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Rearrangement of 2,3-Epoxy Alcohol Dimethylthiocarbamate Derivatives. Synthesis of 2,3-Epithio Alcohol Derivatives under Mild Conditions

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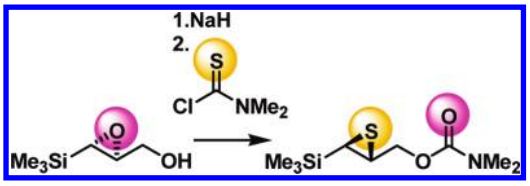
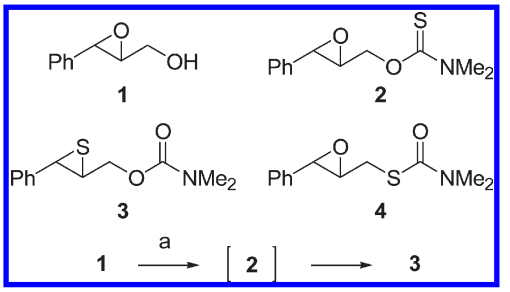


Transformation of representative 2,3-epoxy alcohols, including 3-trimethylsilyl- and 3-triphenylsilylglycidols, into the corresponding 2,3-epithio alcohol dimethylthiocarbamate derivatives under mild alkaline conditions is reported.

In conjunction with a project on the synthesis of certain natural products ongoing in our laboratory, we were interested in preparing dialkylaminothiocarbamate derivatives of a model 2,3-epoxy alcohol. The presence of both strongly nucleophilic (dialkylthiocarbamate) and electrophilic (oxirane) moieties in close proximity was an intriguing feature of such structure. No prior reports of dialkylaminothiocarbamates of 2,3-epoxy alcohols could be found in the literature; however, the dimethylthiocarbamate group has been used as a specific protective group for a range of alcohols,[1] and several reports on the chemistry of 2,3-epoxy alcohol thiocarbonyl imidazolides[2] and some other sulfur-containing derivatives have been published.[3]

The 3-phenylglycidol[4,5] **1** (Scheme 1) was treated first with sodium hydride in THF in the presence of a catalytic amount

SCHEME 1. Attempted Preparation of Thiocarbamate 2[a]



[a]Key: (a) NaH, imidazole (cat.), THF, rt, and then $ClC(S)NMe_2$.

of imidazole[6] and then with the dimethylthiocarbamoyl chloride[1,7] [$ClC(S)NMe_2$] in an attempt to prepare thiocarbamate **2**. The product, isolated in 67% yield, showed the expected elemental composition (HRMS). However, its IR and ^{13}C NMR spectra indicated the presence of the dimethylcarbamate [$-C(O)NMe_2$] group (ν 1705 cm^{-1}, δ 156 ppm for the carbonyl carbon atom) instead of the expected dimethylthiocarbamate [$-C(S)NMe_2$]. The presence of the carbamate group in the product implied that the sulfur−oxygen interchange has occurred at some stage during the process. Two distinct structures were considered as a possible alternative to **2**: the 2,3-epithio alcohol carbamate **3** or epoxy thiol carbamate **4**. The analysis of published data on the NMR spectra of *S*-dimethylthiocarbamate and *O*-dimethylthiocarbamates[8] permitted the assignment of the thiirane structure (**3**) to the product.[9] Compound **3** decomposed with an expulsion of sulfur on heating (to afford the (*E*)-3-phenylprop-2-enyl dimethylcarbamate[10]) in an analogous manner as it was reported for the respective free epithio alcohol.[11,12]

It was anticipated that **3** is formed by the rearrangement of thiocarbamate **2**, but no confirmation of the intermediate presence could be found in the NMR spectra of crude product. Intramolecular oxirane−thiirane interchange reactions involving thiourea and other thiocarbamate derivatives are well-documented. However, an acid catalyst is usually required.[11−13]

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(10) Overman, L. E.; Campbell, C. B.; Knoll, F. M. *J. Am. Chem. Soc.* **1978**, *100*, 4822–4834.
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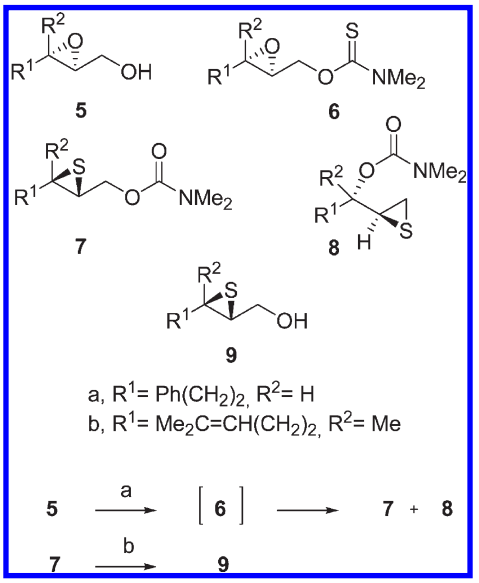
SCHEME 2. Preparation and Rearrangement of 2,3-Epoxy Alcohol Thiocarbamates with a Secondary Carbon Atom at Position 2[a]



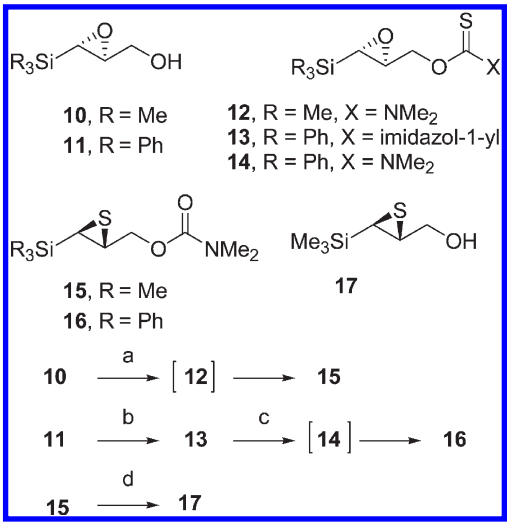
[a]Key: (a) NaH, imidazole (cat.), THF, rt, and then ClC(S)NMe$_2$; (b) LiAlH$_4$, Et$_2$O, −78 °C.

To determine the scope of the rearrangement, a few selected epoxy alcohols were submitted to the reaction with dimethylthiocarbamoyl chloride under analogous conditions, and the products were investigated.

Glycidol **5a**[14] (2*S*,3*S*:2*R*,3*R*, 94:6 er by HPLC, Scheme 2) afforded the intermediate **6a**, which was rearranging into two products at room temperature. ^{1}H and ^{13}C NMR spectra of a sample of the crude material in CDCl$_3$ solution at the 30 min intervals allowed the observation of the declining signals of **6a** (that completely disappear within 6 h). The products (65% yield, 2:1 ratio by ^{1}H NMR) were separated by chromatography and were identified as **7a** and **8a**, respectively. Both products showed in their IR spectra absorption at 1700−1710 cm^{-1} and in their ^{13}C NMR spectra a signal at δ 156.03−155.93 ppm. The ^{1}H NMR spectrum of **7a** (600 MHz) showed signals of two geminal protons at δ 4.12 and 4.07 ppm, indicating that the carbamate substituent is attached to a primary carbon atom. The coupling pattern of C-1, C-2, and C-3 protons determined by the HSQC technique corroborated the internal location of the epithio group. The lack of the NOE effect between protons at C-2 (δ 2.92 ppm) and C-3 (δ 2.76 ppm) and the presence of the NOE effect between protons at C-2 and C-4 (δ Ha, 2.13 and Hb, 1.82 ppm), as well as C-3 and C-1 (δ Ha, 4.12 and Hb, 4.07 ppm), showed their *trans* orientation. In the ^{1}H NMR spectrum of **8a**, the signal of one proton deshielded by the carbamate group appeared at δ 4.45 ppm (C-3). The coupling pattern of the C-2 proton and the vicinal protons corresponded to the epithio group's terminal location, but the relative configuration around C-2 and C-3 could not be confirmed.

The reduction of the epithio carbamate **7a** with lithium aluminum hydride in Et$_2$O at −78 °C afforded the known epithio alcohol **9a** in 84% yield (er 93:7) contaminated with a small amount of (2*E*)-5-phenylpent-2-en-1-ol (>10%). The optical rotation of this product ([α]$^{22}_D$ +125.0 (*c* 1.0, CHCl$_3$)) corresponded to that reported previously.[15] Therefore, on the route from **5a** to **9a**, the inversion of configuration at both stereogenic centers has occurred. Reduction of **8a** with lithium aluminum hydride under similar conditions led to a mixture of products.

SCHEME 3. Preparation and Rearrangement of 3-Silylglycidol Thiocarbamates[a]



[a]Key: (a) NaH, imidazole (cat.) and then ClC(S)NMe$_2$; (b) TCDI, CH$_2$Cl$_2$, rt; (c) Me$_2$NH in Et$_2$O, THF, rt and then CHCl$_3$, reflux, 2 h; (d) LiAlH$_4$, Et$_2$O, −78 °C.

Geraniol 2,3-epoxide[16] **5b** afforded unstable carbamate **6b** that could be identified by the ^{1}H and ^{13}C NMR spectra. This product on standing in a chloroform solution for 6 h afforded a mixture of **7b** and **8b** in a ratio of ca. 1:1 and 80% yield. The isomers were separated by chromatography. Reduction of the epithio carbamate **7b** with lithium aluminum hydride in Et$_2$O at −78 °C gave the epithio alcohol **9b** in 46% yield (Scheme 2).

(2*S*,3*S*)-3-(Trimethylsilyl)glycidol[17] **10** ([α]$^{23}_D$ −24.7, er 95:5, Scheme 3) was converted into the unstable thiocarbamate **12** that rearranged in a CHCl$_3$ solution at rt within 20 h to give (2*R*,3*S*)-silyl thiirane[18] **15** as the only product (62% yield). Reduction of **15** with lithium aluminum hydride in Et$_2$O at −78 °C afforded epithio alcohol **17** (65% yield, [α]$^{21}_D$ −9.1, er 95:5 by HPLC).

Treatment of 3-(triphenylsilyl)glycidol[19] **11** with sodium hydride and then ClC(S)NMe$_2$ provided *O*-[(*E*)-3-phenylprop-2-enyl]dimethylthiocarbamate in line with the earlier reported observation on reaction of triphenylsilyl oxiranes with nucleophilic reagents.[20] However, when **11** was allowed

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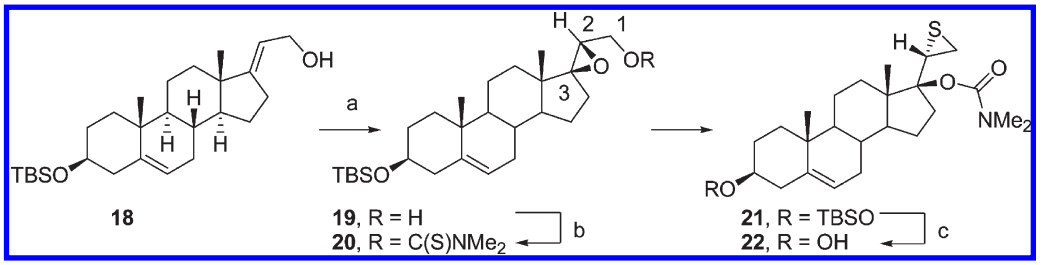
SCHEME 4. Rearrangement of a 2,3-Epoxy Alcohol Thiocarbamate with Position 3 Sterically Hindered[a]



[a]Key: (a) *t*-BuOOH, Ti(O*i*-Pr)$_4$, 4 Å MS, CH_2Cl_2; (b) NaH, imidazole (cat.), THF, rt and then $ClC(S)NMe_2$; (c) Bu_4NF, THF, rt.

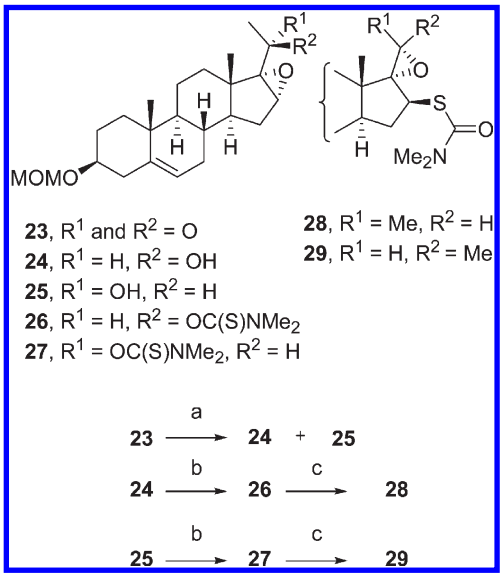
to react with thiocarbonyldiimidazole (TCDI) in THF at room temperature, the stable thiocarbonyl imidazolide **13** was formed. This derivative was treated with dimethylamine to afford epoxy dimethylthiocarbamate **14** that rearranged to afford epithio dimethylcarbamate **16** (80% yield from **13**).

Allylic alcohol **18**[21] (Scheme 4) was subjected to the Sharpless asymmetric epoxidation[4,22] using L-(+)-diisopropyl tartrate. Epoxy alcohol **19**, formed as the major product, was isolated by chromatography (86% yield).[23] This product was treated with sodium hydride and then with $ClC(S)NMe_2$ under the standard conditions. Carbamate **20**, identified by its ^{1}H NMR spectra, was allowed to rearrange in $CHCl_3$ solution at room temperature (6 h). The resulted thiirane **21** was isolated by chromatography (67% yield).[24] Compound **21** was crystalline but formed clusters of thin needles. Gratifyingly, the alcohol **22**, prepared by removal of the protecting group, gave material suitable for the single-crystal X-ray analysis. The X-ray structure of **22** (for the ORTEP projection, see the Supporting Information) confirmed the terminal position of the epithio group and the configuration assignments.

Finally, the epoxy alcohols **24** and **25** (Scheme 5), prepared from known[25] 16α,17α-epoxy-3β-hydroxypregn-5-en-20-one **23** using the standard procedures,[26] were examined. Alcohol **24** was transformed as described above into thiocarbamate **26** that was stable on storage and could be recovered unchanged after heating in refluxing toluene for a few hours. However, when **26** was heated in DMF[27] at 160 °C, a rearrangement occurred, affording a single product in 76% yield. The X-ray analysis of this product revealed structure **28** (for the ORTEP projection, see Supporting Information).

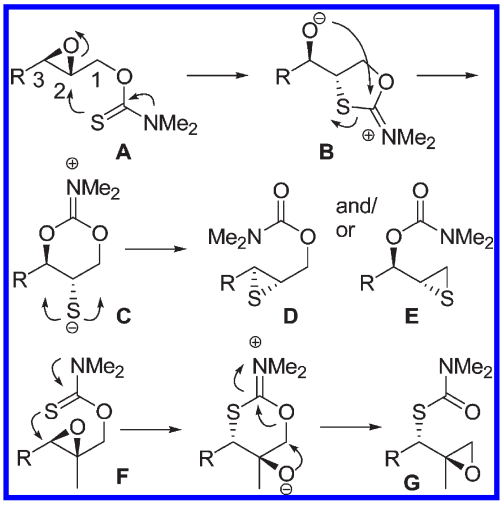
Epimeric alcohol **25** was transformed into the respective dimethylthiocarbamate (**27**) that rearranged in DMF solution at slightly lower temperature (130 °C) to afford thiol carbamate **29** (82% yield). Its structure was elucidated from the IR, ^{1}H, and ^{13}C NMR spectra.

SCHEME 5. Rearrangement of 2,3-Epoxy Alcohol Thiocarbamates with a Tertiary Carbon Atom at Position 2[a]



[a]Key: (a) $NaBH_4$, MeOH; (b) NaH, imidazole (cat.), THF, rt and then $ClC(S)NMe_2$; (c) DMF, heating.

SCHEME 6. Proposed Mechanism for 2,3-Epoxy Alcohol *O*-Thiocarbamate Rearrangements



The following mechanistic explanation of the observed rearrangements is proposed (Scheme 6). In structure **A**, the attack of the thiocarbamate sulfur atom occurred at position

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(23) Gravanis, A.; Calogeropoulou, T.; Castanas, E.; Margioris, A.; Charalambopoulos, I.; Avlonitis, N.; Minas, V.; Alexaki, V.-I.; Tsatsanis, C.; Alexis, M. N.; Remboutsika, E.; Vergou, V.; Neophytou, C. WO Patent 2008155534, 2008.
(24) Thiocarbamate **20** was contaminated with a small amount (~10%) of a byproduct to which the structure of the respective carbamate was assigned. The contamination presumably reflects the presence of dimethylcarbamoyl chloride in the reagent used.
(25) Litvinovskaya, R. P.; Drach, S. V.; Khripach, V. A. *Russ. J. Org. Chem.* **2001**, *37*, 787–792.
(26) Das, R.; Kirk, D. N. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1821–1831. For details, see Supporting Information.
(27) Chochrek, P.; Wicha, J. *J. Org. Chem.* **2007**, *72*, 5276–5284.

2, leading to intermediate **B**. The latter rearranged into **C**, and then the thiolate anion substituted the carbamate C−O bond either in the 3 or 1 position, affording the final product **D** or **E**. When position 3 was activated by a phenyl or silyl group, the substitution occurred exclusively at that position. Conversely, the oxirane derivative with position 3 sterically shielded furnished product with the thiirane group at position 1,2.

In structure **F**, with the tertiary position 2 at higher temperatures in DMF, attack of the sulfur atom at position 3 took place and was followed by repositioning of the epoxide function affording *S*-dimethylthiocarbamate **G**.

In conclusion, a rearrangement of dimethylthiocarbamate derivatives of 2,3-epoxy alcohols leading to the respective dimethylcarbamates of 2,3-epithio alcohols has been observed. The rearrangement appears general for substrates, with position 2 existing as a secondary carbon atom. The transformation of oxirane into thiirane occurs with the inversion of configuration at both stereogenic centers. 3-Silylglycidols are converted into respective 3-silylthiirane derivatives in high yield. The rearrangement provides a new approach to thiirane derivatives under mild alkaline conditions. The mechanism of the rearrangements is proposed.

Some carbamates of epithio alcohols are reduced with lithium aluminum hydride to the respective epithio alcohols.

Experimental Section

[(2*R*,3*S*)-3-(Trimethylsilyl)thiiran-2-yl]methyl dimethylcarbamate (15). Sodium hydride (55%, 44 mg, 0.5 mmol) was added to a stirred solution of [(2*S*,3*S*)-3-(trimethylsilyl)oxiran-2-yl]-methanol[17] (**10**) {$[\alpha]^{23}_D$ −24.7 (*c* 1.9, $CHCl_3$), HPLC, RI detection, Chiralpak AS-H, *i*-PrOH/hexanes, 5:95, 6.3 min (96%), 6.9 min (4%)} (73 mg, 0.5 mmol) and imidazole (3 mg, 0.05 mmol) in THF (3 mL). After 15 min, dimethylcarbamoyl chloride (93 mg, 0.75 mmol) was added and stirring was continued for 30 min. The mixture was then diluted with hexanes (10 mL) and washed with water (2 × 10 mL). The organic solution was dried, and the solvent was evaporated to give crude **12** (130 mg). A solution of this product in $CHCl_3$ (2 mL) was left at rt for 20 h and then evaporated, and the product was chromatographed on silica gel (5 g, EtOAc/hexanes, 5:95) to give **15** (colorless oil, 62%): $[\alpha]^{23}_D$ = −18.3 (*c* 1.41, $CHCl_3$); HPLC UV detection, Chiralpak AS-H, *i*-PrOH/hexanes, 2:98, 4.7 min (95%), 5.0 min (5%); IR 1710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.18 (dd, *J* = 11.3, 6.0 Hz, 1H), 4.11 (dd, *J* = 11.3, 6.6 Hz, 1H), 2.92 (q, *J* = 6.3 Hz, 1H) overlapping 2.90 (s, 6H), 1.75 (d, *J* = 6.6 Hz, 1H), 0.04 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.06, 70.33, 36.39 (br), 36.01, 35.83 (br), 27.89, −3.12. HRMS ESI: calcd for $C_9H_{19}O_2NNaSSi$ $[M + Na]^+$, 256.0798; found, 256.08049.

Signals of *O*-[(2*S*,3*S*)-3-(trimethylsilyl)oxiran-2-yl]methyl dimethylthiocarbamate (**12**) were assigned as follows: ^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (dd, *J* = 12.0, 2.4 Hz, 1H), 4.08 (dd, *J* = 12.0, 7.1 Hz, 1H), 3.35 (s, 3H), 3.17−3.11 (m,1H) overlapping 3.14 (s, 3H), 2.12 (d, *J* = 3.6 Hz, 1H), 0.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.69, 73.54, 53.12, 48.31, 42.80, 37.84, −3.76.

[(2*R*,3*S*)-3-(Trimethylsilyl)thiiran-2-yl]methanol (17). A solution of **15** (80 mg, 0.34 mmol) in Et_2O (3 mL) was added dropwise to $LiAlH_4$ (130 mg, 3.4 mmol) in Et_2O (5 mL) stirred at −78 °C. The suspension was stirred at −78 °C for 24 h, and then the reaction was quenched with saturated aq Na_2SO_4. The mixture was stirred for 30 min at rt and then diluted with Et_2O (10 mL) and hexanes (10 mL), and some Na_2SO_4 was added. After 0.5 h, the mixture was filtered through a plug of cotton and the solid was washed with Et_2O. The combined filtrates were evaporated. The residue was chromatographed on deactivated silica gel (4 g, EtOAc/hexanes, 7:93) to give **17** (36 mg, colorless oil, 65%): $[\alpha]^{21}_D$ −9.1 (*c* 1.6, $CHCl_3$); HPLC UV detection, Chiralpak AS-H, *i*-PrOH/hexanes, 2:98, 6.6 min (5%), 8.5 min (95%); IR 3369 (br), 1249 (s), 840 (s) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.97 (dd, *J* = 11.8, 3.8 Hz, 1H), 3.64 (dd, *J* = 11.8, 4.9 Hz, 1H), 3.04 (ddd, *J* = 6.8, 4.8, 3.9 Hz, 1H), 1.88 (d, *J* = 6.9 Hz, 1H), 1.85 (s, 1H), 0.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 64.77, 41.76, 26.56, −2.98. HRMS EI: calcd for $C_6H_{14}OSiS$ $[M]^+$, 162.05347; found, 162.05292.

Supporting Information Available: General and experimental procedures for **3**, **6a**,**b**−**9a**,**b**, **13**, **14**, **16**, and **19**−**29** and NMR spectra of all new compounds (^1H and ^{13}C). ORTEP plots and crystallographic details (CIF files) for **22** and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.