Facile synthesis of 2-substituted ethyl 2-(2-amino-5-ethoxycarbonylthiazol-4-yl)ethanoates

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An easy and convenient synthesis of highly functionalized 2-aminothiazole derivatives is described. Ethyl 2-bromo-2-(2-amino-5-ethoxycarbonylthiazol-4-yl)ethanoate **4** was obtained by reaction of 2,4-dibromo-3-oxoglutarate with thiourea. It can be transformed to 2-iminoethanoate **10** by nucleophilic displacement of the bromide with an azide ion followed by rearrangement with elimination of the molecule of nitrogen. Hydrolysis of the iminoethanoate **10** affords 2-oxoethanoate **12**, while hydrogenation leads to 2-aminoethanoate **14**. The crystal structure determination of 2-iminoethanoate **11** is reported.

Introduction

2-Aminothiazole carboxylic acids and their esters display a wide assortment of interesting biological properties and serve as important precursors in drug design and development. For instance, alkyl 2-aminothiazolecarboxylates have found application in the synthesis of peptide isosteres,[1] non-natural nucleosides[2] and other agents of biomedical interest.[3] Alkyl 2-(2-amino-5-methoxycarbonylthiazol-4-yl)ethanoates are commonly reported as active analgesic, anticancer and bactericidal drugs,[4] as well as useful building blocks for the synthesis of steroid derivatives[5] or vitamin B1 analogues.[6] α-Amino acids containing the 2-aminothiazol-4-yl moieties were recently used for the preparation of renin inhibitors,[7] while 2-(2-aminothiazol-4-yl)-2-alkoxyiminoacetic acids are intermediates in the synthesis of antibacterial cephalosporins.[8]

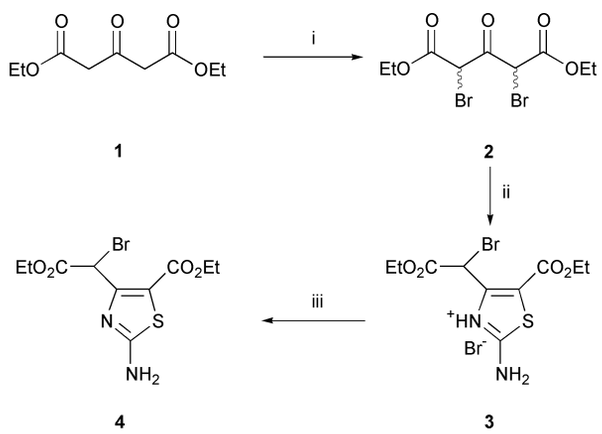
2-Aminothiazole carboxylic acids in the form of their esters are usually prepared following the classical Hantzsch synthesis, which is based on the reaction of thiourea with α-halooxo compounds.[9] For instance, reaction of thiourea with 2-chloro-3-oxobutyrate afforded 2-amino-4-methylthiazole-5-carboxylate,[1] while 3-bromo-2-oxobutyrate gave isomeric 2-amino-5-methylthiazole-4-carboxylate.[3c] Alkyl 2-(2-amino-5-alkoxycarbonylthiazol-4-yl)ethanoates have been synthesized by reaction of thiourea with dialkyl 2-bromo-3-oxoglutarate.[4,6,10]

In the present work we report the Hantzsch synthesis of functionalized 2-aminothiazoles involving 2,4-dibromo-3-oxoglutarate.

Results and discussion

The starting diethyl 2,4-dibromo-3-oxoglutarate **2** was synthesized by bromination of diethyl 3-oxoglutarate **1** with 2.2 equiv. of NBS in carbon tetrachloride, and after separation of succinimide and removal of the solvent it was used in the subsequent step of the synthesis without further purification.

The reaction of **2** with thiourea was carried out in ethanol at room temperature for 48 h to afford the hydrobromide **3** in 72% yield. The use of a higher temperature did not improve the yield. Subsequent treatment of the salt **3** with a base furnished ethyl 2-(2-amino-5-ethoxycarbonylthiazol-4-yl)-2-bromoethanoate **4** (Scheme 1).



Scheme 1 *Reagents and conditions*: i, NBS (2.2 eq.), CCl_4, reflux, 6 h; ii, NH_2CSNH_2, EtOH, rt, 48 h, 72%; iii, sat. Na_2CO_3.

The structure of the compound **4** was confirmed by means of NMR spectroscopy. In the ^{1}H NMR spectrum of **4** the methine proton of the carbon bonded to bromine appears as a singlet at 6.45 ppm. The methylene protons of the ethoxy group in the ethanoate moiety are diastereotopic due to the presence of the chiral center at the atom C-2 and are found as a multiplet in the area of 4.19–4.22 ppm. The ^{13}C NMR spectrum of **4** contains the characteristic signals of the thiazole ring skeleton carbons at 110.2, 155.0 and 161.4 and a signal of the methine carbon at 42.2 ppm. The absorption bands at 1740 and 1690 cm^{-1}, which are due to the carbonyl groups, and the bands in the area 3410–3125 cm^{-1} which correspond to stretching vibrations of the amino group N–H bonds, are observed in the IR spectrum of diester **4**.

Our interest in the synthetic utility of **4** led us to examine the acylation reactions of the amino group, its condensation with 2,5-dimethoxytetrahydrofuran and the introduction of functional groups by nucleophilic substitution of the bromide in the ethanoate moiety.

Attempts to acetylate the amino group of compound **4** with acetic anhydride in the absence of a catalyst were not successful. When **4** was treated with the mentioned acylating agent in the presence of DMAP, the reaction gave *N*-acetylated

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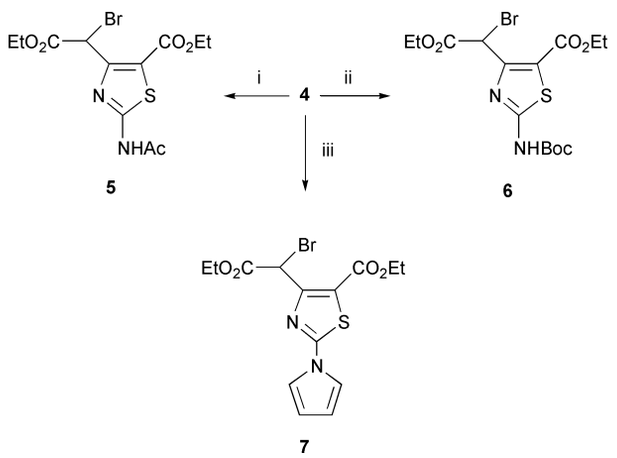
compound **5** in 79% yield. Similarly, *N*-Boc protected thiazole derivative **6** was obtained using Boc_2O as an acylating agent (Scheme 2).



Scheme 2 *Reagents and conditions*: i, Ac_2O, DMAP, CH_2Cl_2, rt, 6 h, 79%; ii, Boc_2O, DMAP, CH_2Cl_2, rt, 7 h, 87%; iii, 2,5-dimethoxytetrahydrofuran, AcOH, reflux, 1 h; sat. Na_2CO_3, 66%.

It is known that reaction of primary amines with 2,5-dimethoxytetrahydrofuran, which is a synthetic equivalent of succindialdehyde, leads to the formation of *N*-substituted pyrroles.[11] Reacting **4** with 2,5-dimethoxytetrahydrofuran in acetic acid gave pyrrole derivative **7**. In the ^1H NMR spectrum of the compound **7** protons attached to the pyrrole ring appear as two triplets (*J* 2.2 Hz) at 6.41 and 7.51 ppm, while in the ^{13}C NMR spectrum the pyrrole carbons C_α and C_β have overlapping signals at 120.5 and 114.0 ppm, respectively.

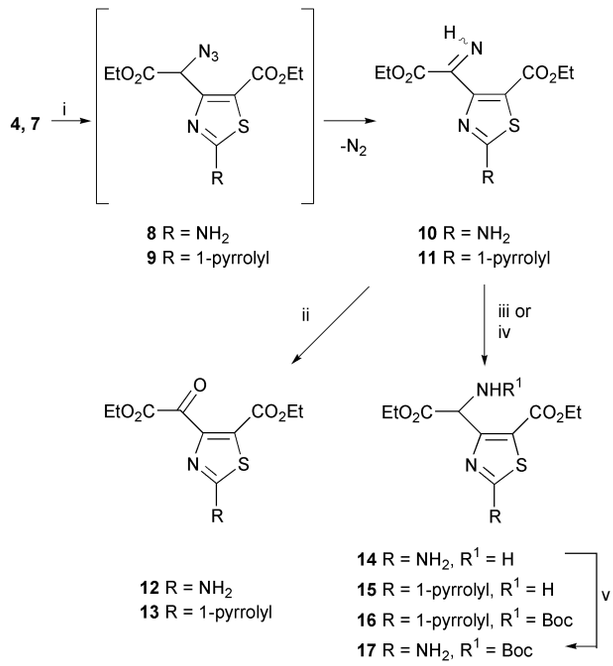
Next, we investigated the reaction of compound **4** with sodium azide. The nucleophilic displacement of a halide at the saturated carbon with an inorganic azide to give the azido derivative, followed by reduction, is a convenient method for the synthesis of amines.[12] Alkyl halides are smoothly converted to the corresponding azides by reaction with inorganic azides in polar solvents.[13] It is also known that α-azido carboxylic acids and esters can easily rearrange with elimination of a molecule of nitrogen to the corresponding imines.[14]

When compound **4** was treated with sodium azide in DMSO, the reaction gave imine **10** in 79% isolated yield. Analogously, displacement of the bromide of compound **7** with an azide ion afforded imine **11** (Scheme 3). It is necessary to point out that the rearrangement of the intermediate azides **8** and **9** proceeded very rapidly. When the course of the reaction was monitored by TLC, no other products were found except the final imine.

The ^1H NMR spectra of imines **10** and **11** showed the presence of two isomers in a ratio 11 : 9, which could be explained by the appearance of *syn–anti* isomerism resulting from the imine C=N double bond. The single crystal of **11** was prepared by recrystallization from diethyl ether of the solid material obtained after azidolysis of bromide **7**. The single crystal was subjected to X-ray diffraction analysis and the relative configuration of the imine determined to be *syn* (Fig. 1).

Utilizing the sensitivity of the imine functionality towards acidic hydrolysis,[15] α-ketoesters **12** and **13** were obtained in high yield by treatment of compounds **10** and **11** with 0.1 M acetic acid.

It is known, that imines can be easily reduced to primary amines with many reducing agents, including hydrogen and a catalyst.[16] Hydrogenation of imine **10** with H_2 in the presence of Pd–C afforded amine **14** in 68% yield. However, when imine **11** was reduced using the same reaction conditions, the yield of the isolated target product **15** was only 16%. The crude amine **15** is highly unstable and was mostly lost during purification. Reduction of imine **11** in the presence of Boc_2O, which



Scheme 3 *Reagents and conditions*: i, NaN_3, DMSO, 60 °C, 6 h (**10** 79%, **11** 90%); ii, 0.1 M AcOH, EtOAc, rt, 12 h (**12** 82%, **13** 86%); iii, H_2, 10% Pd–C, MeOH, rt, 12 h (**14** 68%, **15** 16%); iv, H_2, 10% Pd–C, MeOH, rt, 4 h, Boc_2O (**16** 66%); v, Boc_2O, DMAP, MeOH, rt, 1 h (**17** 84%).

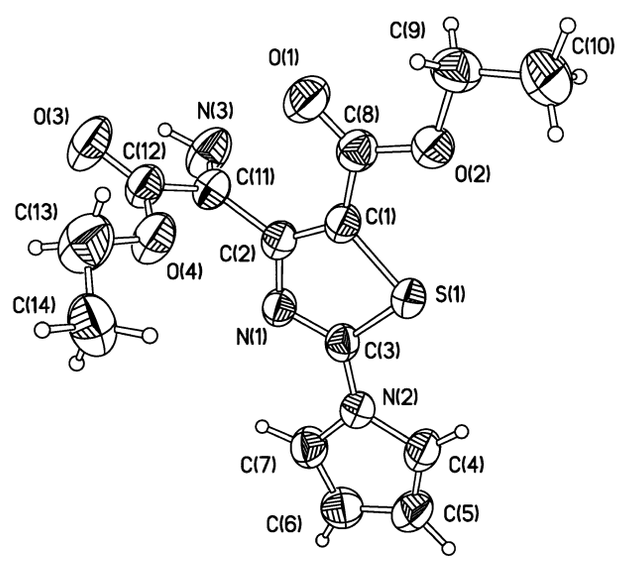


Fig. 1 ORTEP drawing of *syn*-iminoethanoate **11**. The thermal ellipsoids are shown at 50% probability.

removed the primary amine as soon as it was formed, afforded the Boc-protected amino acid ester **16** in 66% yield.

Treatment of amine **14** with Boc_2O in the presence of DMAP gave the *N*-Boc protected amino acid ester **17**. In the ^1H NMR spectra of compounds **16** and **17** the methine proton C(2)H appeared in the area of 5.85 ppm and showed *vicinal coupling* (~8.0 Hz) with the amide NH proton.

In conclusion, this paper describes a practical and facile way to make highly functionalized thiazole derivatives in moderate to good yields starting from readily available 2,4-dibromo-3-oxoglutarate.

Experimental

All melting points were determined on a Kleinfeld melting point apparatus and are uncorrected. Infrared spectra were obtained on a Specord M80 spectrometer with KBr pellets.

^{1}H NMR spectra were measured with a Bruker DPX 200 (200 MHz), a Bruker DPX 300 (300 MHz) and a Bruker DRX 500 (500 MHz) spectrometer. The ^{13}C spectra were recorded at 50, 75 or 125 MHz using the instruments mentioned above. The chemical shifts are reported in ppm downfield from tetramethylsilane, using residual $CHCl_3$ (7.24 ppm), and DMSO (2.49 ppm) as references for the proton spectra and $CDCl_3$ (77 ppm) and [$^2H_6$]DMSO (39.50 ppm) as references for the carbon spectra. The mass spectra under electron impact conditions (EI) were recorded with a VG-Prospect mass spectrometer at 70 eV ionizing potential. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254) were used. Flash chromatography was performed with silica gel 60 (230–400 mesh) from Merck. All reagents were purchased from Aldrich Chemical Co. or Merck and used without further purification.

Ethyl 2-(2-amino-5-ethoxycarbonylthiazol-4-yl)-2-bromoethanoate hydrobromide 3

To a solution of diethyl 3-oxoglutarate (12.13 g, 60 mmol) in carbon tetrachloride (120 cm^3) was added *N*-bromosuccinimide (23.49 g, 132 mmol) and the mixture was refluxed for 6 h, followed by cooling to 5 °C. The precipitated succinimide was filtered off and the solvent removed under reduced pressure to yield diethyl 2,4-dibromo-3-oxoglutarate **2** (20.42 g, 94%), as a mixture of diastereomers, which was used in the subsequent reaction without further purification; δ_H(200 MHz, $CDCl_3$) 1.26–1.45 (12 H, m, 4 × CH_3), 4.20–4.38 (8 H, m, 4 × CH_2), 5.37 (2H, s, 2 × CHBr), 5.40 (2H, s, 2 × CHBr).

The crude 2,4-dibromo-3-oxoglutarate **2** (18.10 g, 50 mmol) was added dropwise to a solution of thiourea (3.81 g, 50 mmol) in dry ethanol (50 cm^3). The solution was stirred at rt for 0.5 h, after which time the precipitated material not soluble in ethanol (1.20 g) was removed by filtration. The filtrate was then stirred at rt for 48 h, the precipitated crystalline substance was filtered off and washed with cold ethanol (15 cm^3) to give 11.48 g of pure hydrobromide **3** as yellowish crystals. The mother liquor was concentrated at reduced pressure to about half volume and left at 5 °C for 18 h to recover an additional amount of the compound. The total yield of hydrobromide **3** was 15.12 g (72%), mp 175 °C (decomp.) (from ethanol) (Found: C, 28.98; H, 3.22; N, 7.00. Calc. For $C_{10}H_{14}Br_2N_2O_4S$: C, 28.73; H, 3.38; N, 6.70%); ν_{max}/cm^{-1} 3100–3300 (NH_2), 1740 (C=O), 1720 (C=O); δ_H(200 MHz, [$^2H_6$]DMSO) 1.26 (3 H, t, *J* 7.1, CH_3), 1.33 (3 H, t, *J* 7.1, CH_3), 4.27–4.35 (4 H, m, 2 × CH_2), 6.36 (1 H, s, CH), 9.83 (2 H, br s, NH_2).

Ethyl 2-(2-amino-5-ethoxycarbonylthiazol-4-yl)-2-bromoethanoate 4

A suspension of the salt **3** (8.36 g, 20 mmol) in water (150 cm^3) was neutralized with saturated aqueous Na_2CO_3 solution (to pH = 8–9) and extracted with ethyl acetate (2 × 50 cm^3). The combined organic extracts were washed with water (20 cm^3) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was crystallized from ethyl acetate to give the title compound **4** as white crystals (5.53 g, 82%), mp 161–162 °C (Found: C, 35.78; H, 4.02; N, 8.14. Calc. for $C_{10}H_{13}BrN_2O_4S$: C, 35.62; H, 3.89; N, 8.31%); δ_H(500 MHz, $CDCl_3$) 1.16 (3 H, t, *J* 7.1, CH_3), 1.25 (3 H, t, *J* 7.1, CH_3), 4.14 (2 H, q, *J* 7.1 Hz, CH_2), 4.19–4.22 (2 H, m, CH_2), 6.45 (1 H, s, CH), 8.01 (2 H, br s, NH_2); δ_C(125 MHz, $CDCl_3$) 14.3, 14.5, 42.2, 61.1, 62.7, 110.2, 155.0, 161.4, 166.0, 171.0; *m*/*z* (EI) 338, 336 (M$^+$, 25, 24%), 292, 290 (19, 19), 257 (24), 184 (20), 157, 155 (47, 100), 69 (38), 43 (11).

Ethyl 2-(2-acetamido-5-ethoxycarbonylthiazol-4-yl)-2-bromoethanoate 5

Acetic anhydride (235 mg, 0.22 cm^3, 2.3 mmol) was added dropwise to a solution of 2-aminothiazole **4** (674 mg, 2 mmol) and DMAP (281 mg, 2.3 mmol) in dichloromethane (30 cm^3). The reaction mixture was stirred at rt for 6 h, after which time the solvent was removed under reduced pressure. The residue material was subjected to flash chromatography with silica gel using a solvent gradient (from 10 to 40% acetone in hexane) to give the title compound **5** as white crystals (600 mg, 79%), mp 117–118 °C (from acetone–hexane) (Found: C, 38.22; H, 4.17; N, 7.20. Calc. for $C_{12}H_{15}BrN_2O_5S$: C, 38.01; H, 3.99; N, 7.39%); ν_{max}/cm^{-1} 3210 (N–H), 1770 (C=O), 1730 (C=O), 1675 (C=O); δ_H(500 MHz, [$^2H_6$]DMSO) 1.15 (3 H, t, *J* 7.1, CH_3), 1.30 (3 H, t, *J* 7.1, CH_3), 2.17 (3 H, s, $COCH_3$), 4.13–4.19 (2 H, m, CH_2), 4.30 (2 H, q, *J* 7.1, CH_2), 6.58 (1 H, s, CH), 12.86 (1 H, s, NH); δ_C(125 MHz, [$^2H_6$]DMSO) 14.2, 14.4, 22.8, 41.7, 61.8, 62.9, 116.5, 152.3, 160.6, 161.5, 166.0, 170.2; *m*/*z* (EI) 380, 378 (M$^+$, 19, 19), 338, 336 (75, 75), 258 (100), 212 (40), 184 (52), 157 (59), 155 (72), 138 (6), 111 (8), 69 (17), 43 (98).

Ethyl 2-(2-*tert*-butoxycarbonylamino-5-ethoxycarbonylthiazol-4-yl)-2-bromoethanoate 6

To a solution of 2-aminothiazole **4** (980 mg, 2.9 mmol) and DMAP (18 mg, 0.14 mmol) in dichloromethane (30 cm^3) was added Boc_2O (655 mg, 3 mmol) and the reaction mixture was stirred at rt for 7 h. The solvent was removed at reduced pressure and the residue was subjected to flash chromatography on silica gel (hexane–ethyl acetate, 4 : 1) to afford the title compound **6** as white crystals (1.10 g, 87%), mp 107–108 °C (Found: C 41.45; H, 5.01; N, 6.23. Calc. for $C_{15}H_{21}BrN_2O_6S$: C, 41.20; H, 4.84; N, 6.41%); ν_{max}/cm^{-1} 3195 (N–H), 1755 (C=O), 1720 (C=O), 1685 (C=O); δ_H(200 MHz, $CDCl_3$) 1.26 (3 H, t, *J* 7.1, CH_3), 1.35 (3 H, t, *J* 7.1, CH_3), 1.57 (9 H, s, 3 × CH_3), 4.14–4.28 (2 H, m, CH_2), 4.37 (2 H, q, *J* 7.1, CH_2), 6.59 (1 H, s, CH), 8.19 (1 H, br s, NH); δ_C(50 MHz, $CDCl_3$) 14.4, 14.6, 28.5 (3C), 40.6, 62.0, 63.3, 84.3, 118.5, 152.1, 152.6, 161.9, 161.95, 166.9; *m*/*z* (EI) 438, 436 (M$^+$, 2, 2%), 382, 380 (11, 10), 338, 336 (27, 26), 292, 290 (13, 13), 257 (28), 157 (34), 155 (42), 69 (17), 57 (100), 41 (29).

Ethyl 2-bromo-2-[5-ethoxycarbonyl-2-(pyrrol-1-yl)thiazol-4-yl]ethanoate 7

To a solution of 2-aminothiazole **4** (1.75 g, 5.2 mmol) in glacial acetic acid (18 cm^3) was added 2,5-dimethoxytetrahydrofuran (0.69 g, 0.68 cm^3, 5.2 mmol). The reaction mixture was heated under reflux for 1 h and the resulting solution was allowed to reach rt before the addition of water (150 cm^3). The pH was then adjusted to pH 8–9 with solid Na_2CO_3. The aqueous solution was extracted with diethyl ether (3 × 30 cm^3), and the combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed at reduced pressure and the residue was crystallized from ethanol to afford the title compound **7** (1.33 g, 66%), mp 89–90 °C (Found: C, 43.36; H, 4.00; N, 7.09. Calc. for $C_{14}H_{15}BrN_2O_4S$: C, 43.42; H, 3.90; N, 7.23%); ν_{max}/cm^{-1} 1770 (C=O) and 1715 (C=O); δ_H(500 MHz, [$^2H_6$]DMSO) 1.17 (3 H, t, *J* 7.1, CH_3), 1.31 (3 H, t, *J* 7.1, CH_3), 4.16–4.27 (2 H, m, CH_2), 4.34 (2 H, q, *J* 7.1, CH_2), 6.41 (2 H, t, *J* 2.2, 2 × C(β)H), 6.54 (1 H, s, CHBr), 7.51 (2 H, t, *J* 2.2, 2 × C(α)H); δ_C(125 MHz, [$^2H_6$]DMSO) 14.2, 14.3, 41.3, 62.5, 63.0, 114.0 (2C), 119.1, 120.5 (2C), 153.9, 160.5, 162.1, 165.7; *m*/*z* (EI) 388, 386 (M$^+$, 67, 65%), 342, 340 (10, 8), 314, 312 (20, 18), 279 (14), 207 (49), 205 (100), 177 (10), 69 (44).

Ethyl 2-(2-amino-5-ethoxycarbonylthiazol-4-yl)-2-iminoethanoate 10

To a solution of 2-aminothiazole **4** (1.20 g, 3.56 mmol) in DMSO (30 cm^3), was added sodium azide (0.65 g, 10 mmol) and the mixture was heated with stirring at 60 °C for 6 h. The reaction mixture was quenched by addition of water (150 cm^3) and extracted with ethyl acetate (3 × 30 cm^3). The combined

organic extracts were washed with water (2 × 50 cm^3) and brine, and dried over Na_2SO_4. The solvent was removed *in vacuo* to give imine **10** as a pale yellow solid (0.76 g, 79%), mp 138–140 °C, which was used in the subsequent reaction without further purification (Found: C, 44.66; H, 5.21; N, 15.54. Calc. for $C_{10}H_{13}N_3O_4S$: C, 44.27; H, 4.83; N, 15.49%); ν_{max}/cm^{-1} 3325–3140 (NH_2), 3250 (N–H imine), 1735 (C=O), 1680 (C=O), 1640 (C=N, imine); δ_H(300 MHz, [$^2H_6$]DMSO, a mixture of *syn* and *anti* isomers) 1.15–1.26 (12 H, m, 4 × CH_3), 3.30–4.25 (8 H, m, 4 × CH_2), 7.96 (2 H, br s, NH_2, minor isomer), 7.99 (2 H, br s, NH_2, major isomer), 11.73 (1 H, s, C=NH, major isomer), 11.90 (1 H, s, C=NH, minor isomer); δ_C(75 MHz, [$^2H_6$]DMSO, a mixture of *syn* and *anti* isomers) 13.7, 13.8, 14.0 (2C), 60.6, 60.8, 61.0, 61.9, 111.7, 112.1, 152.1, 154.1, 159.9, 160.7, 161.0, 163.1, 163.3, 163.8, 170.6, 171.2; *m/z* (EI) 271 (M^+, 17%), 198 (73), 170 (100), 152 (68), 124 (15), 83 (14).

Ethyl 2-[5-ethoxycarbonyl-2-(pyrrol-1-yl)thiazol-4-yl]-2-imino-ethanoate 11

The reaction of 2-(pyrrol-1-yl)thiazole **7** (1.50 g, 3.88 mmol) with sodium azide (0.72 g, 11 mmol) in DMSO (30 cm^3), and workup of the reaction mixture was carried out as described above to afford the title compound **11** (1.12 g, 90%) as a light brown solid, mp 83–85 °C (ethyl acetate) (Found: C, 52.36; H, 5.01; N, 13.22. Calc. for $C_{14}H_{15}N_3O_4S$: C, 52.33; H, 4.70; N, 13.08%); ν_{max}/cm^{-1} 3233 (N–H), 1735 (C=O), 1705 (C=O), 1651 (C=N, imine); δ_H(200 MHz, [$^2H_6$]DMSO, a mixture of *syn* and *anti* isomers) 1.15–1.34 (12 H, m, 4 × CH_3), 4.23–4.35 (8 H, m, 4 × CH_2), 6.44–6.46 (4 H, m, CH), 7.59–7.61 (4 H, m, CH), 12.28 (1 H, s, NH), 12.38 (1 H, s, NH); *m/z* (EI) 321 (M^+, 29%), 248 (58), 220 (100), 202 (32), 174 (13), 110 (18), 92 (17), 83 (10).

X-Ray structural analysis 11.† A single crystal was obtained by recrystallization of imine **11** from diethyl ether. *Crystal data*. $C_{14}H_{15}N_3O_4S$, M = 321.35, monoclinic, $P2_1/c$, a = 7.7843(1), b = 15.848(2), c = 13.053(2) Å, β = 103.42(1)°, V = 1566.4(4) Å^3, Z = 4, D_x = 1.204 mg.m^{-3}, μ = 0.23 mm^{-1}, T = 293(2) K, 26718 measured reflections in 2θ range 8.2–61.0°, R_{int} = 0.039. 259 parameters refined against 3821 F^2, R_1 = 0.040 and wR_2 = 0.097 for $I_o > 2\sigma(I_o)$, R_1 = 0.065 and $wR2$ = 0.113 for all data.

Ethyl 2-(2-amino-5-ethoxycarbonylthiazol-4-yl)-2-oxoethanoate 12

To a solution of imine **10** (425 mg, 1.57 mmol) in ethyl acetate (75 cm^3) was added 0.1 M AcOH (21.30 cm^3, 2.1 mmol) and the mixture stirred at rt for 12 h. The layers were separated, the aqueous layer was neutralized to pH 7–8 by addition of saturated aqueous Na_2CO_3 and extracted with ethyl acetate (2 × 20 cm^3). The extracts were combined with the separated organic layer, washed with water (20 cm^3), dried over $MgSO_4$, and the organic solvent removed under reduced pressure. The residue was recrystallized from ethyl acetate to give the title compound **12** as yellow crystals (352 mg, 82%), mp 164–165 °C (Found: C, 44.27; H, 4.46; N, 10.41. Calc. for $C_{10}H_{12}N_2O_5S$: C, 44.11; H, 4.44; N, 10.29%); ν_{max}/cm^{-1} 3415–3130 (NH_2), 1748 (C=O α-ketoester), 1700 (C=O); δ_H(500 MHz, [$^2H_6$]DMSO) 1.20 (3 H, t, J 7.1, CH_3), 1.25 (3 H, t, J 7.1, CH_3), 4.17 (2 H, q, J 7.1, CH_2), 4.26 (2 H, q, J 7.1, CH_2), 8.16 (2 H, br s, NH_2); δ_C(125 MHz, [$^2H_6$]DMSO) 14.1, 14.3, 61.8, 62.6, 116.4, 152.9, 160.5, 161.1, 171.9, 182.7; *m/z* (EI) 272 (M^+, 11%), 199 (100), 171 (81), 143 (16), 127 (6), 100 (11), 68 (18) (Found: M^+ 272.0464. $C_{10}H_{12}N_2O_5S$ requires M, 272.0466).

† CCDC reference number 175467. See http://www.rsc.org/suppdata/p1/b1/b110022j/ for crystallographic files in .cif or other electronic format.

Ethyl 2-[5-ethoxycarbonyl-2-(pyrrol-1-yl)thiazol-4-yl]-2-oxo-ethanoate 13

Hydrolysis of imine **11** (500 mg, 1.55 mmol) was carried out as described above to yield the title compound **13** as pale yellow crystals (428 mg, 86%), mp 56–57 °C (ethyl acetate) (Found: C, 52.19; H, 4.44; N, 8.52. Calc. for $C_{14}H_{14}N_2O_5S$: C, 52.17; H, 4.38; N, 8.69%); δ_H(200 MHz, $CDCl_3$) 1.38 (3 H, t, J 7.1, CH_3), 1.42 (3 H, t, J 7.1, CH_3), 4.31–4.48 (4 H, m, 2 × CH_2), 6.38–6.40 (2 H, m, 2 × CH), 7.35–7.37 (2 H, m, 2 × CH); δ_C(50 MHz, $CDCl_3$) 14.4, 14.5, 63.1, 63.3, 114.1 (2C), 120.7, 120.4, 125.6, 152.2, 160.6, 160.9, 163.6, 181.4; *m/z* (EI) 322 (M^+, 32%), 249 (95), 221 (100), 193 (6), 177 (8), 110 (41), 94 (13) (Found: M^+ 322.0614. $C_{14}H_{14}N_2O_5S$ requires M, 322.0623).

Ethyl 2-amino-(2-amino-5-ethoxycarbonylthiazol-4-yl)ethanoate 14

A solution of imine **10** (400 mg, 1.47 mmol) in methanol (20 cm^3) was hydrogenated over 10% Pd–C (28 mg) under hydrogen at atmospheric pressure for 14 h. The catalyst was then filtered off and the filtrate evaporated to about half volume. After addition of diethyl ether (1 cm^3), the solution was left at 5 °C to induce the crystallization. The crystalline material was filtered off to give pure product **14** as white crystals (275 mg, 68%), mp 170–171 °C (methanol) (Found: C, 43.88; H, 5.56; N, 15.27. Calc. for $C_{10}H_{15}N_3O_4S$: C, 43.95; H, 5.53; N, 15.37); ν_{max}/cm^{-1} 3375–3120 (2 × NH_2), 1740 (C=O), 1680 (C=O); δ_H(200 MHz, [$^2H_6$]DMSO) 1.13 (3 H, t, J 7.1, CH_3), 1.25 (3 H, t, J 7.1, CH_3), 2.08 (2H, br s, NH_2), 4.00–4.12 (2 H, m, CH_2), 4.20 (2 H, t, J 7.1, CH_2), 5.24 (1 H, s, CH), 7.89 (2 H, br s, NH_2); δ_C(50 MHz, [$^2H_6$]DMSO) 14.9, 15.1, 53.6, 61.0, 61.2, 109.1, 161.2, 162.3, 171.7, 173.3; *m/z* (EI) 273 (M^+, 2%), 200 (100), 154 (46), 126 (13), 85 (8) (Found: M^+ 273.0776. $C_{10}H_{15}N_3O_4S$ requires M, 273.0783).

Ethyl 2-amino-2-[5-ethoxycarbonyl-2-(pyrrol-1-yl)thiazol-4-yl]-ethanoate 15

Hydrogenation of imine **11** (450 mg, 1.40 mmol) as described above gave the title compound **15** as white crystals (80 mg, 16%), mp 71–72 °C (methanol) (Found: C, 51.94; H, 5.44; N, 13.27. Calc. for $C_{14}H_{17}N_3O_4S$: C, 52.00; H, 5.29; N, 12.99%); ν_{max}/cm^{-1} 3400–3300 (NH_2), 1760 (C=O), 1705 (C=O); δ_H(200 MHz, $CDCl_3$) 1.24 (3 H, t, J 7.1, CH_3), 1.41 (3 H, t, J 7.1, CH_3), 2.16 (2 H, br s, NH_2), 4.23 (2 H, q, J 7.1, CH_2), 4.41 (2 H, q, J 7.1, CH_2), 5.54 (1H, s, C*H*NH_2), 6.36–6.38 (2 H, m, 2 × CH), 7.31–7.33 (2 H, m, 2 × CH); δ_C(50 MHz, $CDCl_3$) 14.6, 14.7, 54.0, 62.0, 62.1, 113.5 (2C), 118.5, 120.6 (2C), 159.0, 161.6, 163.0, 172.6; *m/z* (EI) 323 (M^+, 4%), 250 (100), 204 (40), 176 (10), 85 (9), 29 (7).

Ethyl 2-*tert*-butoxycarbonylamino-2-[5-ethoxycarbonyl-2-(1-pyrrol-1–yl)thiazol-4-yl]ethanoate 16

A solution of imine **11** (600 mg, 1.86 mmol) and Boc_2O (462 mg, 2.11 mmol) in methanol (20 cm^3) was hydrogenated over 10% Pd/C (42 mg) under hydrogen at atmospheric pressure for 4 h. The catalyst was filtered off, the filtrate was evaporated at reduced pressure and the residue was purified by flash chromatography on silica gel (hexane–ethyl acetate, 3 : 1) to yield the title compound **16** as white crystals (520 mg, 66%), mp 72–73 °C (hexane–ethyl acetate) (Found: C, 54.14; H, 6.13; N, 9.74. Calc. for $C_{19}H_{25}N_3O_6S$: C, 53.89; H, 5.95; N, 9.92%); ν_{max}/cm^{-1} 3420 (N–H), 1745 (C=O), 1720 (C=O), 1700 (C=O); δ_H(200 MHz, $CDCl_3$) 1.25 (3 H, t, J 7.1, CH_3), 1.43 (3 H, t, J 7.1, CH_3), 1.49 (9 H, s, 3 × CH_3), 4.16–4.24 (2 H, m, CH_2), 4.42 (2 H, q, J 7.1, CH_2), 5.85 (1 H, d, J 8.4, C*H*NH), 6.37–6.42 (3 H, m, NH, 2 × CH), 7.33–7.35 (2 H, m, 2 × CH); δ_C(50 MHz, $CDCl_3$) 14.49, 14.65, 28.73 (3C), 53.0, 62.3, 62.4, 80.6, 113.6 (2C), 119.0, 120.2 (2C), 155.1, 155.4, 161.3, 163.0, 169.6; *m/z* (EI) 423

(M^+, 2%), 350 (8), 294 (6), 250 (100), 204 (35), 176 (9), 85 (7), 57 (12).

Ethyl 2-*tert*-butoxycarbonylamino-2-(2-amino-5-ethoxycarbonylthiazol-4-yl)ethanoate 17

To a solution of amine **14** (598 mg, 2.19 mmol) and DMAP (12 mg, 0.14 mmol) in methanol (35 cm^3) was added Boc_2O (524 mg, 2.40 mmol) and the mixture was stirred at rt for 1 h. The solvent was removed at reduced pressure, and the residue was purified by flash chromatography on silica gel (dichloromethane–methanol, 9 : 1) to yield the title compound **17** as white crystals (690 mg, 84%), mp 153–154 °C (methanol) (Found: C, 48.15; H, 5.97; N, 11.40. Calc. for $C_{15}H_{23}N_3O_6S$: C, 48.24; H, 6.21, N, 11.25%); δ_H(200 MHz, [$^2H_6$]DMSO) 1.08 (3 H, t, *J* 7.1, CH_3), 1.19 (3 H, t, *J* 7.1, CH_3), 1.34 (9 H, s, 3 × CH_3), 4.06 (2 H, q, *J* 7.1, CH_2), 4.14 (2 H, q, *J* 7.1, CH_2), 5.86 (1 H, d, *J* 8.2, C*H*NH), 6.83 (1 H, br d, *J* 8.2, CHN*H*), 7.86 (2 H, br s, NH_2).

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