A New Simple Route to *N,O*-Protected (*S*)-2-Amino-4-oxobutyric Acid

Eckehard Volker Dehmlow,* Ralf Westerheide
Fakultät für Chemie, Universität Bielefeld, D-33615 Bielefeld, Germany
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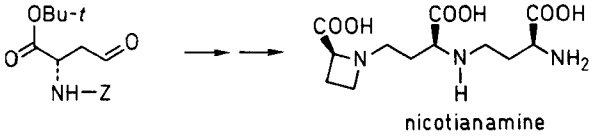
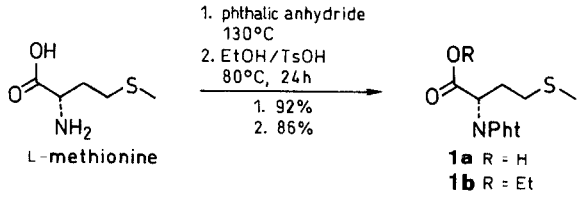
Methionine is converted into the *N,O*-protected derivative **1b**. Chlorination of **1b** with sulfuryl chloride results in a mixture of the α-halosulfides **2a** and **2b** in the ratio of 6:1. Hydrolysis of **2a** gives the title compound **3** in 64% yield.

Derivatives of (*S*)-2-amino-4-oxobutyric acid are interesting chiral intermediates, e.g. for the synthesis of nicotianamine.[1,2,3a] Nozoe et al.[1,2] utilized the very expensive (*S*)-allylglycine derivative shown below as starting material. Further syntheses have been described starting from L-aspartic acid.[3,4] We report here a novel route to **3** using L-methionine as the educt.



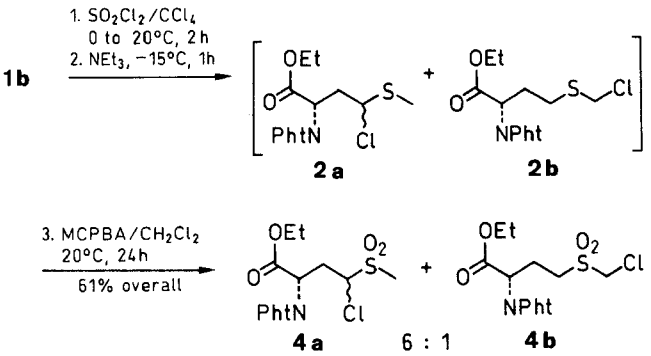
Scheme 1

L-Methionine was protected by reaction with phthalic anhydride[5] to yield **1a**. This in turn was esterified with ethanol/*p*-toluenesulfonic acid to give **1b** in high yield.



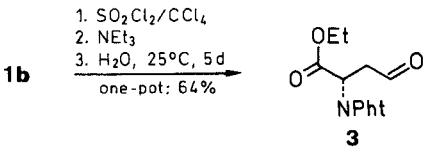
Scheme 2

Chlorination[6] of **1b** with sulfuryl chloride in carbon tetrachloride yielded the halo derivatives **2a** and **2b** in the ratio of 6:1. Because these compounds were rather unstable towards hydrolysis, **2a,b** were identified as the sulfones **4a,b** by ^{1}H NMR spectroscopy and by CHN analysis.



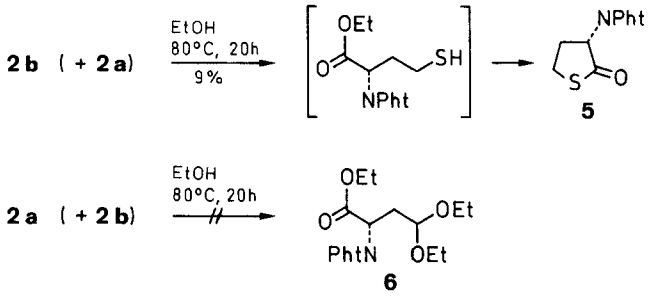
Scheme 3

Aqueous hydrolysis[7] of the mixture of the regioisomers **2a,b** gave the title compound **3** from **2a**. Separation of **2a** and **2b** was neither attempted nor necessary. Starting from **1b** in a one-pot reaction, **3** was obtained in 64% overall yield, without isolation of intermediates **2a,b**.



Scheme 4

Attempted solvolysis of the mixture of **2a,b** with ethanol yielded the thiolane derivative **5** which is formed from **2b** via the shown pathway. Compound **5** was the only product that could be isolated and characterized. In particular, the expected formation of **6** from **2a** was not observed.



Scheme 5

Ramberg–Bäcklund[6] rearrangements of **4a,b** were attempted under a wide variation of conditions, but instead of an allylglycine derivative only intractable decomposition products were obtained.[8]

Melting points were determined on a Büchi apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-360 digital polarimeter in a 10 cm cell. IR spectra were obtained using a Beckman Acculab 8 spectral photometer. ^{1}H NMR spectra were recorded on a Bruker AM 300 spectrometer. All new compounds gave satisfactory microanalyses (obtained: C ± 0.59, H ± 0.36, N ± 0.12).

(*S*)-4-(Methylthio)-2-phthalimidobutyric acid (1a):
Compound **1a** (33.6 g) (92%) was obtained from 20 g (134 mmol) of L-methionine, following the method of lit.,[5] mp 123°C ($MeOH/H_2O$); $[\alpha]_D^{24}$ − 45.2° (*c* = 1, MeOH), [Lit.,[5] mp 124°C; $[\alpha]_D^{23}$ − 47.5° (*c* = 5.2, MeOH)].

IR (KBr): *v* = 3600–3200, 3060, 2990, 1780, 1720, 1400 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 2.00 (s, 3H, SCH_3), 2.46 (m, 4H, $-CH_2CH_2S$); 5.07 (m, 1H, NCHCOOH); 7.77 (m, 4H$_{arom}$).

Ethyl (*S*)-4-(Methylthio)-2-phthalimidobutanoate (1b):
Compound **1a** (30 g, 107.4 mmol) and TsOH (20.9 g, 110 mmol) in EtOH (400 mL) were refluxed for 36 h. The mixture was concentrated, diluted with H_2O (120 mL) and made basic with Na_2CO_3. The aqueous layer was extracted with $CHCl_3$ (3 × 30 mL) and the combined organic layer was dried (Na_2SO_4). Removal of solvent and Kugelrohr distillation gave 28.4 g (86%) of **1b**, bp 120–140°C/0.01 mbar; $[\alpha]_D^{24.4}$ − 16.3° (*c* = 0.98, $CHCl_3$).

IR (neat): *v* = 2960, 2900, 1720, 1260, 1160 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.23 (t, 3H, CH_2CH_3, *J* = 7.2 Hz); 2.09 (s, 3H, SCH_3); 2.53 (m, 4H, SCH_2CH_2); 4.21 (q, 2H, OCH_2CH_3); 5.08 (m, 1H, H_2); 7.76 + 7.88 (2m, 4H$_{arom}$).

Ethyl (*S*)-4-Chloro-4-(methylsulfonyl)-2-phthalimidobutanoate (4a) and Ethyl (*S*)-4-(chloromethylsulfonyl)-2-phthalimidobutanoate (4b) (as a mixture):
SO_2Cl_2 (2.38 g, 17.62 mmol) was added dropwise to an ice cooled solution of **1b** (5.34 g, 17.61 mmol) in CCl_4 (100 mL). Stirring was continued for 1 h at 0°C and 1 h at r.t. Et_3N (1.78 g, 17.62 mmol) was added. After 1 h at − 15°C, the precipitate was filtered off and the solvent was removed in vacuo. The residue was diluted with CH_2Cl_2 (200 mL), and MCPBA (70%) (15.4 g, 89.3 mmol) was added. After 24 h at r.t., the solution was filtered and washed with aq K_2CO_3 (80 mL) and $Na_2S_2O_5$ (25 mL). Removal of solvent after drying (Na_2SO_4) and crystallization from EtOH gave 4 g (61%) of the mixture (**4a**:**4b** = 6:1) as sticky crystals.

IR (neat): *v* = 2970, 2920, 1770, 1730, 1710, 1380, 1320, 1240, 720 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.23 + 1.25 (2t, OCH_2CH_3, *J* = 7.1, 7.2 Hz); 2.41 (m, $CH_2CH_2SO_2$); 2.78–3.37 (m, $CH_2CHClSO_2$/CH_2SO_2); 3.06 + 3.07 ppm (2s, SCH_3); 4.24 (m, OCH_2CH_3); 4.48 (s, SCH_2Cl); 4.56 (dd, $CH_2CHClSO_2$, *J* = 2.7, 11.7 Hz); 4.98 (m, $CH_2CHClSO_2$); 5.19 (m, NCHCOOEt); 7.85 (2m, H$_{arom}$).

Ethyl (*S*)-4-Oxo-2-phthalimidobutanoate (3):
Compound **1b** (5.34 g, 17.61 mmol) was halogenated as described for **4a,b**. The crude residue was diluted with H_2O (100 mL) and the suspension was stirred for 5 d at r.t. The solution was extracted with $CHCl_3$ (3 × 20 mL) and dried (Na_2SO_4). Removal of solvent and Kugelrohr distillation gave 3.08 g (64%) of pure **3** as colorless liquid, bp 110–130°C/0.01 mbar; $[\alpha]_D^{24.4}$ − 7.94° (*c* = 0.46, $CHCl_3$).

IR (neat): *v* = 3360, 2960, 2910, 2830, 2720, 1770–1690, 1600, 1460, 1390–1330, 1290–1180, 1120, 1090, 720 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.61 (t, 3H, OCH_2CH_3, *J* = 7.1 Hz); 3.22 (dd, 1H, CH_2CHO, *J* = 7.8, 18.4 Hz); 3.49 (ddd, 1H, CH_2CHO, *J* = 0.8, 6.0, 18.4 Hz); 4.17 (m, 2H, OCH_2CH_3); 5.43 (dd, 1H, NCH-, *J* = 6.0, 7.8 Hz); 7.70 + 7.81 (2m, 4H$_{arom}$); 9.76 (s, 1H, CHO).

(*S*)-Phthalimidothiolan-2-one (5):
(1b) (3.28 g, 8.77 mmol) was halogenated as described for **4a,b**. The crude residue was diluted with EtOH (150 mL) and refluxed for 20 h. Evaporation of the solvent and Kugelrohr distillation gave 1.7 g of a complex mixture; bp 150–160°C and 0.2 g (9%) of **5** as colorless crystals, bp 170–190°C/0.01 mbar, mp 145°C (Et_2O); $[\alpha]_D^{24.4}$ − 4.5° (*c* = 0.085, $CHCl_3$).

IR (KBr): *v* = 3050, 2895, 1700, 1670, 1380, 1100, 710 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 2.56 (m, 1H, H_4); 2.93 (m, 1H, H_4); 3.46 (m, 2H_5); 5.00 (dd, 1H, H_3, *J* = 7.2, 13.0 Hz); 7.76 + 7.87 (2m, 4H$_{arom}$).

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(1) Fushiya, S.; Sato, Y.; Nakatsuyama, S.; Kanuma, N.; Nozoe, S. *Chem. Lett.* **1981**, 909.
(2) Nakatsuyama, S.; Sato, Y.; Nozoe, S. *Heterocycles* **1981**, *15*, 819.
(3) (a) Faust, J.; Schreiber, K.; Ripperger, H. *Z. Chem.* **1984**, *24*, 330.
(b) Valerio, R.M.; Alewood, P.F.; Johns, R.B. *Synthesis* **1988**, 786.
(4) (a) Ramsamy, K.; Olsen, R.K.; Emery, T. *Synthesis* **1982**, 42.
(b) Wernic, D.; DiMaio, J.; Adams, J. *J. Org. Chem.* **1989**, *54*, 4225.
(c) Tong, G.; Perich, J.W.; Johns, R.B. *Tetrahedron Lett.* **1990**, *31*, 3759.
(5) Guttmann, St.; Boissannas, R.A. *Helv. Chim. Acta* **1958**, *41*, 1852.
(6) Paquette, L.A. *Org. React.* **1975**, *25*, 1.
(7) Tuleen, D.L. *J. Org. Chem.* **1967**, *32*, 4006.
(8) Note added in proof: Using different protecting groups, the transformation of a methionine into an allylglycine derivative has been achieved now:
Taylor, R.; Langley, G.J.; Brisdon, A.K.; Holloway, J.H.; Hope, E.G.; Kroto, H.W.; Walton, D.R.W. *J. Chem. Soc., Chem. Commun.* **1993**, 874.