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Notes

Intramolecular Dehydrohalogenation during Base-Mediated Reaction of Diols with Dihaloalkanes

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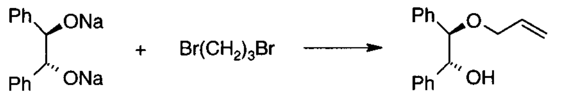
Abstract: Sodium alkoxides of a variety of diols were reacted with dibromoalkanes. It was found that the products of the reaction were alkenyl ethers resulting from intramolecular dehydrohalogenation of the initially formed monobromo ethers.

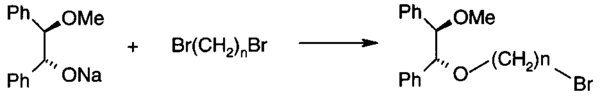
Participation of neighboring groups in nucleophilic displacement reactions is a well-known phenomenon.[1,2] The study of the alkaline hydrolysis of aliphatic bromo acids[3] and chloro alcohols[4] and also solvolysis studies[5] clearly proved the participation of even nonadjacent carboxylate, alcoholate, and phenyl groups. Intramolecular dehydrohalogenation has been observed during the kinetic studies on the cyclization of *o*-*ω*-bromoalkoxyphenoxides.[6] During the course of our work, we were interested in chiral cyclic ethers from some C_2-symmetric diols. During these attempts, we encountered facile intramolecular dehydrohalogenation rather than required cyclic ether formation. This manuscript describes the details of our findings.

The alcohols selected for our study were known chiral 1,2-, 1,3-, and 1,4-diols. A suspension of sodio dialkoxide in THF was obtained by treatment with sodium hydride. The alkoxide was then treated with 1,3-dibromopropane or 1,4-dibromobutane. When (±)-hydrobenzoin was thus reacted, no cyclic ether was obtained with dibromopropane. Instead, the monoallyl ether **1** was isolated in 59% yield (eq 1). The formation of 1-alkenyl ethers was surprising and can only be explained by intramolecular dehydrohalogenation. The confirmation was obtained when monomethyl derivative of the diol was subjected to the same reaction (eq 2).

If the reaction is controlled to provide good yield, the methodology can provide easy access to monoalkenyl ethers of diols. The alternate alkylation with allyl bromide or butenyl bromide leads to a mixture of mono- and dialkylated products. We therefore examined several diols as depicted in Table 1. The substrates were so chosen that one could extend the reaction to homochiral ethers starting from homochiral diols. Normally, 4-, 5-, or 6-membered-ring intermediates would be involved for such elimination. However, the conformationally rigid structure of the present substrates makes it possible to utilize even 9- or 10-membered rings (entries 6 and 7 in Table 1). In conclusion, we present here a methodology for the preparation of monoalkenyl ethers of chiral diols. These products are amenable for further manipulation to obtain a variety of chiral molecules.



(1)



(2)

Experimental Section

All the reactions were performed under dry argon atmosphere. THF was freshly distilled from sodium benzophenone ketyl. DMF was distilled from calcium hydride and stored over 4A molecular sieves. The reactions were monitored by TLC. The products were purified by "flash chromatography" using silica gel (200−400 mesh) as the sorbent and hexanes−ethyl acetate (9:1) mixture as the eluent. ^{1}H NMR spectra were recorded at 200 MHz with TMS as internal standard. ^{13}C NMR spectra were recorded at 50 MHz with CDCl$_3$ ($\delta = 77$) as the reference. (±)-Hydrobenzoin,[7] (±)-1,3-diphenyl-2,2-dimethyl-1,3-propanediol,[8] and (−)-TADDOL[9] were synthesized as described in the literature.

Alkylation Procedure. The following procedure for the alkylation of (±)-hydrobenzoin with 1,3-dibromopropane is representative. To a stirred suspension of NaH (0.16 g, 4 mM, 60% dispersion in oil) in anhydrous THF (1.5 mL) was added dropwise a solution of the diol (0.43 g, 2 mM) in THF (2.5 mL). The reaction mixture was stirred until the evolution of hydrogen ceased (about 0.5 h). To the resulting suspension, the dibromide (0.44 g, 2.2 mM) dissolved in anhydrous DMF (2 mL) was added in one lot. A mildly exothermic reaction ensued, and it was found to be complete (by TLC) in 2 h. The reaction was quenched by the addition of 2 N HCl (1 mL), diluted with water (10 mL), and extracted with ether. The extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography to obtain the (±)-propenyl ether **1** (0.30 g, 59%): ^{1}H NMR δ 3.77 (br s, OH), 3.90 (dd, $J = 4.8$, 9.7 Hz, 1H), 4.10 (dd, $J = 4.8$, 9.6 Hz, 1H), 4.40 (d, $J = 9.7$ Hz, 1H), 4.80 (d, $J = 9.7$ Hz, 1H), 5.15−5.40 (m, 2H), 5.85−6.13 (m, 1H), 6.95−7.40 (m, 10H); ^{13}C NMR δ 69.6, 78.4, 86.6, 117.0, 127.2, 127.7, 127.9, 134.3, 137.7, 139.3; MS *m/z* 236 (M − H$_2$O), 105 (base peak). Anal. Calcd for C$_{17}$H$_{18}$O$_2$: C, 80.27; H, 7.15. Found: C, 80.53; H 7.18.

(±)-Propenyl ether **2**: ^{1}H NMR δ 2.60 (br s, OH), 3.80−4.00 (m, 2H), 4.55 (d, $J = 5.3$ Hz, 1H), 4.95 (d, $J = 5.3$ Hz, 1H), 5.10−

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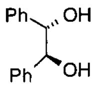
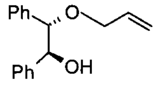
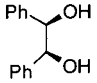
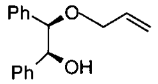
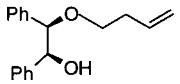
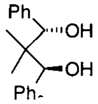
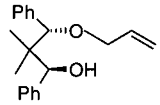
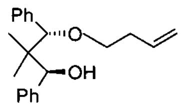
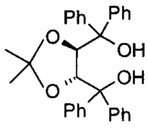
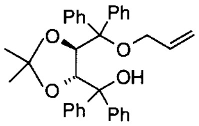
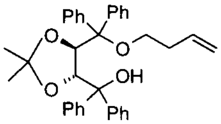
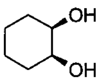
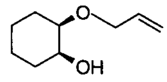
Table 1. Base-Mediated Reaction of Diols with Dihaloalkanes

Entry	Diol	Br(CH$_2$)$_n$Br	Temp., °C	Time, h	Major product
1	 (±)-	n = 3	25	2	 **1** (59%)
2	 *meso-*	n = 3	25	2	 **2** (47%)
3		n = 4	80	2	 **3** (38%)
4	 (±)-	n = 3	25	3	 **4** (86%)
5		n = 4	80	3	 **5** (32%)
6		n = 3	25	2	 **6** (90%)
7		n = 4	80	2	 **7** (65%)
8		n = 3	25	1	 **8** (58%)

5.30 (m, 2H), 5.70−5.80 (m, 1H), 7.15−7.45 (m, 10H); ^{13}C NMR δ 69.8, 78.6, 87.6, 116.7, 127.2, 127.9, 134.3, 137.7, 140.3; MS *m/z* 236 (M − H$_2$O), 105 (base peak). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.27; H, 7.15. Found: C, 80.36; H 7.06.

(±)-Butenyl ether **3**: ^{1}H NMR δ 2.40 (q, *J* = 5.3 Hz, 2H), 3.30−3.62 (m, 2H), 3.58 (br. s, OH), 4.26 (d, *J* = 10.6 Hz, 1H), 4.68 (d, *J* = 10.6 Hz, 1H), 4.98−5.24 (m, 2H), 5.72−6.00 (m, 1H), 6.84−7.39 (m, 10H); ^{13}C NMR δ 34.1, 68.6, 77.0, 86.0, 116.2, 127.1, 127.4, 127.6, 127.9, 135.2, 138.0, 140.4; MS *m/z* 250 (M − H$_2$O), 161 (base peak). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.53; H 7.53. Found: C, 81.12; H 8.15.

(±)-Propenyl ether **4**: ^{1}H NMR δ 0.85 (s, 3H), 0.95 (s, 3H), 3.80 (dd, *J* = 5.3, 10.6 Hz, 1H), 4.00 (dd, *J* = 5.3, 10.6 Hz, 1H), 4.35 (br. s, OH), 4.75 (q, *J* = 5.3 Hz, 1H), 5.15−5.40 (m, 2H), 5.90−6.12 (m, 1 H), 7.30−7.40 (m, 10 H); ^{13}C NMR δ 20.6, 21.5, 42.0, 69.9, 78.9, 88.3, 116.7, 126.8, 127.1, 127.6, 127.9, 128.4, 134.2, 137.8, 141.6; MS *m/z* 132 (base peak). Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.03; H, 8.18. Found: C, 81.12; H, 8.15.

(±)-Butenyl ether **5**: ^{1}H NMR δ 0.80 (s, 3H), 0.90 (s, 3H), 2.40 (q, *J* = 8.0 Hz, 2H), 3.40 (m, 2H), 4.25 (br. s, OH), 4.65 (d, *J* = 5.3 Hz, 1H), 4.80 (d, *J* = 5.3 Hz, 1H), 5.05−5.33 (m, 2H), 5.75−6.02 (m, 1 H), 7.2−7.4 (m, 10H); ^{13}C NMR δ 20.8, 21.8, 34.2, 41.8, 68.5, 79.1, 89.3, 116.8, 126.8, 127.1, 127.6, 127.9, 128.4, 134.9, 137.9, 141.6; MS *m/z* 132 (base peak). Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.23; H, 8.43. Found: C, 81.37; H, 8.47.

(−)-Propenyl ether **6**: mp 220−222 °C; [α]$_D$ −10.6 (*c* = 1, CHCl$_3$); ^{1}H NMR δ 0.95 (s, 3H), 1.10 (s, 3H), 3.35(q, *J* = 5.3 Hz, 1H), 3.85 (q, *J* = 5.3 Hz, 1H), 4.25 (d, *J* = 8.0 Hz, 1H), 4.60 (d, *J* = 8.0 Hz, 1H), 5.20−5.38 (m, 2H), 5.83−6.12 (m, 1 H), 6.25 (s, OH), 7.3−7.5 (m, 20H); ^{13}C NMR δ 26.7, 26.9, 66.2, 79.8, 81.8, 84.9, 108.5, 118.8, 126.8, 129.9, 132.8, 136.8, 139.1, 143.7, 146.2; MS *m/z* 105 (base peak). Anal. Calcd for $C_{34}H_{34}O_4$: C, 80.60; H, 6.78. Found: C, 80.66; H, 6.80.

(−)-Butenyl ether **7**: mp 229−230 °C; [α]$_D$ −31.1 (*c* = 1, CHCl$_3$); ^{1}H NMR δ 0.92 (s, 3H), 1.03 (s, 3H), 2.37 (q, *J* = 10.0 Hz, 2H), 2.85 (q, *J* = 15.1 Hz, 1H), 3.40 (m, 1H), 4.25 (d, *J* =

10.6 Hz, 1H), 4.60 (d, *J* = 10.6 Hz, 1H), 4.95−5.38 (m, 2H), 5.55−5.85 (m, 1 H), 6.25 (s, OH), 7.3−7.5 (m, 20H); ^{13}C NMR δ 26.8, 28.0, 33.7, 64.2, 77.3, 79.9, 81.8, 84.9, 108.6, 117.1, 126.4, 126.9, 127.6, 128.7, 129.8, 130.4, 133.9, 137.2, 139.4, 143.8, 146.4; MS *m*/*z* 237 (base peak). Anal. Calcd for $C_{35}H_{36}O_4$: C, 80.73; H, 6.98. Found: C, 81.00; H, 6.97.

(±)-Propenyl ether **8**: ^{1}H NMR δ 0.85−1.35 (m, 2H), 1.35−1.60 (m, 4H), 1.60−1.93 (m, 2H), 2.35 (br. s, OH), 3.27−3.50 (m, 1 H), 3.70−3.85 (m, 1 H), 3.85−4.15 (m, 2 H), 5.00−5.35 (m, 2 H), 5.74−6.05 (m, 1 H); ^{13}C NMR δ 21.0, 22.0, 26.4, 30.2, 68.5, 69.0, 78.0, 116.0, 135.1; MS *m*/*z* 81 (base peak). Anal. Calcd for $C_9H_{16}O_2$: C, 69.18; H, 10.34. Found: C, 69.20; H, 10.34.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all the new compounds (**1**−**8**). This material is available free of charge via the Internet at http://pubs.acs.org.

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