Heterocyclization of dithiocarbamates and thioureas of the imidazole series with dimethylacetylenedicarboxylate

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A heterocyclic system of imidazo[1,5-*c*][1,3,5]thiadiazine was synthesised by the interaction of polyfunctional imidazolyl thioureas and ethyldithiocarbamates with dimethylacetylenedicarboxylate.

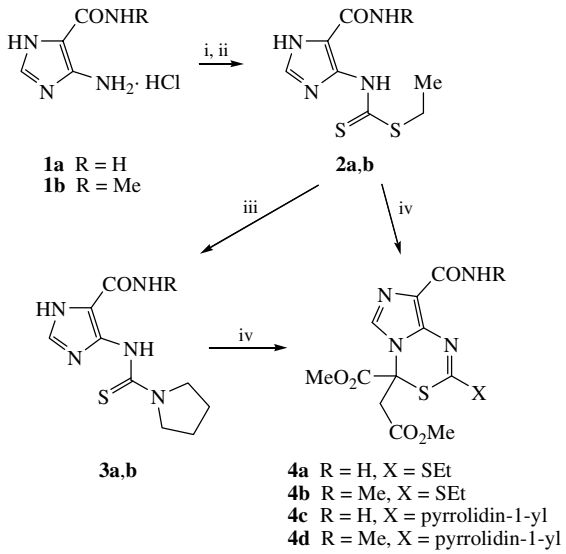
Reactions of acetylenedicarboxylic acid esters with thioamides and thioureas are of great synthetic interest because they serve as a convenient procedure for the construction of heterocyclic systems, such as thiazolidines, thiazines and thiophenes.[1–4]

As a continuation of our studies of heterocyclization reactions of 5-aminoimidazole-4-carboxylic acid derivatives,[5–8] we investigated the interaction of ethyl dithiocarbamates **2a**,**b** and thioureas **3a**,**b** of the imidazole series with such a highly electrophilic agent as dimethylacetylenedicarboxylate (DMAD).

Imidazolyl ethyldithiocarbamates **2a**,**b** were synthesised by the reaction of 5-aminoimidazoles **1a**,**b** with carbon disulfide in the presence of a base with the subsequent alkylation of imidazolyl dithiocarbamate intermediates.† Heating of compounds **2a**,**b** in ethanol in an excess of pyrrolidine for a short time afforded thiourea derivatives **3a**,**b**.‡ The presence of several reactive nucleophilic centres in starting substrates **2**, **3a**,**b** is favourable for the formation of different products and it makes difficult to determine the reaction site. Thus, the cyclization can proceed at one of the nitrogen atoms of the substituents or at the nitrogen atom of the imidazole ring.

It is well known that acetylenedicarboxylic acid esters are very reactive dienophiles and form cycloaddition products or give cyclocondensation products with the elimination of one or two alcohol molecules. However, we found that the reaction of intermediates **2a**,**b** and **3a**,**b** with DMAD results in substances whose ^{1}H NMR spectra show signals of the protons of OMe groups at δ 3.87–3.70 ppm. At the same time, the resonance of protons belonging to the CH_2 group was observed at δ 3.44–3.39 ppm as a doublet of doublets and the molecular weights of compounds corresponded to addition products.§ In ^{13}C NMR spectra, the characteristic triplets for the CH_2 group (43.8–43.1 ppm, J 135.6–134.2 Hz) and the sp^3-hybrid C atom of the thiadiazine ring (64.5–63.7 ppm, J 5.0–4.0 Hz) were also observed.

Hence, we reported the first example of the synthesis of a novel heterocyclic system of imidazo[1,5-*c*][1,3,5]thiadiazine. We also found that only one carbon atom of the acetylene component took part in new ring formation.



Scheme 1 *Reagents and conditions*: i, DMSO, Et_3N, CS_2, 25 °C, 24 h; ii, EtI, 25 °C, 5 h; iii, EtOH, pyrrolidine, reflux, 0.5 h; iv, MeOH, DMAD, reflux, 12 h.

† Carbon disulfide (0.2 ml, 0.25 g, 3.34 mmol) was added to a solution of 5-aminoimidazole **1a**,**b** (2.83 mmol) and Et_3N (0.83 ml, 0.60 g, 5.95 mmol) in DMSO (3.0 ml). The reaction mixture was stirred at 25 °C for 24 h. Then EtI (0.24 ml, 0.46 g, 2.97 mmol) was added and the reaction mixture was kept at 25 °C for 5 h and poured into ice-cold water (25 ml). White crystals were filtered off, recrystallised from ethanol and dried to give compounds **2a**,**b** in 80–95% yields.

*Ethyl (5-carbamoyl-1*H*-imidazol-4-yl)dithiocarbamate* **2a**: yield 95%, mp > 300 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 12.79 (s, 1H, NH), 11.47 (s, 1H, NH), 7.27 (br. s, 2H, $CONH_2$), 7.24 (s, 1H, CH_{Im}), 3.19 (q, 2H, SCH_2, J 7.02 Hz), 1.30 (t, 3H, Me, J 7.02 Hz). MS, *m*/*z*: 230 (54%, M$^+$). Found (%): C, 36.80; H, 4.20; N, 24.62; S, 28.00. Calc. for $C_7H_{10}N_4OS_2$ (%): C, 36.51; H, 4.38; N, 24.33; S, 27.84.

*Ethyl (5-methylcarbamoyl-1*H*-imidazol-4-yl)dithiocarbamate* **2b**: yield 80%, mp > 300 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 12.73 (s, 1H, NH), 12.05 (s, 1H, NH), 7.90 (br. s, 1H, CONH), 7.32 (s, 1H, CH_{Im}), 3.23 (q, 2H, SCH_2, J 7.02 Hz), 2.87 (d, 3H, Me, J 4.91 Hz), 1.37 (t, 3H, Me, J 7.02 Hz). MS, *m*/*z*: 244 (40%, M$^+$). Found (%): C, 39.02; H, 5.01; N, 22.69; S, 26.01. Calc. for $C_8H_{12}N_4OS_2$ (%): C, 39.33; H, 4.95; N, 22.93; S, 26.25.

‡ Pyrrolidine (0.5 ml, 0.43 g, 6.06 mmol) was added to a solution of ethyl dithiocarbamates **2a**,**b** (1.66 mmol) in EtOH (10 ml). The reaction mixture was refluxed for 0.5 h. Then the reaction mixture was cooled. The precipitate formed was filtered off and purified by recrystallization from EtOH.

*5-[(Pyrrolidinocarbothioyl)amino]-3*H*-imidazole-4-carboxamide* **3a**: yield 85%, mp > 300 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 12.65 (s, 1H, NH), 10.87 (s, 1H, NH), 7.21 (s, 1H, CH_{Im}), 7.07 (br. s, 2H, $CONH_2$), 3.68 (br. s, 4H, $2CH_2$), 2.04 (br. s, 4H, $2CH_2$). MS, *m*/*z*: 239 (30%, M$^+$). Found (%): C, 45.00; H, 5.59; N, 29.08; S, 13.74. Calc. for $C_9H_{13}N_5OS$ (%): C, 45.18; H, 5.45; N, 29.27; S, 13.40.

*5-[(Pyrrolidinocarbothioyl)amino]-3*H*-imidazole-4-carboxmethylamide* **3b**: yield 89%, mp > 300 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 12.61 (s, 1H, NH), 10.91 (s, 1H, NH), 7.72 (q, 1H, NH, J 4.89 Hz), 7.20 (s, 1H, CH_{Im}), 3.68 (br. s, 4H, $2CH_2$), 2.80 (d, 3H, Me, J 4.89 Hz), 2.05 (br. s, 4H, $2CH_2$). MS, *m*/*z*: 253 (44%, M$^+$). Found (%): C, 47.74; H, 6.05; N, 27.90; S, 12.39. Calc. for $C_{10}H_{15}N_5OS$ (%): C, 47.41; H, 5.97; N, 27.65; S, 12.66.

§ A mixture of ethyl dithiocarbamate derivatives **2a**–**b** or imidazolylthioureas **3a**,**b** (0.87 mmol) and DMAD (0.16 ml, 0.18 g, 1.30 mmol) in MeOH (10 ml) was refluxed for 12 h and then treated with charcoal. The solvent was evaporated to dryness, and the residue was recrystallised from methanol–diethyl ether (1:1), compounds **4a**,**b** were filtered off and dried.

Methyl 8-carbamoyl-2-ethylthio-4-methoxycarbonylmethylimidazo-[1,5-c][1,3,5]thiadiazine-4-carboxylate **4a**: yield 57%; mp 146–147 °C. ^{1}H NMR (250 MHz, CD_3Cl) δ: 7.65 (s, 1H, CH_{Im}), 7.20 (br. s, 1H, $CONH_2$), 5.79 (br. s, 1H, $CONH_2$), 3.87 (s, 3H, Me), 3.72 (s, 3H, Me), 3.40 (AB, 2H, CH_2, J 17.4 Hz), 3.27 (q, 2H, SCH_2, J 7.32 Hz), 1.43 (t, 3H, Me, J 7.32 Hz). ^{13}C NMR (100 MHz, CD_3Cl) δ: 168.4 (m, CO), 166.7 (m, CO), 162.6 (br. s, CO), 156.5 (t, C-2, J 5.9 Hz), 134.8 (d, C-8a, J 3.6 Hz), 131.8 (d, C-6, J 218.3 Hz), 126.1 (br. s, C-8), 63.7 (t, C-4, J 4.9 Hz), 54.5 (q, OMe, J 149.2 Hz), 52.7 (q, OMe, J 148.5 Hz), 43.1 (t, CH_2, J 135.6 Hz), 26.1 (tq, SCH_2, J' 143.4 Hz, J'' 4.0 Hz), 13.8 (qt, Me, J' 128.1 Hz, J'' 3.5 Hz). MS, *m*/*z*: 372 (71%, M$^+$). Found (%): C, 42.10; H, 4.50; N, 15.00; S, 17.50. Calc. for $C_{13}H_{16}N_4O_5S_2$ (%): C, 41.93; H, 4.33; N, 15.04; S, 17.22.

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Methyl 2-ethylthio-4-methoxycarbonylmethyl-8-methylcarbamoyl-imidazo[1,5-c][1,3,5]thiadiazine-4-carboxylate **4b**: yield 39%, mp 141–142 °C. ^{1}H NMR (250 MHz, CD_3Cl) δ: 7.62 (s, 1H, CH_{Im}), 7.25 (br. s, 1H, NH), 3.87 (s, 3H, Me), 3.70 (s, 3H, Me), 3.39 (AB, 2H, CH_2, J 17.09 Hz), 3.30 (dq, 2H, SCH_2, J' 7.32 Hz, J'' 1.22 Hz), 2.98 (d, 3H, Me, J 4.89 Hz), 1.45 (t, 3H, Me, J 7.32 Hz). ^{13}C NMR (100 MHz, CD_3Cl) δ: 168.4 (m, CO), 166.1 (m, CO), 162.5 (m, CO), 157.2 (t, C-2, J 5.0 Hz), 134.5 (d, C-8a, J 3.6 Hz), 131.5 (d, C-6, J 218.9 Hz), 126.1 (d, C-8, J 9.7 Hz), 64.5 (t, C-4, J 5.0 Hz), 54.5 (q, OMe, J 149.2 Hz), 52.7 (q, OMe, J 146.3 Hz), 43.4 (t, CH_2, J 135.4 Hz), 26.8 (tq, SCH_2, J' 143.4 Hz, J'' 4.6 Hz), 25.7 (qd, NHMe, J' 138.2 Hz, J'' 3.2 Hz), 13.7 (qt, Me, J' 128.8 Hz, J'' 3.5 Hz). MS, *m/z*: 386 (100%, M^+). Found (%): C, 43.77; H, 4.51; N, 14.26; S, 16.40. Calc. for $C_{14}H_{18}N_5O_5S_2$ (%): C, 43.51; H, 4.69; N, 14.50; S, 16.59.

Methyl 8-carbamoyl-4-methoxycarbonylmethyl-2-pyrrolidinoimidazo-[1,5-c][1,3,5]thiadiazine-4-carboxylate **4c**: yield 45%, mp 176–177 °C. ^{1}H NMR (250 MHz, CD_3Cl) δ: 7.48 (s, 1H, CH_{Im}), 7.47 (br. s, 1H, $CONH_2$), 5.47 (br. s, 1H, $CONH_2$), 3.87 (s, 3H, Me), 3.71 (s, 3H, Me), 3.63 (br. s, 4H, $2CH_2$), 3.44 (m, 2H, CH_2), 2.04 (br. s, 4H, $2CH_2$). ^{13}C NMR (100 MHz, CD_3Cl) δ: 168.4 (m, CO), 166.6 (m, CO), 164.6 (br. s, CO), 149.4 (s, C-2), 138.5 (d, C-8a, J 4.5 Hz), 129.3 (d, C-6, J 218.3 Hz), 121.6 (br. s, C-8), 64.2 (t, C-4, J 4.0 Hz), 54.4 (q, OMe, J 149.2 Hz), 52.7 (q, OMe, J 148.2 Hz), 48.4 (t, $2NCH_2$, J 143.2 Hz), 43.8 (t, CH_2, J 134.6 Hz), 25.2 (m, CH_2), 13.8 (m, CH_2). MS, *m/z*: 381 (1.88, M^+). Found (%): C, 47.39; H, 4.91; N, 18.49; S, 8.70. Calc. for $C_{15}H_{19}N_5O_5S$ (%): C, 47.24; H, 5.02; N, 18.36; S, 8.41.

Methyl 4-methoxycarbonylmethyl-8-methylcarbamoyl-2-pyrrolidino-imidazo[1,5-c][1,3,5]thiadiazine-4-carboxylate **4d**: yield 47%, mp 155–157 °C. ^{1}H NMR (250 MHz, CD_3Cl) δ: 7.53 (q, 1H, NH, J 4.89 Hz), 7.45 (s, 1H, CH_{Im}), 3.86 (s, 3H, Me), 3.70 (s, 3H, Me), 3.63 (br. s, 4H, $2CH_2$), 3.44 (m, 2H, CH_2), 2.96 (d, 3H, Me, J 4.89 Hz), 2.05 (br. s, 4H, $2CH_2$). ^{13}C NMR (100 MHz, CD_3Cl) δ: 168.2 (m, CO), 166.7 (m, CO), 163.7 (m, CO), 149.1 (s, C-2), 137.5 (d, C-8a, J 3.4 Hz), 128.8 (d, C-6, J 218.0 Hz), 122.1 (d, C-8, J 9.3 Hz), 64.2 (t, C-4, J 5.0 Hz), 54.4 (q, OMe, J 149.1 Hz), 52.7 (q, OMe, J 147.9 Hz), 48.3 (t, $2NCH_2$, J 143.4 Hz), 43.7 (t, CH_2, J 135.2 Hz), 25.7 (qd, $NHCH_3$, J' 137.7 Hz, J'' 3.1 Hz), 24.8 (m, CH_2). MS, *m/z*: 395 (6.01, M^+). Found (%): C, 48.85; H, 5.20; N, 17.52; S, 8.29. Calc. for $C_{16}H_{21}N_5O_5S$ (%): C, 48.60; H, 5.35; N, 17.71; S, 8.11.