

(S)-3-Aminothioline: A New Chiral Building Block

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Received 19 February 1992

Dedicated to Prof. H.-F. Grützmaier on occasion of his 60th birthday.

Methioninol [2-amino-4-(methylthio)butan-1-ol] is converted into (S)-4,5-dihydro-4-[2-(methylthio)ethyl]-2-phenyl-1,3-oxazole (**1**). An acid-catalyzed rearrangement of **1** gives (S)-(-)-3-(benzoylamino)tetrahydrothiophene (**2**) in a stereospecific fashion. The transformation of the title compound **3** into the respective 3-hydroxytetrahydrothiophene proceeds only under partial inversion.

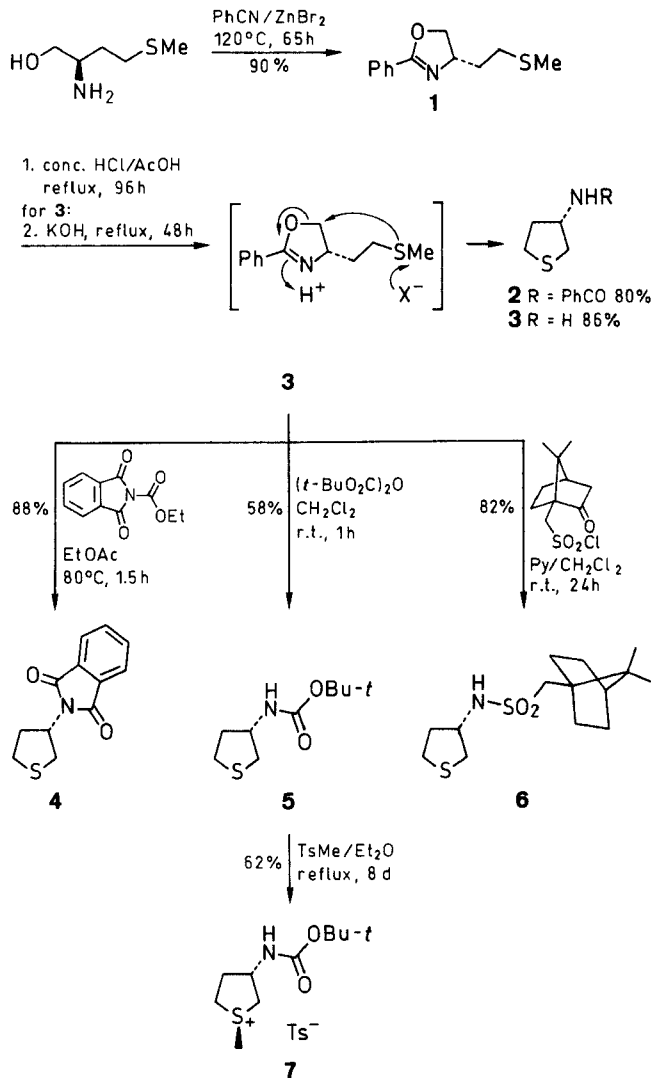
The racemate of the title compound and the respective sulfone have been used extensively as building blocks for diverse pharmacological agents, such as antitumor compounds,¹ antiradiation compounds,² sweeteners,³ gastric antisecretory⁴ and antifertility⁵ agents, analogues of antibiotics,⁶ fungicides,⁷ and others.⁸ Only one enantiomerically pure derivative of 3-aminothioline, sulfonium salt **7**, is known.⁹ We report here on a simple synthesis of the title compound **3** which was discovered incidentally in the course of another project.

D,L-Methioninol [(S,R)-2-amino-4-(methylthio)butan-1-ol] was converted into the 4,5-dihydro-1,3-oxazole derivative D,L-**1** by reaction with benzonitrile and zinc bromide.¹¹ An attempted sulfonium salt formation with ethyl bromoacetate resulted in an unexpected rearrangement under loss of a methyl group; a moderate yield of 3-benzoylaminothioline D,L-**2** was obtained. Subsequent experimentation made clear that the process is acid-catalyzed (see Scheme) and can be improved to a yield of 80% by working with aqueous hydrochloride acid/acetic acid. Basic hydrolysis gave the aminothioline D,L-**3** which in turn was transformed into the known¹² phthalimido derivative D,L-**4**.

All reactions were repeated with optically active material. Without isolation of intermediate **2**, (S)-**3** was obtained in 86% yield from **1** in two steps. It was attempted first to correlate the optical purity of **3** derived from (S)-methioninol with (1S,3S)-**7**. The stereochemistry of this compound rests on X-ray results. (S)-**3** was converted into the *tert*-butoxycarbonyl (Boc) derivative **5** and then methylated with methyl *p*-toluenesulfonate. Here, however, a 1:1 mixture of (1S,3S)- and (1R,3S)-**7** was formed which could not be separated. Therefore, both (R,S)- and (S)-**3** were reacted with (+)-10-camphorsulfonyl chloride to give (R,S)- and (S)-**6**, respectively. The ¹H NMR spectra revealed clearly that the *S*-compound was free from its diastereomer within detection limits.

Due to sulfur neighboring group participation, the diazotization of (S)-**3** might result in the formation of 3-hydroxythioline with net retention. The experiment reveals, however, that this is not so: The chemical yield was only 32% because of extensive elimination, and the optical yield was 50.5% (partial inversion!). The optical purity was estimated by polarimetry after transformation into the known 3-tosyloxythioline.¹³

Melting points were determined on a Büchi apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-360



Scheme

digital polarimeter in a 10 cm cell. IR spectra were obtained using a Beckman Acculab 8 spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Bruker AM 300 spectrometer working at 300 MHz and 75.5 MHz, respectively.

(S)-4,5-Dihydro-4-[2-(methylthio)ethyl]-2-phenyl-1,3-oxazole (1): (S)-Methioninol¹⁰ (26 g, 192.2 mmol), PhCN (44 g, 426 mmol) and ZnBr₂ (1.2 g, 5.4 mmol) were heated at 120°C for 65 h. Vacuum concentration followed by Kugelrohr distillation gave 38.2 g (90%) of **1**, bp 120–130°C/0.02 mbar; [α]_D²³ –80.96° (c = 1, acetone).

C₁₂H₁₅NOS calc. C 65.11 H 6.83 N 6.32
(221.3) found 64.93 6.80 6.60

IR (neat): ν = 3040, 2900, 1640, 1595, 1570, 1440, 1350, 1080, 1060, 1050, 1020, 960 cm⁻¹.

¹H NMR (CDCl₃/TMS): δ = 1.92 (m, 2 H, SCH₂CH₂), 2.12 (s, 3 H, SCH₃), 2.66 (m, 2 H, SCH₂), 4.04 (m, 1 H, CHN), 4.46 (m, 2 H, CH₂O), 7.37–7.95 (m, 5 H_{arom}).

^{13}C NMR (CDCl_3/TMS): δ = 15.48 (SCH_3), 30.60 (SCH_2CH_2), 35.35 (SCH_2CH_2), 65.66 (CHN), 72.28 (CH_2O), 127.61, 128.15, 128.21, 131.24 (C_{arom}), 163.66 ($\text{N}=\text{C}-\text{O}$).

(S)-(-)-3-(Benzoylamino)thiolane (2):

Conc. HCl (32 mL, 385 mmol) was added to **1** (16.5 g, 74.7 mmol) in AcOH (280 mL) and the suspension was refluxed for 96 h. The mixture was concentrated in vacuo and distilled, bp 120–160°C/0.02 mbar. Crystallization from EtOH gave 12.4 g (80%) **2** as colorless crystals, mp 129°C; $[\alpha]_{\text{D}}^{20}$ = -37.62° (c = 0.5, acetone).

$\text{C}_{11}\text{H}_{13}\text{NOS}$ calc. C 63.74 H 6.32 N 6.75
(207.3) found 63.99 6.33 6.78

IR (KBr): ν = 3250, 3040, 2920, 2840, 1620, 1525 cm^{-1} .

^1H NMR (CDCl_3/TMS): δ = 2.17 (m, 2 H_4), 2.78–3.17 (m, 2 H_2 , 2 H_5), 4.89 (m, H_3), 6.54 (d, NH, J = 5.8 Hz), 7.39–7.77 (5 H_{arom}).

^{13}C NMR (CDCl_3/TMS): δ = 28.54 (C_4), 35.74 (C_5), 37.23 (C_2), 54.00 (C_3), 126.94, 128.62, 131.65, 134.31 (C_{arom}), 167.06 ($\text{C}=\text{O}$).

(S)-(-)-3-Aminothioliolane (3):

Conc. HCl (32 mL, 385 mmol) was added to **1** (16.5 g, 74.7 mmol) in AcOH (280 mL) and the suspension was refluxed for 96 h. The mixture was concentrated in vacuo, diluted with 3.7 N KOH (600 mL) and refluxed for another 48 h. After cooling, the solution was extracted with CHCl_3 . Removal of solvent after drying (Na_2SO_4) and Kugelrohr distillation gave 6.62 g (86%) of **3** in > 97% purity, bp 70°C/35 mbar; $[\alpha]_{\text{D}}^{22}$ = -37.77 (c = 1, acetone).

IR (neat): ν = 3340, 3260, 2920, 2840, 1590, 1425, 1200 cm^{-1} .

^1H NMR (CDCl_3/TMS): δ = 1.43 (s, NH_2), 1.93 (m, 2 H_4), 2.59 (dd, H_2 , J = 10.6, 4.4 Hz), 2.95 (m, 2 H_5), 2.98 (dd, H_2 , J = 10.6, 5.2 Hz), 3.71 (m, 1 H_3).

(S)-(-)-3-Phthalimidothioliolane (4):

3 (3.6 g, 35.2 mmol) and *N*-(ethoxycarbonyl)phthalimide (7.2 g, 36.1 mmol) in EtOAc (55 mL) were heated at 80°C for 1.5 h. The crude **4** precipitated as colorless crystals. Recrystallization from acetone gave 7.23 g (88%) of pure **4**, mp 170°C (Lit.¹¹ mp 168–170°C); $[\alpha]_{\text{D}}^{23}$ = -37.82° (c = 1, acetone).

IR (KBr): ν = 1750, 1680, 1595 cm^{-1} .

^1H NMR (CDCl_3/TMS): δ = 2.25–3.47 (m, 2 H_2 , 2 H_4 , 2 H_5), 4.80 (m, 1 H_3), 7.80 (m, 4 H_{arom}).

(S)-3-(tert-Butoxycarbonylamino)thiolane (5):

A solution of **3** (1 g, 9.71 mmol) and (*t*-BuO₂C)₂O (2.3 g, 10.7 mmol) in CH_2Cl_2 (10 mL) was stirred at r.t. for 1 h. Evaporation of the solvent and crystallization from Et₂O gave 1.15 g (58%) of colorless crystals, mp 77°C; $[\alpha]_{\text{D}}^{21}$ = -36.43 (c = 1, acetone).

$\text{C}_9\text{H}_{17}\text{NO}_2\text{S}$ calc. C 53.17 H 8.37 N 6.89
(203.3) found 52.98 8.39 6.77

IR (KBr): ν = 3340, 2930, 1665, 1510, 1290, 1160 cm^{-1} .

^1H NMR (CDCl_3/TMS): δ = 1.45 (s, 9 H), 1.95–2.07 (m, 2 H_4), 2.85 (dd, H_2 , J = 11.1, 3.5 Hz), 2.83–2.93 (m, 2 H_5), 3.04 (dd, H_2 , J = 11.1, 5.2 Hz), 4.42 (m, H_3), 4.87 (m, NH).

(3S,1R,S)-3-(tert-Butoxycarbonylamino)-1-methyltetrahydrothiophenium *p*-Toluenesulfonate (7):

Methyl tosylate (14.34 g, 79 mmol) was added to **5** (0.5 g, 2.46 mmol) in Et₂O (20 mL). The solution was refluxed for 8 d, the colorless crystals were separated by filtration and washed with Et₂O. Yield: 0.6 g (62%), mp 145°C (*cis/trans*, 1:1). Recrystallization from CHCl_3 or acetone did not change the melting point.

IR (KBr): ν = 3220, 3000–2900, 1690, 1510, 1200, 1170 cm^{-1} .

^1H NMR (CDCl_3/TMS): δ = 1.38, 1.39 (2 s, 9 H), 2.34 (s, 3 H_3 , CH_3), 2.38–2.49 (m, 2 H_4), 2.93, 3.19 (2 s, 3 H , $\text{CH}_{3\text{cis}}$, $\text{CH}_{3\text{trans}}$), 3.49–3.97 (m, 2 H_2 , 2 H_5), 4.48 (m, $\text{H}_{3\text{cis}}$), 4.72 (m, $\text{H}_{3\text{trans}}$), 6.78, 6.82 (2 m, $\text{NH}_{\text{cis/trans}}$), 7.43 (dd, 4 H_{arom}), J = 8.0 Hz).

(S)-3-[(+)-10-Camphorsulfonylamino]thiolane (6):

3 (0.5 g, 4.85 mmol), dry pyridine (0.77 g, 9.71 mmol) and *D*-(+)-10-camphorsulfonyl chloride (1.06 g, 4.85 mmol) in CH_2Cl_2 (10 mL) were stirred for 24 h at r.t. The organic layer was washed

with sat. aq Na_2CO_3 , then with H_2O , and dried. Vacuum concentration and crystallization from EtOH/ H_2O gave 1.13 g (82%) of **6**, mp 119°C; $[\alpha]_{\text{D}}^{25}$ + 15.56° (c = 0.62, acetone).

A similar reaction with racemic (*R,S*)-**3** lead to a diastereomeric mixture with mp 97°C.

IR (KBr): ν = 3260, 2930, 1720, 1430, 1410, 1365, 1320 cm^{-1} .

^1H NMR (CDCl_3/TMS): δ = 0.92 (s, CH_3), 1.03 (s, CH_3), 1.43–2.45 (m, 9 H), 2.78–2.95 (m, 3 H), 2.99 (d, 1 H, J = 15.1 Hz), 3.07 (m, 1 H), 3.42 (d, 1 H, J = 15.1 Hz), 4.28 (m, 1 H), 5.65 (d, NH, J = 7.5 Hz).

Diastereomeric mixture (*R,S*)-**6**: δ = 1.03, 1.04 (2 s, 3 H , CH_3), 2.99, 3.00 (2 d, 1 H, J = 15.1 Hz), 3.42, 3.44 (2 d, 1 H, J = 15 Hz), 5.59, 5.65 (2 d, NH, J = 7.5 Hz).

3-Hydroxythiolane (8):

NaNO_2 (0.6 g, 5 mmol) in H_2O (10 mL) was added dropwise to an ice cooled solution of **3** (0.5 g, 4.85 mmol) in 0.01 N HCl (10 mL). After stirring for 2 h at r.t., the solution was extracted with CHCl_3 , dried and concentrated. Vacuum distillation gave 0.16 g (32%) of a colorless liquid, bp 100°C/35 mbar (Lit.¹¹ bp 84–85°C/9 mbar).

IR (neat): ν = 3600–3100, 2900, 1420, 1190, 1160, 1120, 950 cm^{-1} .

^1H NMR (CDCl_3/TMS): δ = 2.01 (m, 2 H_4), 2.78–3.03 (m, 2 H_2 , 2 H_5), 3.23 (s, OH), 4.62 (m, H_3).

3-*p*-Tosyloxythiolane:

Powdered KOH (0.49 g, 8.7 mmol) was added to an ice cooled solution of **8** (0.15 g, 1.45 mmol) and TsCl (0.35 g, 1.81 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 1 h at 0°C and 1 h at r.t. The light yellow suspension was diluted with H_2O (10 mL) and the aqueous layer was extracted with CHCl_3 . The combined organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (eluent: CH_2Cl_2); yield: 0.25 g (66%); syrup; $[\alpha]_{\text{D}}^{20}$ + 8.46° (c = 0.54, MeOH); Lit.¹³ $[\alpha]_{\text{D}}$ + 16.76° (c = 0.7, MeOH).

IR (neat): ν = 3020, 2920, 1590, 1355, 1185, 1165, 1090 cm^{-1} .

^1H NMR (CDCl_3/TMS): δ = 1.92 (m, H_4), 2.29 (m, H_4), 2.44 (s, CH_3), 2.79–3.01 (m, 2 H_2 , 2 H_5), 5.18 (m, H_3), 7.32 (d, 2 H_{arom}), 7.79 (d, 2 H_{arom} , J = 8.0 Hz).

This work was supported by an university grant (OZ 21940/23) and the Fonds der Chemischen Industrie.

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