*, 337.

[6] Farbenindustrie, I.G. Germ. Pat. 523, 436, 1931.

[7] C. C. Price, M. Lund, *J. Am. Chem. Soc.* **1940**, *62*, 3105; R. L. Burwell, S. Archer, *J. Am. Chem. Soc.* **1942**, *64*, 1032.

[8] S. P. Singh, J. Kagan, *J. Org. Chem.* **1970**, *35*, 2203.

[9] G. A. Olah, *Angew. Chem., Int. Ed.* **1993**, 32, 767.

[10] Y. Kobayashi, I. Kumadaki, T. Nagai, A. Takahashi, Y. Yamauchi, *Chem. Pharm. Bull.* **1984**, *32*, 4382; O. Takahashi, K. Furuhashi, M. Fukumasa, T. Hirai, *Tetrahedron Lett.* **1990**, *31*, 7031.

[11] D. E. Ward, C. K. Rhee, *Tetrahedron Lett.* **1991**, *32*, 7165.

Received January 10, 2005