

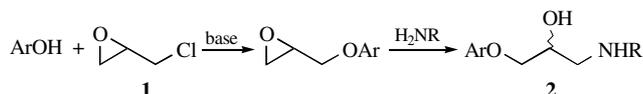
# Cyclic (4*S*)-chloromethyl sulfite and sulfate derivatives of (*S*)-glycidol as valuable synthetic equivalents of scalemic epichlorohydrin

Alexander A. Bredikhin,\* Sergey N. Lazarev, Alexander V. Pashagin and Zemfira A. Bredikhina

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 8432 75 2253; e-mail: baa@iopc.kcn.ru

The interaction of (*S*)-glycidol with SOCl<sub>2</sub> or SO<sub>2</sub>Cl<sub>2</sub> 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  $\beta$ -adrenoreceptor blockers **2**,<sup>1</sup> valuable cardiovascular drugs:



The formation of products of double nucleophilic displacement, (ArOCH<sub>2</sub>)<sub>2</sub>CH(OH), which usually accompanies the main reaction,<sup>2</sup> 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  $\beta$ -blockers as target products. Thus, scalemic **1** is an expensive and not easily available substance.<sup>3</sup> 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 tosylates<sup>4</sup> 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  $\beta$ -blocker acebutolol [**2a**, Ar = 2-(MeCO)-4-(PrCONH)C<sub>6</sub>H<sub>3</sub>, R = Bu<sup>t</sup>].<sup>2</sup>

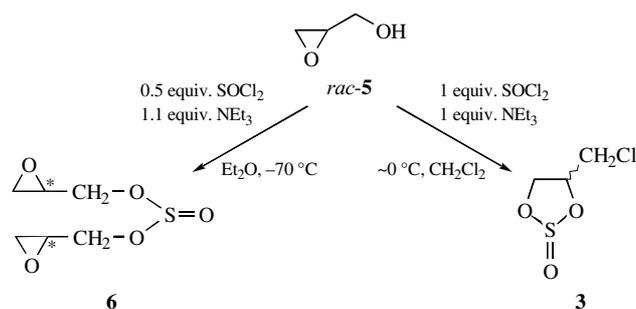
In all published procedures for the synthesis of *rac*-**3**,<sup>5–7</sup> and *rac*-**4**,<sup>8</sup> *rac*-**1**<sup>5</sup> or *rac*-3-chloropropane-1,2-diol<sup>2,6–8</sup> was used as the starting material, and no scalemic **3** and **4** were mentioned in the literature. Here, we report an efficient 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<sub>3</sub> synthons.

We found that the reaction of 1 equiv. of *rac*-**5** with 0.5 equiv. of SOCl<sub>2</sub> in the presence of 1.1 equiv. of NEt<sub>3</sub> 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).<sup>†</sup> 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<sub>2</sub> took place in the presence of 1 equiv. of a tertiary amine or without any base.

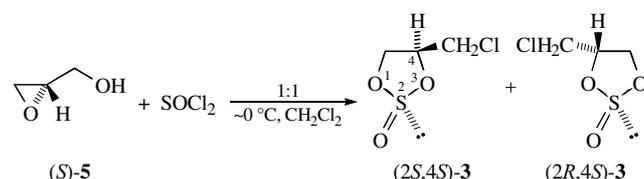
Cyclic sulfites **3** in a scalemic form were obtained in the same yield when the reaction of (*S*)-glycidol (ee = 90.0%;<sup>‡</sup> obtained by Sharpless asymmetric epoxidation<sup>9</sup> of allyl alcohol) and SOCl<sub>2</sub> took place under analogous conditions. The scalemic diastereomers of **3** were separated by column chromatography.<sup>§</sup>

<sup>†</sup> **6**: bp 145–147 °C/1 mmHg. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$ : 4.17–4.05 and 3.70–3.55 (m, OCH<sub>2</sub>), 3.04–2.96 (m, CH), 2.64–2.60 and 2.47–2.43 (m, CH<sub>2</sub>-oxirane). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$ : 62.63, 62.44, 62.34 (OCH<sub>2</sub>), 48.95, 48.94, 48.91 (CH), 43.87, 43.82, 43.80 (CH<sub>2</sub>-oxirane).

<sup>‡</sup> The enantiomeric composition was determined by GLC on a Biochrom-1 chromatograph using a Supelco  $\beta$ -Dex-120 column (30 m $\times$ 0.25 mm).



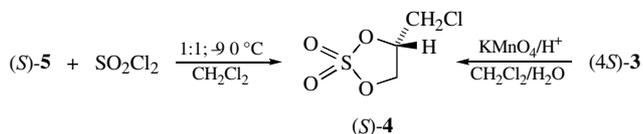
It is well known that a diastereomer of *rac*-**3** with a longer retention time exhibits the *trans* structure.<sup>7</sup> Unfortunately, owing to the similarity of the retention times for two enantiomers we failed to determine the enantiomeric purity for *cis*-**3**. The enantiomeric purity measured 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.



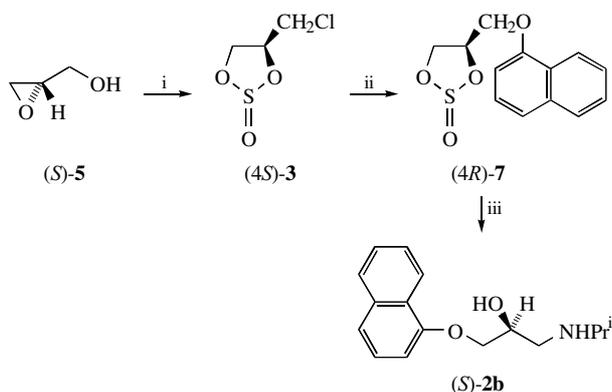
When glycidol was mixed with SO<sub>2</sub>Cl<sub>2</sub> under the above conditions, a viscous sulfur-containing mixture was the main reaction product. Better results were obtained by mixing solutions of SO<sub>2</sub>Cl<sub>2</sub> and (*S*)-**5** in CH<sub>2</sub>Cl<sub>2</sub> without any base at -90 °C. About 50% of cyclic sulfate (*S*)-**4** was isolated from the reaction mixture by distillation. The same product<sup>¶</sup> can be obtained in 35% yield by oxidation of a mixture of isomeric (4*S*)-**3** with aqueous KMnO<sub>4</sub> in a two-phase system. The total yields of target sulfate **4** prepared by direct sulfurization of **5** with SO<sub>2</sub>Cl<sub>2</sub> or by a two-step procedure starting from SOCl<sub>2</sub> are comparable; however, the latter procedure gives the product of higher purity.<sup>¶¶</sup> The yield in the two-step procedure can be considerably improved with the use of the standard RuCl<sub>3</sub>·Na IO<sub>4</sub> oxidising system.<sup>11,12</sup>

<sup>§</sup> Silica gel, light petroleum–diethyl ether. (2*S*,4*S*)-**3**: *R*<sub>T</sub> = 0.31 (light petroleum–diethyl ether, 8:5), [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -6.3 (*c* 0.64, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$ : 4.78–4.68 (m, 1H, OCH), 4.58–4.43 (m, 2H, OCH<sub>2</sub>), 3.81 (d, 2H, CH<sub>2</sub>Cl, <sup>3</sup>*J* 5.3 Hz). <sup>13</sup>C NMR (100.6 MHz, CCl<sub>4</sub> + C<sub>6</sub>D<sub>6</sub>)  $\delta$ : 80.93 (CH), 69.98 (OCH<sub>2</sub>), 43.35 (CH<sub>2</sub>Cl). (2*R*,4*S*)-**3**: *R*<sub>T</sub> = 0.27 (light petroleum–diethyl ether, 8:5), [ $\alpha$ ]<sub>D</sub><sup>20</sup> = 58.2 (*c* 0.3, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.14–5.04 (m, 1H, OCH), 4.66 (dd, 1H, OCH<sub>2</sub>, <sup>3</sup>*J* 5.6 Hz, <sup>2</sup>*J* 9.0 Hz), 4.32 (dd, 1H, OCH<sub>2</sub>, <sup>3</sup>*J* 6.4 Hz, <sup>2</sup>*J* 9.0 Hz), 3.62 (d, 2H, CH<sub>2</sub>Cl, <sup>3</sup>*J* 5.4 Hz). <sup>13</sup>C NMR (100.6 MHz, CCl<sub>4</sub> + C<sub>6</sub>D<sub>6</sub>)  $\delta$ : 78.83 (CH), 68.94 (OCH<sub>2</sub>), 42.56 (CH<sub>2</sub>Cl). Lit. <sup>13</sup>C NMR data for *rac*-**3** see in ref. 10.

<sup>¶</sup> (*S*)-**4**: bp 80–82 °C/0.05 mmHg; *n*<sub>D</sub><sup>20</sup> = 1.4640; [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -2.1 (*c* 3.4, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.15 (approx. quint., 1H, CH), 4.85 (dd, 1H, OCH<sub>2</sub>, <sup>3</sup>*J* 6.8 Hz, <sup>2</sup>*J* 8.9 Hz), 4.65 (dd, 1H, OCH<sub>2</sub>, <sup>3</sup>*J* 6.6 Hz, <sup>2</sup>*J* 8.9 Hz), 3.84 (d, 2H, CH<sub>2</sub>Cl, <sup>3</sup>*J* 5.8 Hz). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$ : 79.50 (CH), 70.25 (OCH<sub>2</sub>), 41.46 (CH<sub>2</sub>Cl).



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<sup>11</sup> have recognised them as being ‘like epoxides only more reactive’. Reviews on the chemistry of these substances were published,<sup>12</sup> and the ‘cyclic sulfite/sulfate route’ became a popular way to a diversity of bioactive products. (*S*)-Propranolol (**2b**, Ar = 1-naphthyl, R = Pr<sup>i</sup>) was also synthesised from a mixture of diastereomeric (*4R*)-naphthylloxymethyl-2-oxo-1,3,2-dioxathiolanes (*4R*)-**7**, which



Reagents and conditions: i,  $\text{SOCl}_2$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-9.0^\circ\text{C}$ ; ii, NaH, 1-naphthol, toluene; iii,  $\text{Pr}^i\text{NH}_2$ , DMF. Diastereomeric mixtures of **3** and **7** were used.

† The distilled sample of **4** obtained by the direct action of  $\text{SO}_2\text{Cl}_2$  on glycidol contains 6–10% of the six-membered cyclic sulfate 5-chloro-2,2-dioxo-1,3,2-dioxathiane.  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$ : 76.38 ( $\text{OCH}_2$ ), 46.74 ( $\text{CHCl}$ ). 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 [ $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$ : 60.87 and 60.20 ( $\text{OCH}_2$ ), 46.92 and 51.64 ( $\text{CHCl}$ ); 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.<sup>14</sup> 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.,<sup>15</sup> mp 194–196 °C,  $[\alpha]_D^{25} = -25.5$  (c 1.05, EtOH).