Reaction of glycidol with dichloroethers: cyclic and acyclic ortho ester formation

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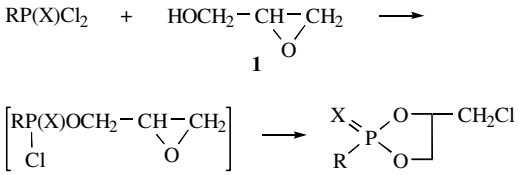
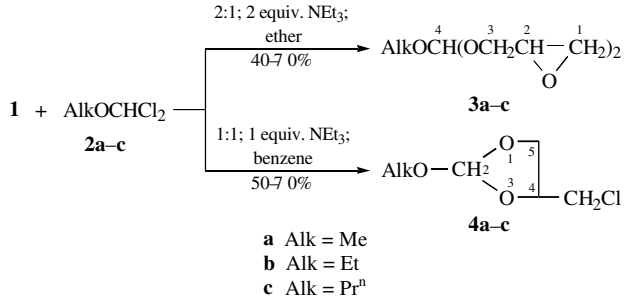
The interaction of stoichiometric quantities of glycidol with alkyl dichloromethyl ethers in the presence of 2 equiv. of NEt_3 in diethyl ether leads to formation of diglycidyloxy alkoxy methanes whereas the same reaction involving equimolar quantities of the reagents in benzene in the presence of 1 equiv. of NEt_3 leads to formation of 4-chloromethyl-2-alkoxy-1,3-dioxolanes.

2,3-Epoxy alcohols and parental glycidol **1** are examples of bifunctional organic compounds widely used in organic synthesis.[1] The value of 2,3-epoxy alcohols as building blocks in organic synthesis has been greatly increased with the development by Sharpless and his group of a simple and straightforward procedure to produce these compounds in enantiopure form with the desired configuration.[2] However, the most common way to use them in synthesis involves the hydroxy and epoxy functions separately in reactions with different reagents.

We recently described the formation of the 4-chloromethyl-1,3,2-dioxaphospholanes in the reactions of glycidol with PCl_3 and other phosphorus compounds possessing a –P(X)Cl_2 fragment (X = lone pair, O).[3]



In these processes, which have usually been achieved as one-pot procedures, a single molecule with at least two active P–Cl bonds takes part in a sequence of substitution and addition reactions involving both the hydroxy and epoxy functions of the glycidol as a substrate. We believe that the scheme for converting the 2,3-epoxy alcohols to the 4-halomethyl-1,3-dioxacyclane fragments through the interaction with activated geminal dihalogenides has general value. Here we report the predominant formation (according to the protocol chosen) of either linear or cyclic ortho esters in the reactions of alkyl dichloro methyl ethers **2a–c** with racemic glycidol. The latter reaction course confirms our above-mentioned expectations.



Scheme 1

It is deemed that , -dichloroethers do not exchange both chlorine atoms by alkoxy groups on reaction with alcohols. The usual result of these reactions is the formation of alkyl chlorides and alkyl formates:[4]

$$AlkOCHCl_2 + ROH \longrightarrow HCOOAlk + RCl + HCl$$

When glycidol reacts with , -dichloromethyl methyl ether **2a** in the absence of any base methyl formate and $(ClCH_2)_2CHOH$ (54%) are the only products isolated.

$$MeOCHCl_2 + \mathbf{1} \longrightarrow HCOOMe + ClH_2CCH(OH)CH_2Cl$$

Their formation is consistent with the above scheme if one takes into account the possibility of subsequent HCl addition to epichlorohydrin (RCl) formed in the early step.

The known method of obtaining linear ortho esters from , -dichloroethers involves reaction of the latter compounds with alcoholates of alkali metals.[5] We found that in the presence of 2 equiv. of NEt_3 glycidol reacts smoothly with **2a–c** forming the ortho esters **3a–c** in moderate to good isolated yields.†

Obviously the compounds **3** are generated from (±)-**1** in diastereoisomeric forms, but they do not manifest themselves in the routine ^{1}H NMR spectra (the numbering of the atoms corresponds to Scheme 1).‡ On the contrary, some signals in the ^{13}C-{H} NMR spectra consist of several (up to three) different lines in an approximate intensity ratio in the last case of 1:1:2 (in any order). This picture agrees well with the simultaneous existence in the mixture of a chiral *R*,*R*(*S*,*S*)-diastereoisomer (signal of double intensity) and two different achiral meso-forms with pseudo chiral *r*- and *s*-atoms C-4.

The alternative reaction path completely dominated when reagents **1** and **2** (1:1) and 1 equiv. of NEt_3 were mixed in benzene at *ca.* 0 °C and then boiled for 2 h. The cyclic ortho esters **4a–c** were isolated as a mixture of almost equal quantities of *cis* and *trans* diastereoisomers (the numbering of the atoms corresponds to Scheme 1).‡ The assignment of the isomers is based on the known fact[6] that the low field signal of the proton bound to C-2 in the ^{1}H NMR spectra and the high field signal of the atom C-2 itself in the ^{13}C NMR spectra of the 2,4-disubstituted 1,3-dioxolanes belong to the *trans* isomers.

The usual method of producing the cyclic ortho esters involves transesterification of linear ones by the corresponding diols or by reaction of 1,3-dioxacycloalkanium salts with the alcoholates of alkali metals.[7] In particular, all known 4-chloromethyl-2-alkoxy-1,3-dioxolanes (and the compound **4b** among them) were obtained from 3-chloropropen-1,2-diol by the former procedure.[8] The method introduced here appears to be a quite new approach to the synthesis of cyclic ortho esters.

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† In a typical procedure an ethereal solution of glycidol (2 equiv.) and NEt_3 (2 equiv.) was added to a stirred ethereal solution of dichloro ether (1 equiv.) at less than –30 °C. The reaction mixture was allowed to warm to room temperature and was then boiled for *ca.* 5 min. After cooling and removal of solid deposit and solvent the crude mixture was fractionated *in vacuo*.

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‡ **3a**: yield 46%, bp 99–104 °C (1 mmHg). ^{1}H NMR (250.132 MHz, $CDCl_3$) δ: 4.73 (s, 1H, 4-H), 3.38–3.32 and 3.00–2.92 (m, 2H, 3-H), 2.85 (s, 3H, 4-H), 2.69–2.64 (m, 1H, 2-H), 2.32–2.27 and 2.13–2.09 (m, 2H, 1-H); ^{13}C NMR (100.624 MHz, $CDCl_3$) δ: 112.38 (d, C-4, $^1J_{CH}$ = 189.6, 189.3 and 192.5 Hz), 64.11 and 64.01 (t, C-3, $^1J_{CH}$ = = 143.5 and 143.7 Hz), 50.93, 50.89 and 50.88 (q, C-4, $^1J_{CH}$ = 143.4, 143.3 and 143.3 Hz), 49.48 (d, C-2, $^1J_{CH}$ = 176.7 Hz), 43.41 (t, C-1, $^1J_{CH}$ = 175.7 Hz).

3b: yield 49%, bp 105–108 °C (1 mmHg). ^{1}H NMR (250.132 MHz, $CCl_4 + C_6D_6$) δ: 5.30 (s, 1H, 4-H), 3.88–3.81 and 3.53–3.44 (m, 2H, 3-H), 3.67 (q, 2H, 4-H, $^3J_{HH}$ = 7.1 Hz), 3.17–3.13 (m, 1H, 2-H), 2.78–2.73 and 2.60–2.57 (m, 2H, 1-H), 1.27 (t, 3H, 4-H, $^3J_{HH}$ = 7.1 Hz); ^{13}C NMR (100.624 MHz, $CCl_4 + C_6D_6$) δ: 112.37 (d, C-4, $^1J_{CH}$ = 188.7 and 191.5 Hz), 64.65, 64.57 and 64.48 (t, C-3, $^1J_{CH}$ = 143.3, 143.3 and 143.3 Hz), 59.95 and 59.92 (t, C-4, $^1J_{CH}$ = 142.9 and 142.8, 142.9 Hz), 49.99 and 49.97 (d, C-2, $^1J_{CH}$ = 175.9 and 175.9 Hz), 43.71 (t, C-1, $^1J_{CH}$ = 175.4 Hz), 14.71 (q, C-4, $^1J_{CH}$ = 126.2 Hz).

3c: yield 72%, bp 107–110 °C (1 mmHg). ^{1}H NMR (250.132 MHz, $CCl_4 + C_6D_6$) δ: 5.30 (s, 1H, 4-H), 3.88–3.82 and 3.56–3.46 (m, 2H, 3-H), 3.55 (q, 2H, 4-H, $^3J_{HH}$ = 7.0 Hz), 3.17–3.12 (m, 1H, 2-H), 2.77–2.75 and 2.61-2.58 (m, 2H, 1-H), 1.75–1.61 (m, 2H, 4-H), 1.04 (t, 3H, 4-H, $^3J_{HH}$ = 7.4 Hz); ^{13}C NMR (100.624 MHz, $CCl_4 + C_6D_6$) δ: 112.39 (d, C-4, $^1J_{CH}$ = 188.5 and 185.7 Hz), 66.01 and 65.98 (t, C-4, $^1J_{CH}$ = 146.6 and 145.1 Hz), 64.52, 64.45 and 64.35 (t, C-3, $^1J_{CH}$ = = 144.3, 144.3 and 144.3 Hz), 49.93 and 49.92 (d, C-2, $^1J_{CH}$ = 175.8 and 175.8 Hz), 43.68 and 43.65 (t, C-1, $^1J_{CH}$ = 174.3 and 174.9 Hz), 22.59 (t, C-4, $^1J_{CH}$ = 127.6, 126.1 and 124.6 Hz), 10.42 and 10.41 (q, C-4, $^1J_{CH}$ = 125.6, 125.5 and 125.5 Hz).

4a: yield 54%, *cis*:*trans* 1:1, bp 93–97 °C (30 mmHg). ^{1}H NMR (250.132 MHz, $CDCl_3$) δ: 5.58 (s, 1H, *trans*-2-H), 5.54 (s, 1H, *cis*-2-H), 4.33–4.25 and 4.20–4.09 (m, 1H, 4-H), 3.99–3.92 and 3.71–3.65 (m, 2H, 5-H), 3.55–3.46 and 3.42–3.30 (m, 2H, 4-H), 3.10 (s, 3H, *cis*-2-H), 3.09 (s, 3H, *trans*-2-H); ^{13}C NMR (100.624 MHz, $CDCl_3$) δ: 115.90 (d, *cis*-C-2, $^1J_{CH}$ = 200.8 Hz), 115.59 (d, *trans*-C-2, $^1J_{CH}$ = = 199.1 Hz), 74.83 (d, *cis*-C-4, $^1J_{CH}$ = 155.7 Hz), 74.20 (d, *trans*-C-4, $^1J_{CH}$ = 154.3 Hz), 66.56 (t, *cis*-C-5, $^1J_{CH}$ = 150.7 Hz), 65.72 (t, *trans*-C-5, $^1J_{CH}$ = 151.0 Hz), 50.82 (q, *cis*-C-2, $^1J_{CH}$ = 143.0 Hz), 50.57 (q, *trans*-C-2, $^1J_{CH}$ = 143.0 Hz), 44.24 (t, *cis*-C-4, $^1J_{CH}$ = 152.1 Hz), 43.56 (t, *trans*-C-4, $^1J_{CH}$ = 151.5 Hz).

4b: yield 69%, *cis*:*trans* 1.4:1, bp 77–81 °C (12 mmHg). ^{1}H NMR (250.132 MHz, $CDCl_3$) δ: 5.50 (s, 1H, *trans*-2-H), 5.46 (s, 1H, *cis*-2-H), 4.34–3.95 and 4.18–4.11 (m, 1H, 4-H), 3.85–3.76 and 3.58–3.49 (m, 2H, 5-H), 3.41–3.35 and 3.27–3.17 (m, 2H, 4-H), 3.23 (q, 2H, 2-H, $^3J_{HH}$ = 7.1 Hz), 0.85 (t, 3H, 2-H, $^3J_{HH}$ = 7.1 Hz); ^{13}C NMR (100.624 MHz, $CDCl_3$) δ: 115.22 (d, *cis*-C-2, $^1J_{CH}$ = 198.3 Hz), 114.91 (d, *trans*-C-2, $^1J_{CH}$ = 198.4 Hz), 74.77 (d, *cis*-C-4, $^1J_{CH}$ = 156.2 Hz), 74.11 (d, *trans*-C-4, $^1J_{CH}$ = 154.4 Hz), 66.69 (t, *cis*-C-5, $^1J_{CH}$ = 150.5 Hz), 65.67 (t, *trans*-C-5, $^1J_{CH}$ = 150.9 Hz), 59.77 (t, *cis*-C-2, $^1J_{CH}$ = = 143.4 Hz), 59.53 (t, *trans*-C-2, $^1J_{CH}$ = 142.4 Hz), 44.27 (t, *cis*-C-4, $^1J_{CH}$ = 152.2 Hz), 43.51 (t, *trans*-C-4, $^1J_{CH}$ = 150.2 Hz), 14.31 (q, C-2, $^1J_{CH}$ = 126.8 Hz).

4c: yield 69%, *cis*:*trans* 1.5:1, bp 93–98 °C (18 mmHg). ^{1}H NMR (250.132 MHz, $CDCl_3$) δ: 5.66 (s, 1H, *trans*-2-H), 5.63 (s, 1H, *cis*-2-H), 4.35–4.27 and 4.20–4.13 (m, 1H, 4-H), 4.01–3.93 and 3.75–3.67 (m, 2H, 5-H), 3.57–3.48 and 3.43–3.34 (m, 2H, 4-H), 3.29 (t, 2H, 2-H, $^3J_{HH}$ = 7.0 Hz), 1.48–1.34 (m, 2H, 2-H), 0.74 (t, 3H, 2-H, $^3J_{HH}$ = = 7.5 Hz). ^{13}C NMR (100.624 MHz, $CCl_4 + C_6D_6$) δ: 115.88 (d, *cis*-C-2, $^1J_{CH}$ = 198.0 Hz), 115.53 (d, *trans*-C-2, $^1J_{CH}$ = 197.8 Hz), 75.11 (d, *cis*-C-4, $^1J_{CH}$ = 154.3 Hz), 74.50 (d, *trans*-C-4, $^1J_{CH}$ = 154.5 Hz), 67.12 (t, *cis*-C-5, $^1J_{CH}$ = 149.8 Hz), 66.12 (t, *trans*-C-5, $^1J_{CH}$ = 150.7 Hz), 66.07 (t, *cis*-C-2, $^1J_{CH}$ = 148.5 Hz), 65.71 (t, *trans*-C-2, $^1J_{CH}$ = = 148.2 Hz), 44.71 (t, *cis*-C-4, $^1J_{CH}$ = 152.2 Hz), 43.84 (t, *trans*-C-4, $^1J_{CH}$ = 151.3 Hz), 22.61 (t, C-2, $^1J_{CH}$ = 126.7 Hz), 10.38 (q, *cis*-C-2, $^1J_{CH}$ = 125.4 Hz), 10.34 (q, *trans*-C-2, $^1J_{CH}$ = 125.7 Hz).