A facile one-pot synthesis and heterocyclisation of (*R*)-2-amino-3-((aroylcarbamothioyl)thio)propanoic acids

Razieh Mohebat* and Elahe Kafrizi

Department of Chemistry, Islamic Azad University, Yazd Branch, PO Box 89195-155, Yazd, Iran

A series of (*R*)-2-amino-3-((aroylcarbamothioyl)thio)propanoic acid derivatives have been synthesised by a one-pot, three-component reaction of L-cysteine with ammonium thiocyanate in the presence of various acid chlorides under solvent-free conditions in excellent yields. These compounds were converted to (*R*)-2-thioxothiazolidine-4-carboxylic acid in water under reflux conditions.

Keywords: (*R*)-2-amino-3-((aroylcarbamothioyl)thio)propanoic acid, (*R*)-2-thioxothiazolidine-4-carboxylic acid, acid chlorides, L-cysteine, ammonium thiocyanate

L-Cysteine, a naturally occurring amino acid, has an important role in many biological processes.[1,2] Cysteine and its derivatives are present in various cosmetic and pharmaceutical preparations.[3] Recently, the chemistry of isothiocyanates has been studied, as these compounds are strong cancer chemopreventors.[4–6] Many different isothiocyanates (more than 25) block the carcinogenic effects of more than 12 chemically different types of carcinogens in at least 10 different target sites in three species of rodent[7]. Isothiocyanates are extremely useful in organic synthesis.[8,9] Several methods to prepare isothiocyanates and the corresponding mercapturic acids have been developed.[10–15]

Thiazolidine-2-thiones and their derivatives exhibit a range of biological activities, such as hepatoprotective,[16] antibacterial,[17] antifungal,[18] analgesic,[19] insecticide,[20] protein modification,[21] antiinflammatory and immunosuppressive activities.[22]

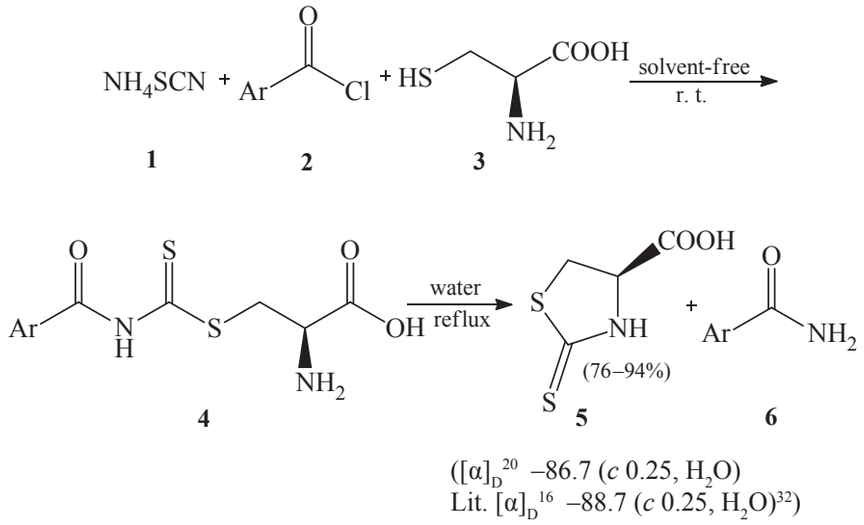
As part of our current studies on the development of new routes to sulfur-containing organic compounds synthesis,[23–25] we now describe a simple one-pot synthesis of six mercapturic acids derived from aroyl isothiocyanates and L-cysteine under solvent-free conditions. We have also converted these isothiocyanate-derived mercapturic acids into (*R*)-2-thioxothiazolidine-4-carboxylic acid in water under reflux conditions.

Results and discussion

(*R*)-2-amino-3-((aroylcarbamothioyl)thio)propanoic acids **4** were synthesised by the one-pot, three-component reaction of L-cysteine with ammonium thiocyanate in the presence of aroyl chlorides under solvent-free conditions in excellent yields. The compounds **4** were then converted into (*R*)-2-thioxothiazolidine-4-carboxylic acid **5** with high purity (Scheme 1). The synthesis of compound **5** and compounds **6** has previously been described.[26–31] The melting point and NMR data were identical with those reported (see Table 1).

The structures of compounds **4a–f**, **5**, **6a–f** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, LCMS, and elemental analysis. For example, the ^{1}H NMR spectrum of **4a** showed two singlets (δ=7.20 and 9.02 ppm) assigned to the protons of the NH groups with a singlet at δ=11.14 for the COOH group. These disappear after the addition of a few drops of D_2O to DMSO solution of **4a**. The aromatic protons resonated between 8.12 and 8.34 ppm.

The ^{13}C NMR spectrum of compound **4a** shows nine distinct signals, consistent with the proposed structure. The mass spectrum of **4a** displayed the molecular ion peak at *m/z*=329. The IR spectrum of compound **4a** also supported the suggested structure since strong absorption bands were observed at 3385, 3105 and 1670 cm^{-1} respectively for the NH and carbonyl groups.



Scheme 1 Synthesis and interconversion of (*R*)-2-amino-3-((aroylcarbamothioyl)thio)propanoic acids.

* Correspondent. E-mail: mohebat@iauyazd.ac.ir

Table 1 Yields of (*R*)-2-amino-3-((aroylcarbamothioyl)thio)propanoic acids **4a–f** and benzamides **6a–f** from the reaction between L-cysteine and acid chlorides in the presence of ammonium thiocyanate (Scheme 1)

No.	Ar	4	Yield/%[a]	6	Yield/%[a]	M.p./°C	Lit.[9] m.p./°C
1	4-NO_2–C_6H_4	**4a**	97	**6a**	94	198–200	201
2	3-NO_2–C_6H_4	**4b**	93	**6b**	91	141–143	142
3	4-Br–C_6H_4	**4c**	91	**6c**	87	190–192	189
4	2-CH_3–C_6H_4	**4d**	80	**6d**	76	141–142	143
5	3-CH_3–C_6H_4	**4e**	83	**6e**	78	94–96	95
6	C_6H_5	**4f**	88	**6f**	84	127–129	129

[a]Yields refer to the pure isolated products.

A tentative mechanism for this transformation is shown in Scheme 2.

It is conceivable that the aroyl chloride **1** reacts with ammonium thiocyanate to form aroyl thiocyanate **2.** The addition of L-cysteine **3** generates **4** which is converted to compound **5** by the elimination of benzamide.

In conclusion, we have developed a straightforward method for the synthesis of isothiocyanate-derived mercapturic acids under solvent-free conditions. (*R*)-2-Thioxothiazolidine-4-carboxylic acid is formed in water under reflux conditions. This procedure provides several advantages such as cleaner reactions, shorter reaction times and affords excellent yields.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS–O analyser at analytical laboratory of Islamic Azad University Yazd branch. Optical rotations were determined at 589 nm (sodium D line) using a Atago-Ap-300 digital polarimeter, products were dissolved in DMSO (g 100 mL^{-1}). Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer for solutions in d_6-DMSO using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Synthesis of compounds **4***; general procedure*

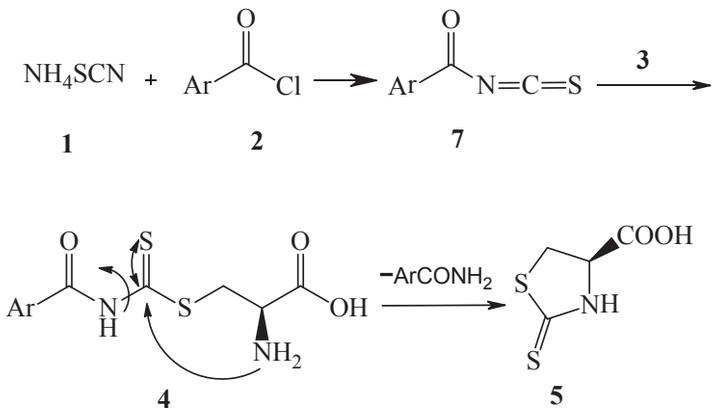
Aroyl chloride (2 mmol) was added to ammonium thiocyanate (2 mmol) in a 50 mL flask at room temperature. The reaction mixture was stirred in a water bath at about 60 °C for 5 min. Then, L-cysteine **2** (2 mmol) was added slowly and the contents were stirred for 2 h at room temperature under solvent-free conditions. The progress of the reaction was monitored by TLC. After completion of the reaction, distilled water (15 mL) was added over 5 min to the reaction mixture. The resulting precipitate was collected by filtration on a Buchner funnel and recrystallised from EtOH to afford the pure title compounds.

Synthesis of compound **5** *and benzamides; general procedure*

The reaction mixture was stirred at room temperature for 2 h under solvent-free conditions. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting mixture was refluxed in water (5 mL) for 1 h and extracted with ethyl acetate (3 × 5 mL). After evaporation of the solvent, the resulting crude material was purified by column chromatography on silica using n-hexane/ethyl acetate (2 : 1) as eluent to give compound **5** and benzamides.

(R)-*2-Amino-3-(((4-nitrobenzoyl)carbamothioyl)thio)propanoic acid* (**4a**): White powder, yield (97%), m.p. 163–165 °C; $[\alpha]_D^{21}$ –13.2 (*c* 1.00, DMSO); IR (KBr) (ν_{max}): 3385, 3105, 2995, 1670, 1607, 1535, 1396, 1348, 1297, 1204 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.89 (1H, dd, *J* = 13.8, 8.7, SCH_2), 3.03 (1H, dd, *J* = 13.8, 3.8, SCH_2), 4.54 (1H, m, C*H*COOH), 7.20 (2H, s, NH_2), 8.12 (2 H, d, *J* = 8.7 Hz, 2CH_{arom}), 8.34 (2 H, d, *J* = 8.7 Hz, 2CH_{arom}), 9.02 (1H, s, N*H*), 11.14 (1H, s, COO*H*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 34.2 (CH_2), 53.2 (CH), 124.3, 131.4, 138.3 and 150.9 (carbons of aromatic), 166.9 and 170.1 (2C=O), 197.5 (C=S) ppm; MS (*m/z*, %): 329 (M^+, 4). Anal. calcd for $C_{11}H_{11}N_3O_5S_2$, C, 40.11; H, 3.37; N, 12.76; S, 19.47; found: C, 39.91; H, 3.40; N, 12.73; S, 19.37%;

(R)-*2-Amino-3-(((3-nitrobenzoyl)carbamothioyl)thio)propanoic acid* (**4b**): White powder, yield (93%), m.p. 156–158 °C; $[\alpha]_D^{21}$ –16.4 (*c* 1.01, DMSO); IR (KBr) (ν_{max}): 3415, 3185, 2995, 1670, 1613, 1524, 1494, 1382, 1346, 1294, 1204 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.92 (1H, dd, *J* = 14.1, 8.7, SCH_2), 3.02 (1H, dd, *J* = 13.7, 4.1, SCH_2), 4.56 (1H, m, C*H*COOH), 7.15 (2H, s, NH_2), 7.80 (1H, t, *J* = 8.0 Hz, 1CH_{arom}), 8.34 (1H, d, *J* = 7.9 Hz, 1CH_{arom}), 8.41 (1H, d, *J* = 7.5 Hz, 1CH_{arom}), 8.74 (1H, s, 1CH_{arom}), 9.09 (1H, s, N*H*), 11.30 (1H, s, COO*H*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 33.3 (CH_2), 51.9 (CH), 122.1, 126.2, 129.9, 131.3, 133.0 and 150.6 (carbons of aromatic), 166.5 and 170.1 (2C=O), 196.6 (C=S) ppm; MS (*m/z*, %): 329 (M^+, 4). Anal. calcd for $C_{11}H_{11}N_3O_5S_2$, C, 40.11; H, 3.37; N, 12.76; S, 19.47; found: C, 39.94; H, 3.47; N, 12.74; S, 19.42%.



Scheme 2 Suggested mechanism for formation compounds **4** and **5.**

(R)-*2-Amino-3-(((4-bromobenzoyl)carbamothioyl)thio)propanoic acid* (**4c**): White powder, yield (91%), m.p. 136–144 °C; $[\alpha]_D^{21}$ –20.6 (*c* 1.02, DMSO); IR (KBr) (ν_{max}): 3400, 3185, 2925, 1675, 1617, 1589, 1484, 1382, 1301, 1206 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.95 (1H, dd, *J* = 12.8, 8.5, SCH_2), 3.08 (1H, dd, *J* = 12.8, 4.4, SCH_2), 4.64 (1H, m, C*H*COOH), 7.24 (2H, s, NH_2), 7.43 (2 H, d, *J* = 8.4 Hz, 2CH_{arom}), 7.58 (2 H, d, *J* = 8.4 Hz, 2CH_{arom}), 9.12 (1H, s, N*H*), 11.29 (1H, s, COO*H*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.1 (CH_2), 53.50 (CH), 125.0, 129.6, 131.3 and 133.3 (carbons of aromatic), 169.8 and 170.2 (2C=O), 195.0 (C=S) ppm; MS (*m/z*, %): 363 (M^+, 2). Anal. calcd for $C_{11}H_{11}BrN_2O_3S_2$, C, 36.37; H, 3.05; N, 7.71; S, 17.65; found: C, C, 36.21; H, 3.11; N, 7.68; S, 17.63%.

(R*)-2-Amino-3-(((2-methylbenzoyl)carbamothioyl)thio)propanoic acid* (**4d**): White powder, yield (80%), m.p. 112–114 °C; $[\alpha]_D^{21}$ –11.1 (*c* 1.00, DMSO); IR (KBr) (ν_{max}): 3312, 3130, 2918, 1677, 1600, 1487, 1396, 1297, 1207 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.53 (3H, s, CH_3), 2.93 (1H, dd, *J* = 13.9, 8.5, SCH_2), 3.02 (1H, dd, *J* = 13.9, 4.4, SCH_2), 4.55 (1H, m, C*H*COOH), 7.12 (2H, s, NH_2), 7.26 (1H, t, *J* = 7.8 Hz, 1CH_{arom}), 7.33 (1H, d, *J* = 8.0 Hz, 1CH_{arom}), 7.64 (1H, t, *J* = 8.0 Hz, 1CH_{arom}), 7.91 (1H, d, *J* = 7.8 Hz, 1CH_{arom}), 9.03 (1H, s, N*H*), 11.35 (1H, s, COO*H*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.30 (CH_3), 34.8 (CH_2), 52.5 (CH), 126.1, 127.3, 131.9, 132.3, 134.7 and 138.4 (carbons of aromatic), 168.5 and 170.1 (2C=O), 190.6 (C=S) ppm; MS (*m/z*, %): 298 (M^+, 5). Anal. calcd for $C_{12}H_{14}N_2O_3S_2$, C, 48.30; H, 4.73; N, 9.39; S, 21.49; found: C, 48.21; H, 4.63; N, 9.37; S, 21.46%.

(R)-*2-Amino-3-(((3-methylbenzoyl)carbamothioyl)thio)propanoic acid* (**4e**): White powder, yield (83%), m.p. 118–120 °C; $[\alpha]_D^{21}$ –12.4 (*c* 1.01, DMSO); IR (KBr) (ν_{max}): 3345, 3150, 2909, 1675, 1598, 1485, 1396, 1295, 1204 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.45 (3H, s, CH_3), 2.96 (1H, dd, *J* = 13.7, 8.7, SCH_2), 3.06 (1H, dd, *J* = 13.7, 4.3, SCH_2), 4.55 (1H, m, C*H*COOH), 7.05 (2H, s, NH_2), 7.34 (1H, d, *J* = 7.8 Hz, 1CH_{arom}), 7.40 (1H, t, *J* = 8.0 Hz, 1CH_{arom}), 7.67 (1H, d, *J* = 8.0 Hz, 1CH_{arom}), 7.85 (1H, s, 1CH_{arom}), 9.05 (1H, s, N*H*), 11.34 (1H, s, COO*H*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.62 (CH_3), 34.5 (CH_2), 53.1 (CH), 126.3, 129.0, 130.8, 132.3, 134.9 and 138.8 (carbons of aromatic), 168.9 and 170.4 (2C=O), 190.4 (C=S) ppm; MS (*m/z*, %): 298 (M^+, 5). Anal. calcd for $C_{12}H_{14}N_2O_3S_2$, C, 48.30; H, 4.73; N, 9.39; S, 21.49; found: C, 48.23; H, 4.66; N, 9.35; S, 21.45%.

(R)-*2-Amino-3-((benzoylcarbamothioyl)thio)propanoic acid* (**4f**): White powder, yield (88%), m.p. 126–128 °C; $[\alpha]_D^{21}$ –16.7 (*c* 1.04, DMSO); IR (KBr) (ν_{max}): 3315, 3110, 2915, 1665, 1600, 1489, 1380, 1292, 1206 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.90 (1H, dd, *J* = 13.6, 8.4, SCH_2), 3.01 (1H, dd, *J* = 13.6, 4.8, SCH_2), 4.54 (1H, m, C*H*COOH), 7.20 (2H, s, NH_2), 7.46–7.91 (m, 5CH_{arom}), 9.02 (1H, s, N*H*), 11.40 (1H, s, COO*H*) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.3 (CH_2), 52.1 (CH), 127.3, 128.3, 132.2 and 133.6 (carbons of aromatic), 169.3 and 171.9 (2C=O), 191.0 (C=S) ppm. MS (*m/z*, %): 284 (M^+, 6). Anal. calcd for $C_{11}H_{12}N_2O_3S_2$, C, 46.46; H, 4.25; N, 9.85; S, 22.55; found: C, 46.31; H, 4.32; N, 9.80; S, 22.53%.

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