Cyclic (4*S*)-chloromethyl sulfite and sulfate derivatives of (*S*)-glycidol as valuable synthetic equivalents of scalemic epichlorohydrin

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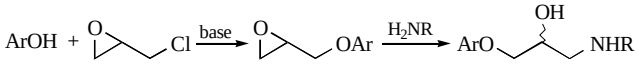
The interaction of (*S*)-glycidol with $SOCl_2$ or SO_2Cl_2 in stoichiometric amounts leads to the formation of cyclic (4*S*)-chloromethyl sulfite or sulfate derivatives with the same enantiomeric purity; based on this reaction, a new procedure for the synthesis of (*S*)-propranolol was developed.

1-Chloro-2,3-epoxypropane (epichlorohydrin) **1** is one of the epoxy compounds most frequently used in organic synthesis. In particular, racemic epichlorohydrin is a key starting material in commercial processes for the production of β-adrenoreceptor blockers **2**,[1] valuable cardiovascular drugs:



1 **2**

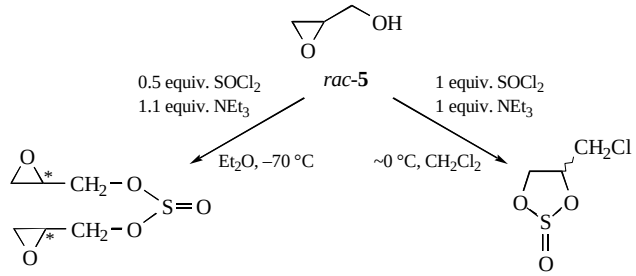
The formation of products of double nucleophilic displacement, $(ArOCH_2)_2CH(OH)$, which usually accompanies the main reaction,[2] is a minor limitation for the use of **1** in the above and related processes. Some other weak points of epichlorohydrin-based synthetic strategies may appear on going from racemic to scalemic β-blockers as target products. Thus, scalemic **1** is an expensive and not easily available substance.[3] On the other hand, the nucleophilic displacement of a chlorine atom in **1** may be accompanied by the Payne-type rearrangement, which is well known for analogous processes in glycidyl tosilates[4] and causes partial racemization of the final products.

It is hoped that the use of 4-chloromethyl-2-oxo- and 4-chloromethyl-2,2-dioxo-1,3,2-dioxathiolanes **3** and **4** as synthetic equivalents of epichlorohydrin can allow us to avoid the disadvantages of compound **1**. For example, racemic **4** was successfully used in the synthesis of a key intermediate for preparing the racemic β-blocker acebutolol [**2a**, Ar = 2-(MeCO)-4-(PrCONH)C_6H_3, R = Bu^t].[2]

In all published procedures for the synthesis of *rac*-**3**[2,5–7] and *rac*-**4**,[2,8] *rac*-**1**[5] or *rac*-3-chloropropane-1,2-diol[2,6–8] was used as the starting material, and no scalemic **3** and **4** were mentioned in the literature. Here, we report an efficient new way to cyclic chloromethyl-substituted sulfites and sulfates starting from 2,3-epoxypropan-1-ol (glycidol) **5**. Note that at present scalemic glycidol is one of the easily accessible chiral C_3 synthons.

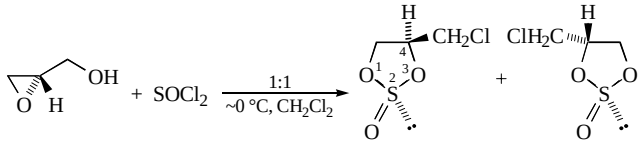
We found that the reaction of 1 equiv. of *rac*-**5** with 0.5 equiv. of $SOCl_2$ in the presence of 1.1 equiv. of NEt_3 results in trivial diglycidyl sulfite **6** formed as a mixture of three diastereomers (two achiral *meso*- and racemic chiral isomers approximately in the 1:1:2 ratio).† However, along with main product **6**, up to 20% of cyclic chloromethyl sulfite **3** (two diastereomers in the *cis*:*trans* ratio 41:59) was isolated and identified. Cyclic sulfites **3** became major products (isolated yield up to 90%) when the reaction of equimolar amounts of glycidol and $SOCl_2$ took place in the presence of 1 equiv. of a tertiary amine or without any base.

Cyclic sulfites **3** in a scalemic form were obtained in the same yield when the reaction of (*S*)-glycidol (ee = 90.0%;‡ obtained by Sharpless asymmetric epoxydation[9] of allyl alcohol) and $SOCl_2$ took place under analogous conditions. The scalemic diastereomers of **3** were separated by column chromatography.§



6 **3**

It is well known that a diastereomer of *rac*-**3** with a longer retention time exhibits the *trans* structure.[7] Unfortunately, owing to the similarity of the retention times for two enantiomers we failed to determine the enantiomeric purity for *cis*-**3**. The enantiomeric purity measured for the *trans* isomer (*ee* = 89.3%) was practically equal to that of parent glycidol. Based on this fact, the (2*R*,4*S*)-configuration was easily attributed to the *trans* isomer and the (2*S*,4*S*)-configuration, to the other.



(*S*)-**5** (2*S*,4*S*)-**3** (2*R*,4*S*)-**3**

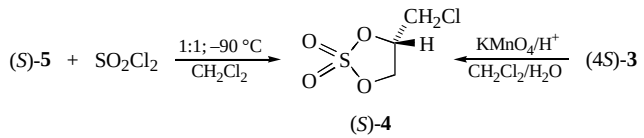
When glycidol was mixed with SO_2Cl_2 under the above conditions, a viscous sulfur-containing mixture was the main reaction product. Better results were obtained by mixing solutions of SO_2Cl_2 and (*S*)-**5** in CH_2Cl_2 without any base at –90 °C. About 50% of cyclic sulfate (*S*)-**4** was isolated from the reaction mixture by distillation. The same product¶ can be obtained in 35% yield by oxidation of a mixture of isomeric (4*S*)-**3** with aqueous $KMnO_4$ in a two-phase system. The total yields of target sulfate **4** prepared by direct sulfurization of **5** with SO_2Cl_2 or by a two-step procedure starting from $SOCl_2$ are comparable; however, the latter procedure gives the product of higher purity.†† The yield in the two-step procedure can be considerably improved with the use of the standard $RuCl_3$–$NaIO_4$ oxidising system.[11,12]

† **6**: bp 145–147 °C/1 mmHg. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.17–4.05 and 3.70–3.55 (m, OCH_2), 3.04–2.96 (m, CH), 2.64–2.60 and 2.47–2.43 (m, CH_2-oxirane). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 62.63, 62.44, 62.34 (OCH_2), 48.95, 48.94, 48.91 (CH), 43.87, 43.82, 43.80 (CH_2-oxirane).

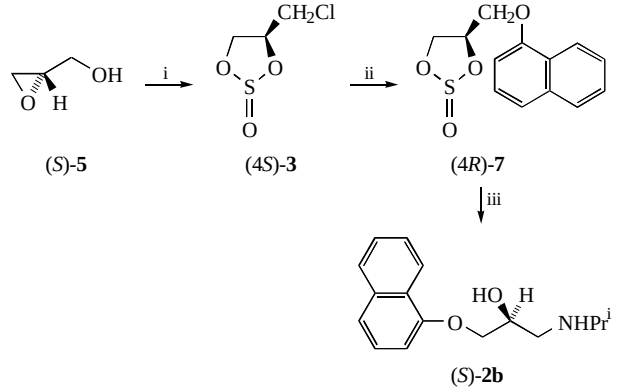
‡ The enantiomeric composition was determined by GLC on a Biochrom-1 chromatograph using a Supelco β-Dex-120 column (30 m×0.25 mm).

§ Silica gel, light petroleum–diethyl ether. (2*S*,4*S*)-**3**: R_f = 0.31 (light petroleum–diethyl ether, 8:5), $[\alpha]_D^{20}$ = –6.3 (*c* 0.64, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.78–4.68 (m, 1H, OCH), 4.58–4.43 (m, 2H, OCH_2), 3.81 (d, 2H, CH_2Cl, ^3J 5.3 Hz). ^{13}C NMR (100.6 MHz, CCl_4 + C_6D_6) δ: 80.93 (CH), 69.98 (OCH_2), 43.35 (CH_2Cl). (2*R*,4*S*)-**3**: R_f = 0.27 (light petroleum–diethyl ether, 8:5), $[\alpha]_D^{20}$ = 58.2 (*c* 0.3, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.14–5.04 (m, 1H, OCH), 4.66 (dd, 1H, OCH_2, ^3J 5.6 Hz, ^2J 9.0 Hz), 4.32 (dd, 1H, OCH_2, ^3J 6.4 Hz, ^2J 9.0 Hz), 3.62 (d, 2H, CH_2Cl, ^3J 5.4 Hz). ^{13}C NMR (100.6 MHz, CCl_4 + C_6D_6) δ: 78.83 (CH), 68.94 (OCH_2), 42.56 (CH_2Cl). Lit. ^{13}C NMR data for *rac*-**3** see in ref. 10.

¶ (*S*)-**4**: bp 80–82 °C/0.05 mmHg; n_D^{20} = 1.4640; $[\alpha]_D^{20}$ = –2.1 (*c* 3.4, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.15 (approx. quint., 1H, CH), 4.85 (dd, 1H, OCH_2, ^3J 6.8 Hz, ^2J 8.9 Hz), 4.65 (dd, 1H, OCH_2, ^3J 6.6 Hz, ^2J 8.9 Hz), 3.84 (d, 2H, CH_2Cl, ^3J 5.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 79.50 (CH), 70.25 (OCH_2), 41.46 (CH_2Cl).



Cyclic sulfites and sulfates, which have been known for a long time, were considered as a minor and peripheral class of organic compounds until Gao and Sharpless[11] have recognised them as being "like epoxides only more reactive". Reviews on the chemistry of these substances were published,[12] and the "cyclic sulfite/sulfate route" became a popular way to a diversity of bioactive products. (*S*)-Propranolol (**2b**, Ar = 1-naphthyl, R = Pr^i) was also synthesised from a mixture of diastereomeric (4*R*)-naphthyloxymethyl-2-oxo-1,3,2-dioxathiolanes (4*R*)-**7**, which



Reagents and conditions: i, $SOCl_2$, CH_2Cl_2, ~0 °C; ii, NaH, 1-naphthol, toluene; iii, Pr^{i}NH$_2$, DMF. Diastereomeric mixtures of **3** and **7** were used.

[††] The distilled sample of **4** obtained by the direct action of SO_2Cl_2 on glycidol contains 6–10% of the six-membered cyclic sulfate 5-chloro-2,2-dioxo-1,3,2-dioxathiane. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 76.38 (OCH_2), 46.74 (CHCl). Only trace amounts of this impurity were detected in a sample of **4** obtained by the two-step procedure. The two pairs of signals of diastereomeric 5-chloro-2-oxo-1,3,2-dioxathianes [^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 60.87 and 60.20 (OCH_2), 46.92 and 51.64 (CHCl); *cf.* ref. 13] with the total integral intensity lower than 2% can also be found in the spectra of crude **3**.

were prepared from rather exotic (*R*)-3-benzyloxypropane-1,2-diol by a four-step procedure.[14] In a preliminary run, we prepared (*S*)-**2b**[‡‡] in three steps starting from (*S*)-glycidol with the overall yield of about 75%.

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[‡‡] (*S*)-**2b**·HCl: mp 185–187 °C, $[\alpha]_D^{25}$ = –22.6 (*c* 0.66, EtOH). Lit.,[15] mp 194–196 °C, $[\alpha]_D^{25}$ = –25.5 (*c* 1.05, EtOH).