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A Convenient Synthesis of 2-Substituted Thiazole-5-carboxylates

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The photolysis of ethyl 5-oxo-2-phenyl-2,5-dihydroisoxazole-4-carboxylate in acetonitrile containing 0.5% trifluoroacetic acid in the presence of thioamides gives moderate (40–60%) yields of thiazole-5-carboxylate esters. In the absence of trifluoroacetic acid, the intermediate vinyl thioesters can be isolated. That addition of the thioamide to the first formed carbene was, through sulfur, confirmed by X-ray crystal structures of 2-methylthiazole-5-carboxylic acid and a byproduct.

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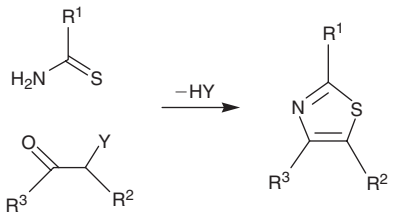
Introduction

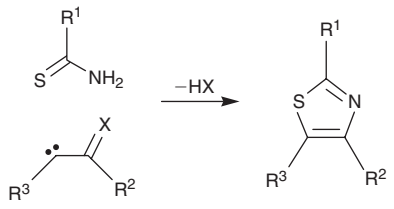
In connection with a project directed toward the synthesis of a series of cyclic peptide mimetics based on aminoalkyloxazole and -thiazole carboxylic acids,[1,2] we have reported an approach to the synthesis of the former, using our methodology based on the formation of imidoylcarbenes from isoxazolones.[3–5] We have also reported that photolysis of *N*-thioacylisoxazolones leads to thiazoles.[6] Both these reactions involve the intramolecular rearrangement of the carbene (Scheme 1).

The synthesis of 2,4-disubstituted thiazoles is generally readily achieved by the Hanzsch synthesis[7] (Scheme 2), the reaction of thioamides with α-bromoketones,[8,9] or variations with α-diazoketones,[10] α-bromoamides or lactones,[11] 2-nitrooxiranes,[12] or alkynyl(aryl)iodonium mesylates[13] or equivalents,[14] although the reaction sometimes fails.[15] 2-Substituted thiazole-5-carboxylates, the subject of this paper, have been obtained similarly from chlorinated β-ketoesters[16] or from vinylphosphonium salts,[17] and are of interest for their antilipolytic and hypotriglyceridemic activity.[16] The route shown in Scheme 3, the reaction of thioamides with α-oxo or α-iminocarbenes, appears to proceed only with certain substrates[18] but would readily lead to 2,5-disubstituted thiazoles, provided that the sulfur underwent addition to the carbenoid centre.

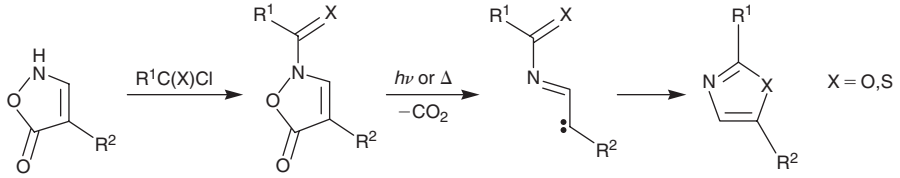
The analogous reaction of carboxamides with carbenoids during rhodium(II)-catalyzed decomposition of diazomalonates and diazo β-ketoesters,[19] and diazophosphono esters,[20] which generates 2,4-disubstituted oxazoles,[21]



Scheme 2.



Scheme 3.



Scheme 1.

* Deceased.

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involves addition of the nitrogen atom to the unsaturated centre. The NH moiety of amides also reacts with 1,3-dithiolium carbenes.[22] However, the conversion of carboxamides to nitriles by dichlorocarbene[23] would appear to require reaction of the amide oxygen atom with the carbene. The realization of the pathway shown in Scheme 3 is the subject of this paper.

Discussion

Ethyl 5-oxo-2-phenyl-2,5-dihydroisoxazole-4-carboxylate **1** is readily available from the reaction of phenylhydroxylamine with diethyl methoxymethylenemalonate,[24] and the phenyl group is known[25,26] to activate the molecule to form the carbene **2** on photolysis or flash vacuum pyrolysis. Photolysis of **1** in the presence of three equivalents of thioacetamide in acetone or ether at 300 nm (pyrex filter) gave a complicated mixture of products, but the addition of acid gave a cleaner product. While the use of acetic acid led to the capture of the carbene by acetic acid,[27] the presence of 0.5% trifluoroacetic acid (TFA) led to the isolation of ethyl 2-methylthiazole-5-carboxylate **3** in 58% yield after chromatography. Since the ^{1}H NMR spectrum of **3** and the isomeric 4-ester are rather similar,[28] the ester **3** was converted to the crystalline 2-methythiazole-5-carboxylic acid (mp 138–140°C). Schoberl and Stock[29] have reported the synthesis of both the 4- and the 5-carboxylic acids (mp 143–145°C and 209°C), but we believe their assignments are incorrect in the light of the X-ray structures for 2-methylthiazole-5-carboxylic acid, derived from **3** (Fig. 1) and **4**, below. A similar yield (62%) of **3** was obtained in ether containing 0.5% TFA, but the byproducts were now more difficult to remove.

In addition to **3**, a second compound (10%) was isolated, whose structure was inferred to be **4** from its spectral data and confirmed by X-ray crystallography. The structure of **4** was deduced from its NMR spectra, which showed the presence of two alkenyl protons by signals at 7.85 and 6.81 ppm, the latter of which slowly exchanged with D_2O, and a thioketone group with a ^{13}C resonanance at 204.6 ppm. The ORTEP structure, deduced from single crystal X-ray data, is shown in Fig. 2. The structure of this product is important, as it presumably arises as shown in Scheme 4, and suggests that, unlike amides,[19–22,30] thioamides react with carbenes through the sulfur atom. Subsequent work (see below) supports the intermediacy of compounds of the type **5**.

Photolysis of **1** as above in the presence of thiobenzamide until reaction was complete required 12 h at a one-gram scale. Chromatography gave only a single pure compound (44%), identified as ethyl 2-phenylthiazole-5-carboxylate **6**. Brief photolysis gave **6** (23%) and a second product (20%) which could not be separated from it. This product is believed to be a 3 : 1 mixture of *trans*- (**7a**) and *cis*- (**7b**) isomers, as deduced from the coupling constants of the vicinal protons [**7a**: 6.58 (H-5, d, *J* 5), 4.47 (H-4, d, *J* 5); **7b**: 6.35 (H-5, d, *J* 9.2), 4.78 (H-4, d, *J* 9.2)], Scheme 5. Treatment of the total mixture with TFA gave **6** in 44% yield and **7** was no longer present. The identity of **6**

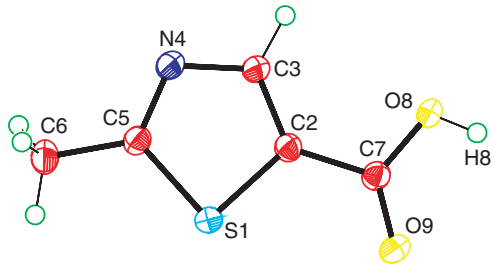


Fig. 1. The molecular structure of 2-methylthiazole-5-carboxylic acid, showing crystallographic labelling and with displacement ellipsoids drawn at the 50% probability level.

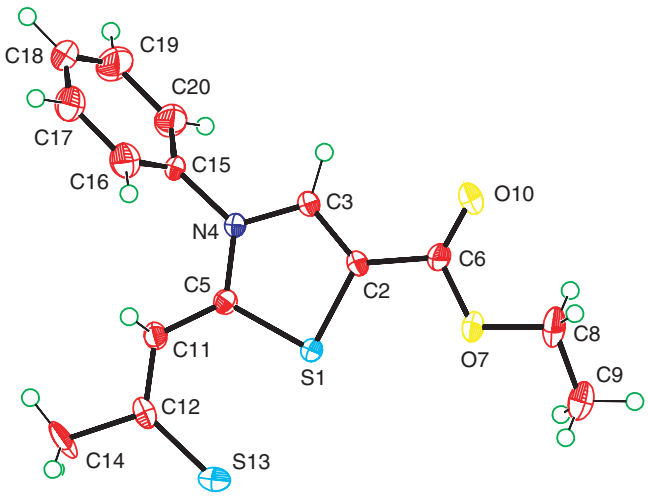
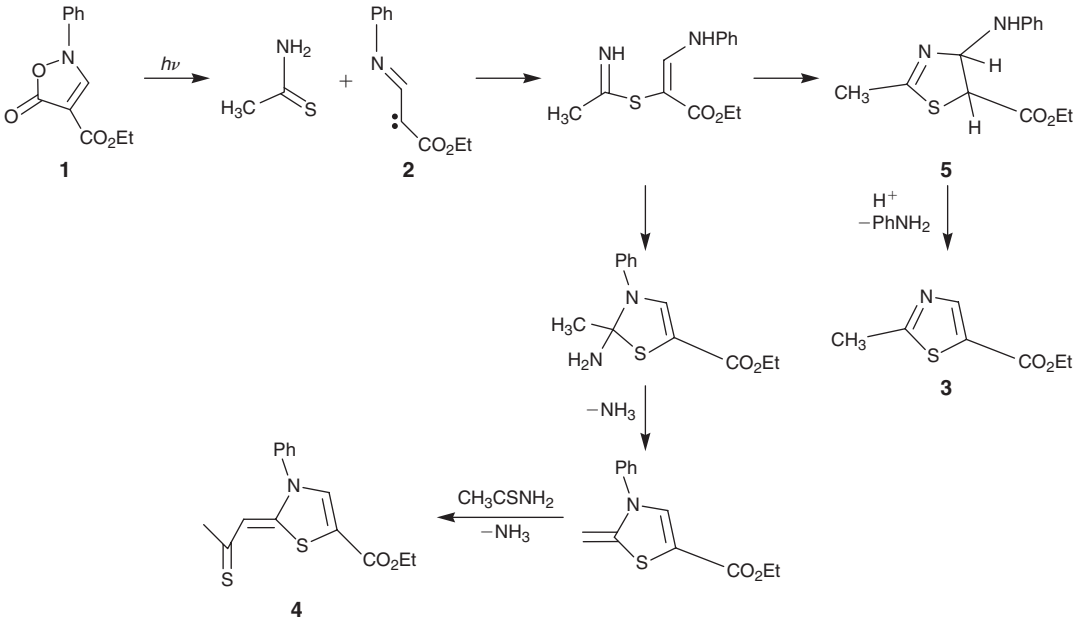


Fig. 2. The molecular structure of **4**, showing crystallographic labelling and with displacement ellipsoids drawn at the 50% probability level.

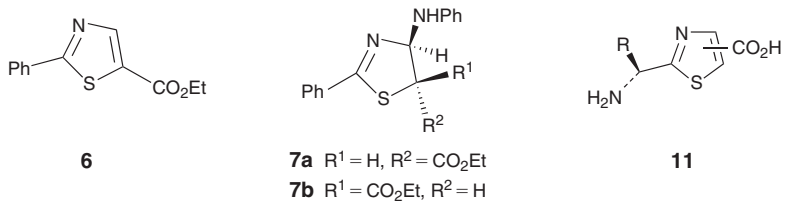
was confirmed by comparison of the melting point (65°C) with that reported in the literature[31] (60°C; that of the 4-ester is 47°C[31]). In addition, the 4-ester was synthesized[32] and had clearly distinct ^{1}H and ^{13}C NMR spectra.

Photolysis of **1** in the presence of acetone semithiocarbazone gave a crude product containing what is believed to be the uncyclized adduct **8**, probably as a mixture of diastereoisomers. NMR evidence showed compound **8** contained no sp^3-hybridized carbons other than those associated with the ester and 2-propylidene groups. Cyclization was best achieved by refluxing with *p*-toluenesulfonic acid in dry benzene, and chromatography then allowed isolation of the thiazole ester **9** in 48% yield. The product was clearly not the same as the isomeric ester **10**, which was obtained by Hanzsch synthesis using ethyl bromopyruvate and acetone semithiocarbazone as described by Johne and coworkers.[33]

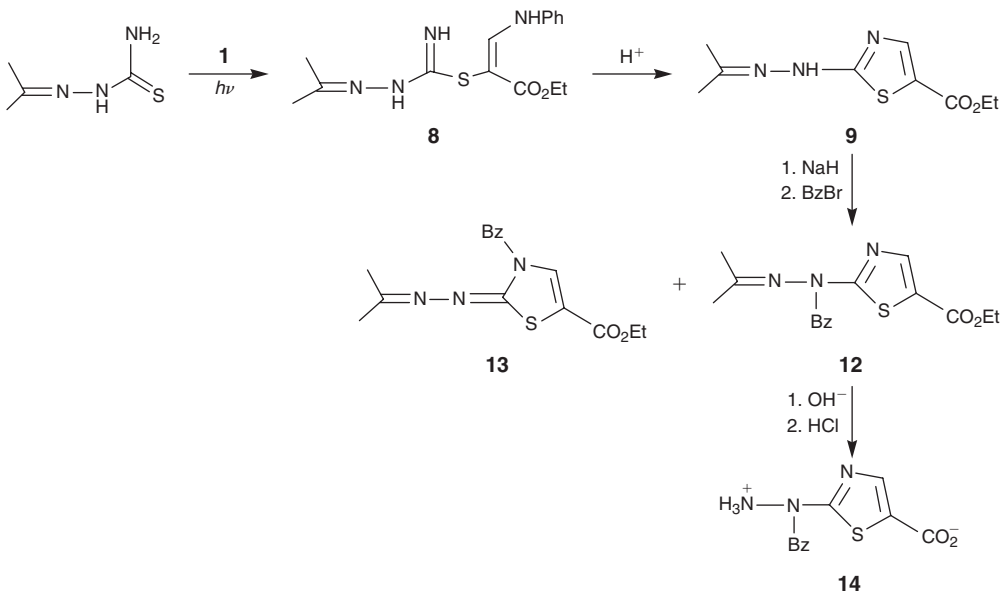
Since our ultimate aim was to develop strategies for the synthesis of novel 2-aminoalkylthiazole-4- and -5-carboxylic acids **11** and their analogues, selective α-alkylation of the hydrazino group was investigated. The ester **9** could not be alkylated in the absence of base, but conversion to the sodium salt by sodium hydride in tetrahydrofuran allowed alkylation with methyl iodide or benzyl bromide. The latter gave a mixture of the two *N*-benzyl isomers, **12** and **13**, which could be readily separated by chromatography. The assignment of structures to the two isomers (Scheme 6) was achieved by



Scheme 4.

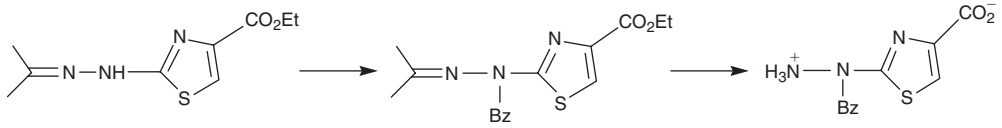


Scheme 5.



Scheme 6.

comparison of the ^{1}H NMR chemical shifts of H-4, which have been studied in the two series by Forlani.[34] The more polar ester **12** was then converted to the desired amino acid using a base followed by protonation. Drying the resulting hydrochloride led to formation of the zwitterionic hydrazino acid **14**. In the same way, the isomeric thiazole ester **10** was alkylated, but in this case only a single alkylated product **15** was formed and again its structure was confirmed by



Scheme 7.

^{1}H NMR spectroscopy. Hydrolysis then gave the zwitterionic hydrazino acid **16** (Scheme 7).

Conclusions

The photolysis of ethyl 5-oxo-2-phenyl-2,5-dihydroisoxazole-4-carboxlate in the presence of thioamides, followed by acidic treatment, leads to moderate yields of thiazole-5-carboxylates. The reaction is possibly complicated by photochemically induced reactions of thioamides,[31] including the [2+2] photocycloaddition of thioamides with the intermediate aminoalkene.[32,35] Oda and coworkers[36] have recently reported the synthesis of 2-arylthiophenes from the photochemically induced reaction of arene thiocarboxamides with methyl furans, emphasizing the synthetic utility of thioamides.

Experimental

Proton and carbon NMR spectra were recorded using a Varian Gemini Spectrometer at 300 MHz and 75.5 MHz respectively, in deuteriochloroform ($CDCl_3$), unless otherwise stated. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer; solids were analyzed as Nujol mulls, and liquids as films. High resolution mass spectra were recorded at Monash University, and microanalyses at the University of Otago. Melting points were determined on a Reichert hot-stage apparatus and remain uncorrected. Radial chromatography was performed with silica gel 60 PF 254 coated glass rotors using a Chromatotron (model 7924T). GC-MS analysis was performed on a Varian Saturn 4D instrument, using a 5% phenylmethyl polysiloxane column (30 m, 0.25 mm ID, 0.25 mm thickness). Photolyses were performed under nitrogen in freshly distilled solvents, using a Hanovia medium-pressure mercury arc source considered to be nominally 300 nm or above.

*Photolysis of **1** with Thioacetamide*

(*a*) A solution of **1**[24] (100 mg, 0.4 mmol) and thioacetamide (70 mg, 2.3 equiv.) in acetonitrile (100 mL) and trifluoroacetic acid (0.5 mL) was degassed and irradiated for 3 h under nitrogen at 300 nm through pyrex. The solvent was removed, replaced with ether (20 mL), and the solution was washed with sat Na_2CO_3, and 1 M HCl. Chromatography on silica in ether/light petroleum (4 : 1) gave **3** (40 mg, 58%) as a colourless oil, R_F (silica, ether) 0.65. (Found: $M^{+\bullet}$ 171.0353. $C_7H_9NO_2S$ requires 171.0354). ν_{max}/cm^{-1} 1715, 1443, 1303, 1258, 1091. δ_H 8.24 (1H, s), 4.35 (2H, q *J* 7.2), 2.75 (3H, s), 1.37 (3H, t *J* 7.0). δ_C 172.0, 161.3, 148.1, 129.3, 61.5, 19.7, 14.3. *m*/*z* 171 (M, 56%), 143 (54), 126 (100), 98 (53), 57 (74).

A colourless solid **4** (6 mg), mp 228°C, remained undissolved in the ethereal phase above and was recrystallized from ethanol. (Found: C 59.3, H 5.1, N 4.6%, $M^{+\bullet}$ 305.0554. $C_{15}H_{15}NO_2S_2$ requires C 59.0, H 4.95, N 4.6%, $M^{+\bullet}$ 305.0544.). ν_{max}/cm^{-1} 1716, 1484, 1274, 1221. δ_H 7.85 (1H, s), 7.64–7.62 (3H, m), 7.41–7.38 (2H, m), 6.81 (1H, s, (slow D_2O exch), 4.37 (2H, q *J* 7.2), 2.61 (3H, s), 1.38 (3H, t *J* 7.2). δ_C 204.6, 163.8, 161.6, 137.8, 136.0, 130.5, 130.5, 126.5, 110.3, 61.8, 37.5, 14.3. *m*/*z* 305 (M, 36%), 196 (100), 168 (22), 77 (22). **4** decomposed on GC analysis.

Repetition of the above on a ten-fold greater scale required 8 h for completion, chromatography allowing the isolation of **3** and **4** in 43% and 12% yields respectively.

(*b*) When acetic acid (1 mL) replaced trifluoroacetic acid in the photolysis, NMR analysis indicated the product (26%) was the acetoxy enamine, ethyl 2-acetoxy-3-phenylaminoacrylate.

2-Methylthiazole-5-carboxylic Acid

Ester **3** (276 mg, 1.61 mmol) was refluxed in methanol (3 mL) containing sodium hydroxide (69 mg, 1.73 mmol) for 2 h. The solvent was removed, the residue acidified with HCl, and the product was extracted with dichloromethane and recrystallized from water as white needles, mp 138–140°C after vacuum drying. The X-ray structure is shown in Fig. 1. (Found: $M^{+\bullet}$ 143.0045. $C_5H_5NO_2S$ requires 143.0041). ν_{max}/cm^{-1} 2472, 1697, 1374, 1316, 1280, 1090. δ_H ([D_6]DMSO) 8.16 (1H, s), 2.28 (3H, s). δ_C ([D_6]DMSO) 172.3, 162.4, 147.8, 130.3, 19.6.

*Photolysis of **1** with Thiobenzamide*

Isoxazolone **1** (1.0 g, 4.3 mmol) was photolyzed as above in the presence of thiobenzamide (1.77 g, 12.9 mmol) in acetonitrile (1000 mL) and TFA (5 mL), requiring 12.5 h for completion (^{1}H NMR monitoring). Chromatography on silica with mixtures of dichloromethane-light petroleum gave **6** (439 mg, 44%), mp 64–65°C (lit[31] 58–60°C). (Found: $M^{+\bullet}$ 233.0514. $C_{12}H_{11}NO_2S$ requires 233.0511). ν_{max}/cm^{-1} 1711, 1415, 1297, 1246, 1092. δ_H 8.42 (1H, s), 7.97–7.6 (2H, m), 7.48–7.46 (3H, m), 4.39 (2H, q *J* 7.2), 1.40 (3H, t *J* 7.5). δ_C 173.3, 161.4, 149.1, 133.0, 131.2, 129.1, 129.0, 126.9, 61.7, 14.3. *m*/*z* 233 (M, 100%), 188 (46), 160 (32), 105 (29), 57 (38).

The isomeric ethyl 2-phenylthiazole-4-carboxylate, mp 47°C, was synthesized following the literature procedure.[32] ν_{max}/cm^{-1} 1712, 1415, 1300, 1249, 1149, 1093. δ_H 8.16 (1H, s), 8.05 (2H, m), 7.44 (3H, m) 4.45 (2H, q *J* 7.6), 1.43 (3H, t *J* 7.6). δ_C 169.0, 161.6, 148.2, 132.8, 130.7, 129.1, 127.1, 126.7, 61.4, 14.2. *m*/*z* 233 (M, 100%), 205 (50), 188 (50), 160 (45), 104 (24), 57 (48).

When the above photolysis was interrupted after 3.5 h, the presence of an intermediate product **7** could be seen. Chromatography at this stage allowed its isolation as a pale yellow oil (43%), containing the isomers **7a** and **7b** (20%) in the ratio of 3 : 1, in addition to **6** (23%). They were characterized by doublets at 6.58 and 4.47 ppm (*J* 5.0), and at 6.35 and 4.78 ppm (*J* 9.2), respectively. These signals disappeared, and were replaced by those characteristic of the thiazole, on addition of TFA to the solution.

*Photolysis of **1** in the Presence of Acetone Thiosemicarbazone*

A solution of **1** (2.3 g, 10 mmol), acetone thiosemicarbazone[37] (1.6 g, 12 mmol), and TFA (1 mL) in acetonitrile (800 mL) was irradiated for 8 h under nitrogen through pyrex. After removal of solvent, the product was chromatographed on silica (CH_2Cl_2/EtOAc). The first two fractions contained aniline and unreacted thiosemicarbazone. The third fraction, containing what is believed to be intermediate **8**, was refluxed with *p*-toluenesulfonic acid (1 g) in benzene (100 mL) for 1 h, and then ether (100 mL) was added. After being washed with cold saturated Na_2CO_3 and water, the solution was evaporated and chromatographed. The first fraction (CH_2Cl_2) contained *ethyl 2-[2-(1-methylethylidene)hydrazino]thiazole-5-carboxylate* **9** and was recrystallized from acetone as pale yellow crystals (1.07 g, 48%), mp 178–179°C. (Found: C 47.75, H 5.4, N 18.4%. $C_9H_{13}N_3O_2S$ requires C 47.6, H 5.8, N 18.5%). δ_H 9.1 (1H, br, exch.), 7.90 (1H, s), 4.32 (2H,

q, *J* 7.5), 2.08 (3H, s), 1.96 (3H, s), 1.30 (3H, t, *J* 7.5). δ_C 174.9, 162.2, 151.8, 146.6, 118.1, 60.8, 25.1, 17.8, 14.4.

Benzylation of Thiazole ***9***

To a suspension of sodium hydride (48 mg, 2 mmol) in THF (15 mL) was added a solution of thiazole **9** (470 mg, 2 mmol) in THF (10 mL), and the mixture was stirred under nitrogen for 15 min at RT. Benzyl bromide (342 mg, 2 mmol) was added, and the mixture was stirred for 2 days at RT. Ether (40 mL) was added, and the mixture washed with sat NaCl. Chromatography of the residue on silica eluted two products. The first (CH_2Cl_2) was isolated as yellow crystals, mp 122–123°C (150 mg, 24%), identified as *ethyl 3-benzyl-2-[(1-methylethylideneamino)imino]-2,3-dihydrothiazole-5-carboxylate* **13**. (Found: C 60.8, H 6.1, N 13.1%, $M^{+\bullet}$ 317.1199. $C_{16}H_{19}N_3O_2S$ requires C 60.5, H 6.0, N 13.2%, $M^{+\bullet}$ 317.1198). ν_{max}/cm^{-1} 1698, 1630. δ_H 7.40 (1H, s), 7.28 (5H, m), 5.00 (2H, s), 4.21 (2H, q *J* 7.5), 2.05 (3H, s) 2.02 (3H, s), 1.38 (3H, t *J* 7.5). δ_C 164.1, 161.8, 161.5, 135.7, 135.4, 128.9, 128.3, 128.3, 108.5, 61.0, 50.7, 24.9, 18.5, 14.3.

The second fraction, *ethyl 2-[1-benzyl-2-(1-methylethylidene)-hydrazino]thiazole-5-carboxylate* **12**, was isolated as a colourless oil (280 mg, 44%). (Found: $M^{+\bullet}$ 317.1197. $C_{16}H_{19}N_3O_2S$ requires $M^{+\bullet}$ 317.1198). ν_{max}/cm^{-1} 1700. δ_H 8.00 (1H, s), 7.3 (5H, m), 5.05 (2H, s), 4.31 (2H, q *J* 7.5), 2.08 (3H, s), 1.75 (3H, s), 1.33 (3H, t *J* 7.5). δ_C 177.8, 174.5, 162.2, 147.8, 135.8, 128.5, 127.7, 118.5, 60.7, 56.8, 24.6, 20.0, 14.4.

Ethyl 2-[1-Benzyl-2-(1-methylethylidene)hydrazino]thiazole-4-carboxylate ***15***

The thiazole **10**[33] (470 mg, 2 mmol) was reacted with benzyl bromide as above. Column chromatography gave the pure *title compound* (580 mg, 92%) as a colourless oil. (Found: $M^{+\bullet}$ 317.1199. $C_{16}H_{19}N_3O_2S$ requires 317.1198). ν_{max}/cm^{-1} 1713, 1650, 1480, 1385, 1092. δ_H 7.55 (1H, s), 7.3 (5H, m), 4.88 (2H, s), 4.15 (2H, q, *J* 7), 2.02 (3H, s), 1.74 (3H, s), 1.38 (3H, t, *J* 7).

2-(1-Benzylhydrazino)thiazole-5-carboxylic Acid ***14***

The thiazole ester **12** (650 mg, 2 mmol) was refluxed in methanol (10 mL) and water (5 mL) with NaOH (120 mg, 1.5 equiv.) for 2 h. The mixture was acidified with 5 M HCl and extracted with ether. After evaporation, the residue was refluxed for 30 min with benzene (20 mL) and water (1 mL), and the residue, after removal of the solvent, was recrystallized from ether as *colourless needles*, mp 168–169°C (335 mg, 68%). (Found: $M^{+\bullet}$ 249.0572. $C_{11}H_{11}N_3O_2S$ requires 249.0572). ν_{max}/cm^{-1} 3618, 3019, 2361, 1665. δ_H 7.83 (1H, s) 7.4–7.3 (5H, m), 4.91 (2H, s), 4.5 (3H, br, exch.). δ_C 178.6, 164.1, 148.1, 135.0, 128.8, 128.4, 128.0, 118.7, 56.6.

2-(1-Benzylhydrazino)thiazole-4-carboxylic Acid ***16***

The ester **15** (1.26 g, 4 mmol) was treated with NaOH (5 mmol) as above for 30 min at 50°C. After acidification, the product was extracted into dichloromethane, evaporated, and the residue stirred with water (10 mL) containing one drop of conc HCl. After 30 min, the water was decanted, and the solid product was recrystallized from ether as colourless crystals (690 mg, 69%), mp 189–190°C. (Found: C 53.0, H 4.2, N 16.8%. $C_{11}H_{11}N_3O_2S$ requires C 53.0, H 4.45, N 16.9%). ν_{max}/cm^{-1} 3424 br, 3019, 1679. δ_H ([D_6]DMSO) 7.58 (1H, s), 7.4–7.3 (5H, m), 4.82 (2H, s), 4.0 (3H, br, exch.). δ_C ([D_6]DMSO) 174.7, 162.7, 144.2, 136.4, 128.7, 128.2, 127.6, 118.7, 56.7.

Crystal Data for 2-Methylthiazole-5-carboxylic Acid

$C_5H_5NO_2S$, *M* 143.17. Orthorhombic, space group *Pna*2_1, *a* 13.675(1), *b* 11.473(1), *c* 3.853(1) Å, *V* 604.51(17) Å^3, *T* 203(2) K. D_c (*Z* 4) 1.573 Mg m^{-3}. μ_{Mo} 0.448 mm^{-1}; specimen 0.37 × 0.12 × 0.12 mm^3. $\Delta\rho_{max}$ 0.23(2) e Å^{-3}. CCDC deposition no. 219844.

Crystal Data for ***4***

$C_{15}H_{16}NO_2S_2$, *M* 306.44. Monoclinic, space group $P2_1/n$, *a* 6.770(1), *b* 11.683(1), *c* 18.849(1) Å, β 92.22(1)°, *V* 1489.7(3) Å^3, *T* 203(2) K. D_c (*Z* 4) 1.366 Mg m^{-3}. μ_{Mo} 0.357 mm^{-1}; specimen 0.43 × 0.16 × 0.14 mm^3. $\Delta\rho_{max}$ 2.10 e Å^{-3}.

Crystal Structure Determination and Refinement

Unit-cell and intensity data for both compounds were measured on a Siemens SMART CCD diffractometer using graphite-monochromated $Mo_{K\alpha}$ X-radiation at the University of Auckland, New Zealand. The structures were solved by using *SIR97*;[38] otherwise computer programs of the *Xtal 3.7* system[39] were used for all calculations. Non-hydrogen atomic coordinates and anisotropic displacement parameters for all atoms were refined by full-matrix least-squares on F^2.

For 2-methylthiazole-5-carboxylic acid a total of 3233 reflections were measured which when averaged (R_{int} 0.009) gave 708 unique reflections, of which there were 705 with $F^2 > 0$. The structure was refined on 705 reflections with $F^2 > 0$ and 82 variables to convergence [$R(F^2 > 2\sigma(F^2))$ 0.022, *wR* 0.063, *S* 1.139]. Hydrogen atoms were placed from the penultimate difference map and not refined.

For **4** a total of 8206 reflections were measured which when averaged (R_{int} 0.062) gave 3019 unique reflections, of which there were 2990 with $F^2 > 0$). The structure was refined on 2497 reflections with $F^2 > 2\sigma(F^2)$ and 181 variables to convergence [$R(F^2 > 2\sigma(F^2))$ 0.123, *wR* 0.303, *S* 2.22]. Hydrogen atoms were placed in calculated positions and not refined. Although the plot of displacement ellipsoids (Fig. 2) did not show any abnormalities, the final difference map showed several large peaks that could not be interpreted. Consequently, the data for **4** was not deposited.

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