A practical synthesis of chiral 3-aryloxy-1,2-propanediols

Mehmet Karakaplan*, Yılmaz Turgut and Halil Hoşgören

Department of Chemistry, Science and Art Faculty, Dicle University, 21280 Diyarbakır, Turkey

Chiral 3-aryloxy-1,2-propanediols (**1–5**) of >96 % ee were obtained in high yield by the nucleophilic addition of substituted phenols to chiral glycidol in the presence of piperidine hydrochloride as catalyst.

Keywords: chiral 3-aryloxy-1,2-propanediols, ring opening of glycidol

Many racemic 3-aryloxy-1,2-propanediols and their derivatives are pharmaceutically important intermediates in for example the synthesis of β-blockers.[1] β-Blockers are still sold as racemates despite the need to change to enantiopure forms.[2] The enantiomers, are commonly prepared from enantiomerically enriched glycidol or related chiral three carbon synthons.[3] The simplest protocol makes use of nucleophilic attack of phenols on oxiranes. The reactions of glycidols with nucleophiles comprise two types of transformations, ring opening and substitution (Scheme 1).

Ring opening reactions require regiospecific attack of a nucleophile on the C-3 position. Another versatile reaction is the substitution at the C-1 position when X is a good leaving group as in epichlorohydrin or a glycidyl ether. The reaction of racemic glycidol with phenols in the presence of alkali hydroxide or alkali alcoholate[4] and tertiary amine or quaternary ammonium salts[5] has been used for the synthesis of racemic 3-aryloxy-1,2-propanediols. This approach has not been reported for chiral synthesis. Ti(O-*i*-Pr)$_4$-mediated ring opening reaction of chiral glycidol has been shown to provide excellent regioselectivity.[6] However, there were problems in the work-up due to the moderate solubility of these compounds in water. A similar reaction using substituted phenols was conducted in the presence of triethylamine.[7] In general, the desired 1,2-diols were obtained with the slight decrease in the enantiopurity together with a 1,3-diol by-product (3–4 % yield). The epoxide-opening reaction of chiral glycidols with various phenols by using catalytic amount of caesium floride in DMF[8] and sodium hydroxide in water[9] has also been reported recently. Surprisingly, the ring-opening reaction of chiral glycidol with phenols by catalytic amount of piperidine hydrochloride is not known. Because of the simplicity of these conditions we investigated the opening of (*S*)-glycidol with various phenols using catalytic amount of piperidine hydrochloride (Scheme 2). The results are summarised in Table 1.

Results and discussions

The reaction of glycidol with substituted phenols took place much more efficiently in the absence of solvent. Treatment of (*S*)-glycidol with various phenols in the presence of 5 % of piperidine hydrochloride at 70–80°C provided the desired (*S*)-3-aryloxy-1,2-propanediols (**1–5**) in excellent yields (Table 1). In this reaction, a decrease of % ee were not detected. However, the loss to side products *e.g.* 1, 3-diol, was 6–8 %.

Table 1 Ring-opening reaction of chiral glycidol with phenols

Diols	Phenol	Hours / Yield /%	ee /%
1	Phenol	4 / 88	97
2	4-Chlorophenol	6 / 83	96
3	4-Methoxyphenol	4 / 86	98
4	4-*ter*-Butylphenol	5 / 85	98
5	1-Naphthol	4 / 78	96

The nucleophilie attack occurred mainly on the C-3 position of the oxirane. Exclusive regioselective ring opening is evident from the configuration of diols without decrease of % ee and ^{13}C NMR of diols **1** and **2**. Regioselectivity is not a problem at all in this case because the C-3 position is also a terminal centre. Instead, the major concerns here are the synthetic utility and practical convenience in handling the ring opened products.

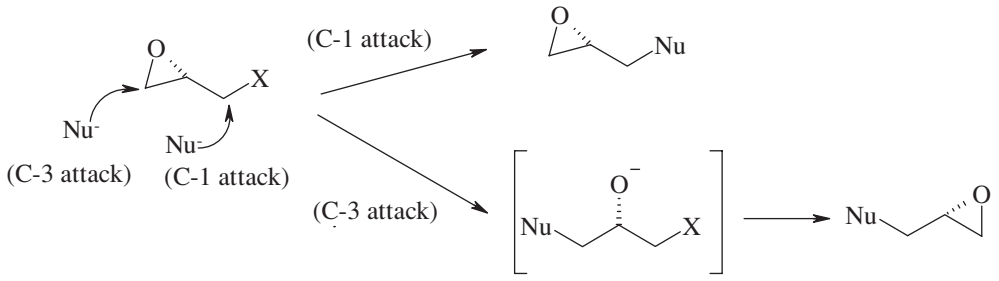
If the reaction is carried out at room temperature by using this catalysis, it proceeds only very slowly. For example, when starting from racemic glycidol, the reaction time of **1–5** diols were found to be 15, 30, 4, 5, and 50 days respectively. We have also found that under otherwise identical reaction conditions, no ring opening occurs when piperidine hydrochloride was omitted.

In summary, a convenient and a new practical method is described for the preparation of chiral 3-aryloxy-1,2-propanediols. Remarkable, % ee of the starting material is preserved perfectly and hence, these reactions provide convenient access to enantiopure β–blockers.

Experimental

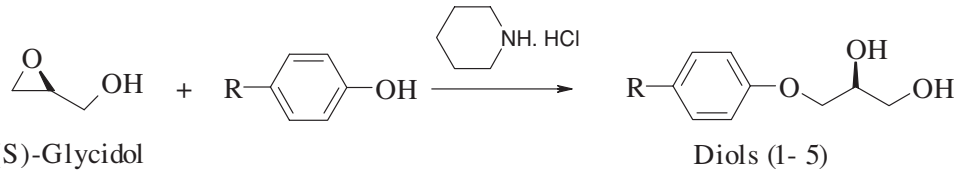
General information

(S)-Glycidol (97 %ee), phenol and piperidine hydrocholoride were purchased from Fluka without further purification. Melting points were determined with a Gallenkamp Model apparatus with open capillaries. Elemental analyses were performed with a Carlo-Erba



Scheme 1

* Correspondent. E-mail: mkkaplan@dicle.edu.tr



Scheme 2

1108 model instrument and enantiomeric excesses were determined by a chiral detector (Hawlett Packard) combined Cecil 1100 HPLC instrument on a chiralcel OD column (4.6 mm, eluent, hexane-2-propanol, 90:10). Optical rotations were taken on a Perkin Elmer 341 model polarimeter.

Synthesize of (S)-3-phenoxypropane-1, 2-diol (**1**): Phenol (381 mg, 4 mmol), (*S*)-glycidol (300 mg, 4 mmol) and piperidine hydrochloride (24 mg, 0.2 mmol) were stirred at 70–80°C for 4 h. The mixture was monitored by TLC during the reaction time, and then it was purified by column chromatography on silica gel (1:3 / hexane: EtOAc). Solid was dried at 50°C (25 mmHg) for 2 h to afford pure **1** (591 mg, 88 %); m.p. 62-63°C, lit. (8) mp 62.5-64.5 °C; $[\alpha]_D^{20}$ +9.3 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ*:* 2.45 (bs, 2H, OH), 3.75–3.88 (ddd, 2H), 4.05–4.11 (m, 2H), 4.12–4.16 (m, 1H), 6.92–7.02 (m, 3H), 7.28–7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ*:* 64.15, 69.26, 71.09, 114.98, 121.63, 129.99, 158.87. Anal. Calcd. For $C_9H_{12}O_3$; C, 64.00; H, 7.00. Found: C, 64.24; H, 7.02%.

Synthesis of (S)-3-(p-chlorophenoxy)propane-1, 2-diol (**2**): Diols **2–5** were prepared following the procedure described for the preparation of **1**: M.p. 83–84 °C (lit. 7,9 m.p. 78–80, 83 °C respectively); $[\alpha]_D^{20}$ +10.4 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ*:* 2.47 (bs, 2H, OH), 3.74–3.86 (ddd, 2H), 4.01–4.03 (m, 2H), 4.10–4.14 (m, 1H), 6.84–6.86 (m, 2H), 7.24–7.27 (m, 2H); ^{13}C NMR ($CDCl_3$) δ*:* 63.15, 69.70, 71.24, 115.45, 123.20, 129.20, 157.85. Anal. Calcd. For $C_9H_{11}O_3Cl$: C, 53.46; H, 5.44. Found: C, 53.76; H, 5.40%.

Synthesis of (S)-3-(p-methoxyphenoxy)propane-1,2-diol (**3**): M.p. 80–82 °C, (lit. 7 m.p. 80 °C); $[\alpha]_D^{20}$ +10.5 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ*:* 3.65–3.77 (m, 7H), 3.93–3.94 (m, 2H), 4.01 (m, 1H), 6.76–6.83 (m, 4H). Anal. Calcd. For $C_{10}H_{14}O_4$: C, 60.60; H, 7.07. Found: C, 60.00; H, 7.10%.

Synthesis of (S)-3-(p-ter-buthylphenoxy)propane-1,2-diol (**4**): M.p. 86–88°C; $[\alpha]_D^{20}$ +9.8 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ*:* 1.32 (s, 9H), 2.30 (bs, 2H, OH), 3.74–3.87 (ddd, 2H), 4.04–4.05 (m, 2H), 4.11–4.16 (m, 1H), 6.86–6.88 (m, 2H), 7.32–7.34 (m, 2H). Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.64; H, 8.92. Found: C, 69.55; H, 8.88%.

Synthesise of (S)-3-(naphtoxy)propane-1,2-diol (**5**): M.p. 111–112°C, (Lit. 7,9 m.p. 104–106 °C), 112 °C respectively. $[\alpha]_D^{20}$ +11.5 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ*:* 2.10 (bs, 2H, OH), 3.70–3.78 (ddd, 2H), 3.86–3.92 (m, 2H), 4.05–4.14 (m, 1H), 6.99 (m, 1H), 7.25–7.60 (m, 4H), 7.83 (m, 1H), 8.17 (m, 1H). Calcd. For $C_{13}H_{14}O_3$: C, 71.56; H, 6.42. Found: C, 71.50; H, 6.38%.

This work was supported by TUBITAK (Turkish Scientific and Technical Research Council; TBAG-2152 (102T035)).

Received 30 September 2004; accepted 1 November 2004
Paper 04/2792

References

1 A. Kleemann and J. Engel, *Pharmazeutische Wirkstoffe*, Georg Thieme Verlag, 1982.
2 S.C. Stinson, *Chem. Eng. News* 1997, June 2, p 28.
3 S.C. Hanson, *Chem. Rev*., 1991, **91**, 437.
4 W. Merk, O.P. Wagner, P. Werle and R.S. Nygren, U.S. Patent, 1983, 4, **390**, 732.
5 British Pat. No. 628497
6 M. Caron and K.B.J. Sharpless, *Org. Chem*. 1985, **50**, 1557.
7 J. Chen and W. Shum, *Tetrahedron Lett*., 1995, **36**, 2379.
8 K. Kitaori, Y. Furukawa, H. Yoshimoto and J. Otera, *Tetrahedron* 1999, **55**, 14381.