A Convenient Synthesis of Ethyl 3-Aminopropanedithioate (β-Alanine Ethyl Dithioester)

Olivier Josse,[a,b] Daniel Labar,[b] Jacqueline Marchand-Brynaert[a*]

[a] Laboratoire de Chimie Organique de Synthèse, Université Catholique de Louvain, Département de Chimie, Bâtiment Lavoisier, Place L. Pasteur 1, B-1348 Louvain-La-Neuve, Belgium

[b] Laboratoire de Tomographie par Positron, Université Catholique de Louvain, Département de Chimie, Bâtiment Lavoisier, Place L. Pasteur 1, B-1348 Louvain-La-Neuve, Belgium

Fax +32(10)474168, E-mail: marchand@chor.ucl.ac.be

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Abstract: A five-step sequence allowing the preparation of ethyl 3-aminopropanedithioate from *N*-(Boc)-β-alanine via the key intermediate *N*-(Boc)-β-alaninethioacyl-*N*-phthalimide is described.

Key words: dithioester, thioacyl-*N*-phthalimide

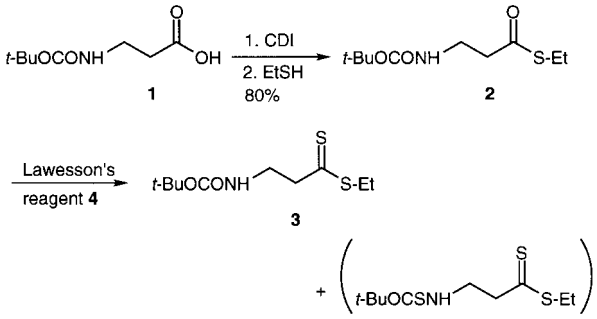
Esters of dithiocarboxylic acids are versatile tools in organic synthesis.[1,2] Their traditional precursors are dithioacid salts and thioacyl halides, the related thioacids are prepared by the reaction of carbon disulfide either with organometallic reagents and nucleophilic carbanions, or with aromatic compounds under Friedel–Crafts conditions.[3,4] Thiohydrolysis of imidothiolates prepared from nitrile- or thioamide precursors constitutes another valuable method of dithioesters synthesis.[3,4] Lastly, thionation of thioesters has been achieved by the use of Lawesson's reagent **4**.[5,6]

The previous methods can be readily applied to the simple cases of aromatic and non-functionalized aliphatic compounds. On the other hand, the preparation of aminodithioester derivatives appeared somewhat more difficult. Amino nitriles are the usual precursors[7–9] and, recently, a modified procedure of the Pinner reaction has also been proposed.[10]

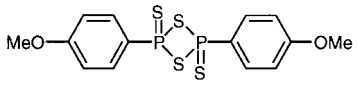
In the course of the total synthesis of a drug precursor, we required the β-alanine dithioester building block. We tried to prepare the *N*-protected compound using the classical methods, i.e. a) by the reaction of 2-(*N*-phthalimido)aminobromoethane with magnesium, followed by CS_2 and MeI and b) by the reaction of ethyl 3-(*N*-*tert*-butoxycarbonyl)aminopropanethioate **(2)** with Lawesson's reagent **4** (Scheme 1).

The first route failed. The second one gave only poor yields of the required dithioester **3**, probably as a result of the lack of selectivity of the thionation reagent **4** towards the thioester carbonyl versus the carbamate function. Therefore, we decided to consider the primary amide **5** as the starting material (Scheme 2). The selective thionation of primary carboxamides in the presence of carbamate protecting groups has been well established.[11,12]

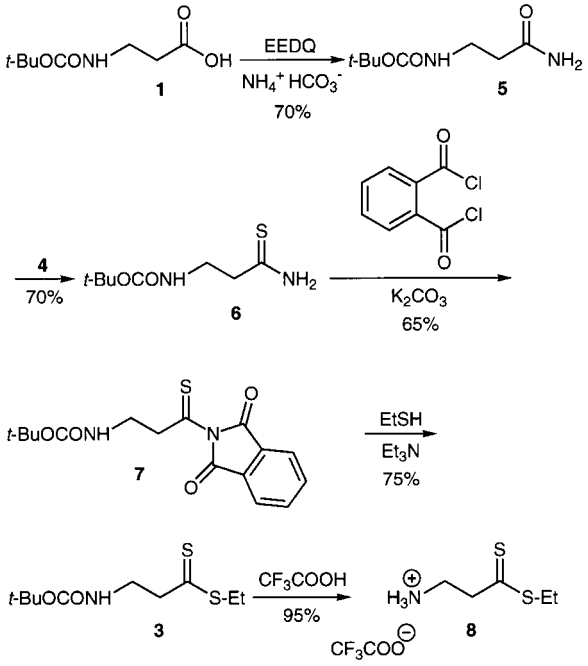
N-(Boc)-β-alanine **(1)** was activated with 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) in the presence of ammonium bicarbonate[13] to furnish the corresponding amide **5**, which was purified by crystallization.



Conditions	Yield **3** (isolated)
0.6 equiv. **4**, THF, 20°C, 17h	no reaction
1.2 equiv. **4**, toluene, 80°C, 4 d	untractable mixture
0.6 equiv. **4**, toluene, 80°C, 7h	12%
0.6 equiv. **4**, toluene, 100°C, 12h	23%



Scheme 1



Scheme 2

Subsequent treatment of **5** with Lawesson's reagent **4** followed by chromatography gave the pure thioamide **6**. The direct transformation of primary thioamides into dithioesters has been described in the α-amino acids family;[12] however, hard conditions are needed (R-I, NaF, H_2S in large excess) and yields are low. We found that thioamide **6** could be activated by transformation into the corresponding thioacyl-*N*-phthalimide **7**. The thioacyl-*N*-phthalimides were recently disclosed as powerful thioacylation reagents useful in modified peptide syntheses.[14,15] Thus, the precursor **6** was reacted with phthaloyl dichloride in the presence of potassium carbonate to yield **7** (red solid) purified by chromatography. This intermediate **7** was readily transformed into the dithioester **3** by treatment with ethanethiol and triethylamine at 0°C. After chromatography, we obtained 75% of product **3** (yellow oil) which could be quantitatively deprotected by simple dissolution into trifluoroacetic acid at 0°C. Ethyl 3-aminopropanedithioate (**8**, β-alanine ethyl dithioester) was further involved in peptide coupling reactions using classical coupling agents.

In conclusion, we have shown that the readily accessible thioacyl-*N*-phthalimide **7** constitutes a valuable key intermediate for preparing the dithioester **3**. All the reactions outlined in Scheme 2 can be carried out on a gram scale, and the intermediates are easily purified; the overall yield from **5** (34%) is reasonable. We believe that this strategy could be applied for the synthesis of dithioesters derived from α-amino acids.

Solvents were dried prior to use. Reagents and solvents (Aldrich) were used as purchased. Melting points (uncorrected) were determined on an Electrothermal apparatus. ^{1}H (200 or 300 MHz) and ^{13}C (50 MHz) NMR spectra were recorded on Varian Gemini 200 and 300 spectrometers. Chemical shifts are reported as δ values downfield from TMS. The mass spectra (FAB or CI modes) were obtained on a Finnigan MAT TSQ-70 instrument. HRMS (FAB mode) spectra were performed on a VG-Autospec-Q apparatus. IR spectra were obtained using a Biorad FTS 135 spectrometer calibrated with polystyrene. TLC were carried out using silica gel 60 F_{254} (0.2 mm, Merck) and spots were visualised by UV. Silica gel 60, mesh size 0.04–0.063 mm (Merck) was used for column chromatography.

Ethyl 3-(*N*-*tert*-Butoxycarbonyl)aminopropanethioate (2)
A mixture of **1** (1 g, 5.28 mmol) and carbonyldiimidazole (CDI) (0.943 g, 5.8 mmol) in THF (5 mL) was stirred 30 min at 20°C under an argon atmosphere. Then, ethanethiol (1.17 mL, 15.87 mmol) was added and the mixture was stirred overnight at r.t. After the addition of 4 N NaOH (10 mL), the mixture was rapidly extracted with CH_2Cl_2 (3 × 6 mL). Drying ($MgSO_4$) and concentration under reduced pressure gave pure **2** as a colorless liquid; yield: 0.983 g (80%).

^{1}H NMR ($CDCl_3$/TMS, 200 MHz): δ = 1.26 (t, 3 H, *J* = 7.4 Hz, SCH_2CH_3), 1.44 (s, 9 H, *t*-C_4H_9), 2.77 (t, 2 H, *J* = 6.0 Hz, CH_2CS_2Et), 2.89 (q, 2 H, *J* = 7.4 Hz, SCH_2CH_3), 3.42 (dt, 2 H, *J* = 6.1, 6.0 Hz, CH_2NHBoc), 4.99 (br t, 1H, *J* = 6.1 Hz, N*H*Boc).

^{13}C NMR ($CDCl_3$/TMS, 50 MHz): δ = 14.45 (SCH_2CH_3), 23.07 (SCH_2CH_3), 28.16 [$(CH_3)_3C$], 36.38 (CH_2COSEt), 43.72 (CH_2NHBoc), 79.06 [$(CH_3)_3C$], 155.60 (O*C*ONH), 198.23 (*C*OSEt).

IR (film): ν = 3361 (NH), 2976, 2932, 1716 (COS), 1695 (OCONH), 1520, 1366, 1272, 1251, 1172, 1075, 1008, 972 cm^{-1}.

MS (CI/CH_4-N_2O): *m/z* (%) = 232.1 ([M – H]–, 25.6), 115.9 (100), 102.9 (14.5), 72.9 (12.4), 60.8 (89.4), 41.8 (31.8).

Anal. Calc. for $C_{10}H_{19}NO_3S$: C 51.48; H 8.21; N 6.00; S 13.74. Found: C 51.41; H 8.32; N 6.09; S 13.95.

Ethyl 3-(*N*-*tert*-Butoxycarbonyl)aminopropanedithioate (3) from 2 and Lawesson's Reagent
A mixture of **2** (1 g, 4.3 mmol) and **4** (1.045 g, 2.58 mmol) in toluene (25 mL) was stirred at 100°C for 12 h under an argon atmosphere. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (EtOAc/hexane, 10:90) to give pure **3** as a yellow oil; yield: 0.245 g (23%).

N-(*tert*-butoxycarbonyl)-β-alaninamide (5)
A mixture of **1** (5 g, 26.4 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ, 7.188 g, 29.1 mmol) and NH_4HCO_3 (6.267 g, 79.3 mmol) in $CHCl_3$ (75 mL) was stirred overnight at 20°C under argon atmosphere. The precipitate was filtered, the organic phase washed with water (2 × 50 mL), dried ($MgSO_4$) and concentrated. The residue was crystallized from EtOAc/hexane to furnish the carboxamide **5**. Some more product could be recovered from the aqueous phase (extraction with CH_2Cl_2) and the mother liquor which was purified by column chromatography on silica gel (*i*-PrOH/hexane 20:80); total yield: 3.481 g (70%); white crystals; mp 158.3–158.9°C.

^{1}H NMR ($CDCl_3$/TMS, 200 MHz): δ = 1.44 (s, 9 H, *t*-C_4H_9), 2.46 (t, 2 H, *J* = 5.8 Hz, CH_2CONH_2), 3.42 (dt, 2 H, *J* = 5.8, 5.8 Hz, CH_2NHBoc), 5.19 (br t, 1 H, *J* = 5.8 Hz, N*H*Boc), 5.60 and 5.80 (2 br s, 2 H, $CONH_2$).

^{13}C NMR (acetone-d_6, 50 MHz): δ = 28.71 [$(CH_3)_3C$], 36.18 (CH_2CONH_2), 37.69 (CH_2NHBoc), 78.78 [$(CH_3)_3C$], 156.69 (O*C*ONH), 174.15 ($CONH_2$).

IR (KBr): ν = 3335–3160 (NH), 2976, 1661 (C=O), 1539, 1456, 1435, 1412, 1365, 1296, 1169, 1009, 918 cm^{-1}.

MS (CI/CH_4-N_2O): *m/z* (%) = 187.0 ([M – H]–, 29.6), 112.9 (100), 72.9 (10.0), 41.8 (25.6).

Anal. Calc. for $C_8H_{16}N_2O_3$: C 51.05; H 8.57; N 14.88. Found: C 51.08; H 8.73; N 14.69.

***N*-(*tert*-Butoxycarbonyl)-β-thioalaninamide (6)**
A mixture of **5** (3.4 g, 18 mmol) and **4** (4.384 g, 10.8 mmol) in THF (75 mL) was stirred at 20°C for 24 h, under an argon atmosphere. After concentration, the residue was purified by flash chromatography on silica gel (EtOAc/hexane, 50:50; R_f 0.3). Recrystallization from EtOAc/hexane gave pure **6** as white crystals; yield: 2.583 g (70%); mp 114.2–114.8°C.

^{1}H NMR ($CDCl_3$/TMS, 200 MHz): δ = 1.43 (s, 9 H, *t*-C_4H_9), 2.85 (t, 2 H, *J* = 6.1 Hz, CH_2CSNH_2), 3.55 (dt, 2 H, *J* = 6.1, 6.2 Hz, CH_2NHBoc), 5.20 (br t, 1 H, *J* = 6.2 Hz, N*H*Boc), 7.82 (br s, 2 H, $CSNH_2$).

^{13}C NMR ($CDCl_3$/TMS, 50 MHz): δ = 28.28 [$(CH_3)_3C$], 39.17 (CH_2CSNH_2), 44.53 (CH_2NHBoc), 79.76 [$(CH_3)_3C$], 156.31 (O*C*ONH), 207.59 ($CSNH_2$).

IR (KBr): ν = 3335–3160 (NH), 2976, 1661 (C=O), 1539, 1435, 1364, 1296, 1169, 1009, 918 cm^{-1}.

MS (CI/CH_4-N_2O): *m/z* (%) = 202.9 ([M – H]–, 72), 128.8 (100), 85.8 (7.3), 73.0 (8.7), 41.8 (34.3).

Anal. Calc. for $C_8H_{16}N_2O_2S$: C 47.03; H 7.89; N 13.71; S 15.69. Found: C 47.03; H 7.98; N 13.65; S 15.66.

3-(*N-tert*-Butoxycarbonyl)aminopropanethioacyl *N*-Phthalimide (7)

To a mixture of **6** (2.5 g, 12.2 mmol) and K_2CO_3 (2.029 g, 14.7 mmol) in THF (30 mL), cooled at 0 °C, was added dropwise (within 4 h, stirring under argon atmosphere) a solution of phthaloyl dichloride (2.11 mL, 14.7 mmol) in THF (30 mL). After the addition was complete, the mixture was further stirred for 3 h at 20 °C, then poured into H_2O (50 mL) and extracted with EtOAc (3 × 15 mL). Drying ($MgSO_4$), concentration and purification by flash chromatography on silica gel (EtOAc/hexane, 30:70; R_f 0.72 for EtOAc/hexane, 50:50) gave pure **7** as an amorphous red solid; yield: 2.660 g (65%). No melting point could be determined due to decomposition.

^{1}H NMR ($CDCl_3$/TMS, 200 MHz): δ = 1.39 (s, 9 H, *t*-C_4H_9), 3.48 (t, 2 H, *J* = 5.7 Hz, C*H*$_2$CSNphth), 3.63 (dt, 2 H, *J* = 5.7, 6.1 Hz, C*H*$_2$NHBoc), 4.95 (br t, 1 H, N*H*), 7.83–7.88 (m, 2 H_{arom}), 7.96–8.01 (m, 2 H_{arom}).

^{13}C NMR ($CDCl_3$/TMS, 50 MHz): δ = 28.21 [(*C*H$_3$)$_3$C], 38.61 (*C*H$_2$CSNphth), 49.33 (*C*H$_2$NHBoc), 79.32 [(CH$_3$)$_3$*C*], 124.57, 130.66, 135.39, 155.68 (O*C*ONH), 164.54 (phth-*C*=O), 209.91 (C=S).

IR (KBr): ν = 3349 (NH), 2970, 1724 (C=O, Ft), 1684 (OCONH), 1531, 1456, 1367, 1319, 1252, 1163, 1014, 872 cm^{-1}.

MS (CI/CH_4-N_2O): *m/z* (%) = 333.0 ([M – H]–, 43.2), 185.9 (5.0), 146.9 (15.0), 145.9 (100).

HRMS (FAB): *m/z* calcd for $C_{16}H_{19}N_2O_4S$ (MH^+) 335.1066, found 335.1070.

Ethyl 3-(*N-tert*-Butoxycarbonyl)aminopropanedithioate (3)

To a cold (0 °C) solution of **7** (2.6 g, 7.7 mmol) in CH_2Cl_2 (25 mL), were added dropwise successively (stirring under argon atmosphere) ethanethiol (2.88 mL, 38.8 mmol) and Et_3N (1.081 mL, 7.7 mmol). The mixture was allowed to reach 20 °C within 1 h and left for another 1 h at 20 °C. After addition of 4 N NaOH (75 mL), the mixture was rapidly extracted with CH_2Cl_2 (3 × 25 mL). Drying ($MgSO_4$), concentration and purification by flash chromatography on silica gel (EtOAc/hexane, 10:90; R_f 0.75 for EtOAc/hexane, 30:70), gave pure **3** as a yellow oil; yield: 1.452 g (75%).

^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ = 1.32 (t, 3 H, *J* = 7.5 Hz, SCH$_2$C*H*$_3$), 1.44 (s, 9 H, *t*-C_4H_9), 3.16 (t, 2 H, *J* = 6.3 Hz, C*H*$_2$CS$_2$Et), 3.22 (q, 2 H, *J* = 7.5 Hz, SC*H*$_2$CH$_3$), 3.57 (dt, 2 H, *J* = 6.0, 6.3 Hz, C*H*$_2$NHBoc), 4.90 (br t, 1 H, *J* = 6.0 Hz, N*H*Boc).

^{13}C NMR ($CDCl_3$/TMS, 50 MHz): δ = 11.96 (SCH$_2$*C*H$_3$), 28.25 [(*C*H$_3$)$_3$C], 30.58 (S*C*H$_2$CH$_3$), 40.55 (*C*H$_2$CS$_2$Et), 51.03 (*C*H$_2$NHBoc), 79.21 [(CH$_3$)$_3$*C*], 155.62 (O*C*ONH), 235.61 (*C*S$_2$Et).

IR (Film): ν = 3353 (NH), 2975, 1699 (OCONH), 1507, 1456, 1365, 1250, 1168, 911 cm^{-1}.

MS (CI/CH_4-N_2O): *m/z (%)* = 248.0 ([M – H]–, 100), 186.0 (10.7), 130.9 (9.1), 118.9 (19.8), 115.9 (78.6), 41.8 (34.0).

Anal. Calc. for $C_{10}H_{19}NO_2S_2$: C 48.16; H 7.68; N 5.62; S 25.71. Found: C 48.24; H 7.72; N 5.74; S 25.63.

Ethyl 3-Aminopropanedithioate (8)

The dithioester **3** (1.4 g, 5.6 mmol) was dissolved in cold (0 °C) trifluoroacetic acid (10 mL) and left 1 h under an argon atmosphere. After evaporation under vacuum, the residue was dissolved in CH_2Cl_2 (20 mL) and extracted with H_2O (3 × 7 mL, HPLC grade). Lyophilization of the aqueous phases gave pure **8** (trifluoroacetate salt) as a yellow amorphous solid; yield: 1.405 g (95%); mp 60.2–61.2 °C.

^{1}H NMR (D_2O, 300 MHz): δ = 1.10 (t, 3 H, *J* = 7.5 Hz, SCH$_2$C*H*$_3$), 3.07 (q, 2 H, *J* = 7.5 Hz, SC*H*$_2$CH$_3$), 3.15 (t, 2 H, *J* = 6.2 Hz, C*H*$_2$CS$_2$Et), 3.29 (t, 2 H, *J* = 6.2 Hz, C*H*$_2$NH$_2$).

^{13}C NMR (D_2O, 50 MHz): δ = 12.17 (SCH$_2$*C*H$_3$), 31.79 (S*C*H$_2$CH$_3$), 39.87 (*C*H$_2$CS$_2$Et), 47.61 (*C*H$_2$NH$_2$), 117.18 (q, *J* = 288.7 Hz, *C*F$_3$CO$_2$H), 163.59 (q, *J* = 35.4 Hz, CF$_3$*C*O$_2$H), 235.38 (*C*S$_2$Et).

IR (KBr): ν = 3000–2600, 1670 (C=O, carboxylate salt), 1522–1539 (NH_3^+), 1456, 1435, 1136, 1196, 910, 839, 798, 723 cm^{-1}.

MS (FAB/glyc.): *m/z* (%) = 150.0 (MH^+, 73.6), 133.0 (100), 121.0 (46.3), 105.0 (17.3), 87.0 (19.8), 58.9 (28.8), 29.8 (28.0).

HRMS (FAB): *m/z* calcd for $C_5H_{11}NS_2$ (MH^+ without counter-ion) 150.0411, found 150.0411.

Anal. Calc. for $C_7H_{12}F_3NO_2S_2$: C 31.93; H 4.59; N 5.32; S 24.35. Found: C 31.98; H 4.49; N 5.23; S 23.97.

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