Synthesis of Novel 2-Amino-1,3-thiazole-5-carboxylates Utilising Ultrasonic and Thermally Mediated Aminolysis

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Novel 2-amino-1,3-thiazole-5-carboxylates have been synthesised in high yield by unprecedented ultrasonic and thermally mediated nucleophilic displacement of bromide from ethyl 2-bromo-1,3-thiazole-5-carboxylate by primary, secondary and aryl amines.

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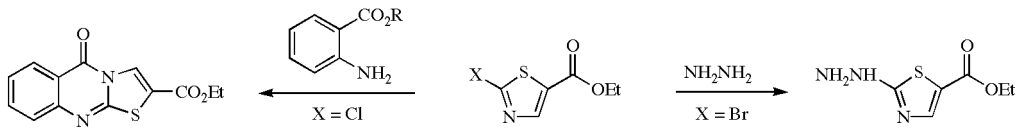
Introduction.

A number of drug leads [1] and biologically active substances [2] which contain the 2-aminothiazole-5-carboxylate moiety have recently emerged propagating interest in developing new synthetic methods [3]. These recent methods are significant improvements on more well known procedures, such as Hantzsch [4]. However, the method of 2-halo- thiazole aminolysis (nucleophilic displacement) [5], well known for the construction of 2-amino-5-nitrothiazoles [6], is poorly represented when position 5 contains alkyloxycarbonyl functionality. To our knowledge only two reports exist. Erlenmeyer [7] reported, the unexpected, thermally mediated displacement of bromide from ethyl 2-X-1,3-thiazole-5-carboxate **1** (X = Br) by hydrazine, giving **2**. LeMahieu [8] later adapted Erlenmeyer's protocol for the synthesis of thiazolo[2,3-*b*]quinazoline derivatives **3** from anthranilates and **1** (X = Cl) (Scheme 1) [9].

Scheme 1



3 **1** **2**

Considering the lack of attention this reaction has received, and the requirement of these types of compounds by our group, we decided to investigate the reaction scope and suitability.

Results and Discussion.

Our initial investigations concentrated on reacting primary and secondary alkyl- and arylamines with **1** (X = Br [7]) thermally, which in each case gave good to excellent yields of the corresponding products **4**-**13** (Entries 1-10, Table 1). Generally temperatures around 100 °C were required except in the case of 1-adamantanamine (Entry 2), which due to large steric bulk, required a higher reaction temperature of 150 °C. Although, 100 °C was the optimum temperature, lower temperatures (*eg.* 60 °C) also afforded products **4**, **9**-**11** (Entries 1,6,7 and 8), but longer reaction times were required [10].

When the reaction of prolinol and **1** (X = Br) were under investigation it was discovered that placing the reaction mixture in an ultrasonic bath, to increase the rate of solvation, resulted in an immediate reaction. Analysis (GC/MS) showed the presence of product **11**, obtained thermally, suggesting sonication had promoted the reaction. Optimisation afforded the product in 70 mins in 78% yield using 1,2-dichloroethane. This result prompted reinvestigation of all amines investigated thermally (Table 1) [10]. However, only selected amines (Entries 1,4,6,7 and 8) reacted using ultrasound, albeit in good yield, but with longer reaction time compared with the thermal process. The poor reactivity of 1-adamantanamine, aniline and 1-napthylamine (Entries 2, 9 and 10) is obvious, however, to our surprise, even slightly sterically encumbered amines failed to react (Entries 3 and 5) under these conditions. At this stage it is unclear as to whether the lack of reactivity, and poor yield, (Entries 2, 3, 5, 9 and 10) is due to amine nucleophilicity or ultrasound physical phenomena, for example, cavitation [11]. Although ultrasound (*i.e.* cavitation) has similarities to thermolytic processes, that is, producing very high temperatures and pressures, it undergoes rapid temperature quenching. It is therefore possible that the cavitation time duration (~10^{-6} sec) [11] is not sufficient to promote these reactions. Additionally, when reactions were conducted on larger scale (>1g of **1**) using ultrasound, the yields remained the same but longer reaction times were required.

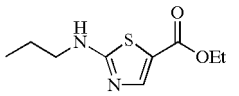
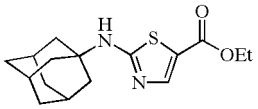
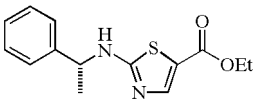
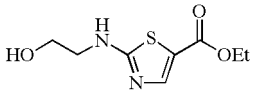
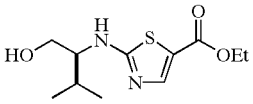
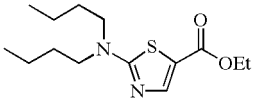
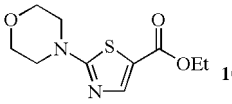
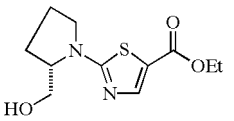
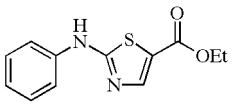
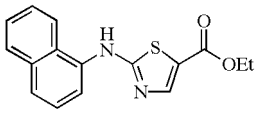
All reported reactions were conducted using three equivalents of starting amine, however, the use of one equivalent in conjunction with triethylamine (1 equiv.) as base gives similar results. Furthermore by-products resulting from thiazole ring rearrangement, as reported with the 5-nitro analogues [12], were not detected with either method.

Conclusion.

A new method for the synthesis of 2-amino-1,3-thiazole-5-carboxylates has been presented, which is an adaptation of the well known 2-halo-5-nitro-1,3-thiazole nucleophilic substitution reaction. The thermally mediated method accommodates a wide variety of functionalised amines, but only in selected cases does ultrasound promote reaction.

Table 1

Ethyl 2-Amino-1,3-thiazole-5-carboxylates Resulting from Aminolysis of **1** (X = Br) [10]

Entry	Product	Thermal (°C/hr/yield%)	Sonication (°C/hr/yield%)
1	 **4**	100/0.66/61	30/2/76
2	 **5**	150/24/62	N/R
3	 **6**	105/10/80	30/12/3
4	 **7**	95/19/60	30/29/20
5	 **8**	105/24/73	N/R
6	 **9**	105/0.33/93	30/4/76
7	 **10**	105/0.25/73	30/1/76
8	 **11**	100/0.66/74	30/1.20/78
9	 **12**	105/8/81	30/12/6
10	 **13**	105/20/73	N/R

N/R = no reaction.

EXPERIMENTAL

^{1}H and ^{13}C nmr spectra were recorded on a Bruker ACF200 in deuteriochloroform ($CDCl_3$) unless otherwise stated. Accurate and low resolution mass spectral data were obtained on a KRATOS MS 25 RFA. Micro analyses were performed in-house by the University of Queensland's micro analytical service. GC/MS data were recorded on a Hewlett-Packard 5890A chromatograph fitted with a (DBS EC-5 Alltech column 30m x 0.25 mm), coupled to a 5970 series mass spectrometer. Chromatography was undertaken using either a chromatotron [Model 7924T using Silica Gel PF—254 with $CaSO_4$ 0.5 H_2O type 60 for TLC (Merck 7749)] (radial chromatography) or column (Flash Silica gel 230–400 mesh) on silica gel, with distilled solvents. Anhydrous solvents were prepared according to Perrin and Armarego, 'Purification of laboratory solvents', 3rd Ed. Melting points were determined on a Fischer Johns Melting Point apparatus and are uncorrected. Ultrasonic bath: Elma Transsonic 460, 35kHz output. Reactions involving a pressure vessel were encased with a protective shield.

Representative Procedures: Ethyl 2-*N*-Propylamino-1,3-thiazole-5-carboxylate (**4**).

(i) Ethyl 2-bromothiazole-5-carboxylate (167 mg, 0.71 mmol) and *n*-propylamine (176µL, 126 mg, 2.12 mmol) were dissolved in 1,4-dioxane (0.5 mL) in a sealed nmr tube (or pressure vessel) and sonicated at room temperature. After 2 h the solvent was removed *in vacuo*, and the residue dissolved in dichloromethane (20 mL), and washed with saturated sodium carbonate solution (20 mL). The aqueous phase was extracted with dichloromethane (4 x 20 mL), and the combined organic layers washed with distilled water (50 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was preadsorbed onto silica gel and subjected to column chromatography (diethyl ether/petroleum spirit; 1:1) affording the title compound (115 mg, 76%) as a white solid after sublimiation (85 °C/ 0.05 mmHg), mp 82-83 °C.

(ii) Ethyl 2-bromothiazole-5-carboxylate (74 mg, 0.314 mmol) and *n*-propylamine (56 mg, 0.941 mmol) were dissolved in 1,4-dioxane (0.5 mL) in a sealed nmr tube (or pressure vessel) and heated at 100 °C for 40 mins. Work-up as above afforded a residue, which was subjected to radial chromatography (ethyl acetate/dichloromethane; 1:10) affording the title compound (41 mg, 61%) further purified by sublimation. ^{1}H nmr: δ 0.99 (t, 3H, J 7.24); 1.32 (t, 3H, 7.15); 1.71 (sextet, 2H, J 7.24); 3.21 (t, 2H, J 7.24); 4.28 (q, 2H, J 7.15); 7.0 (bs, NH); 7.78 (s, 1H). ^{13}C nmr: δ 11.4; 14.4; 22.1; 48.3; 60.9; 116.0; 145.9; 161.8; 174.1. Mass spectrum m/z (EI) 214 ($M^{+\bullet}$, 70%), 199 (14), 185 (74), 172 (100), 169 (39), 157 (92), 144 (18), 140 (27), 127 (18), 113 (9), 98 (26).

Anal. Calcd for $C_9H_{14}N_2O_2S$: C, 50.45; H, 6.59; N, 13.07; $M^{+\bullet}$ 214.0775. Found: C, 50.30; H, 6.58; N, 12.92; 214.0777.

Ethyl 2-*N*-Adamantylamino-1,3-thiazole-5-carboxylate (**5**).

1-Adamantanamine (157 mg, 1.04 mmol) and ethyl 2-bromothiazole-5-carboxylate (82 mg, 0.348 mmol) in 1,4-dioxane (0.5 mL) were heated at 150 °C. After 24 hr approximately 95% conversion had taken place as monitored by GC. Work-up as above afforded a residue which was subjected to column chromatography (diethyl ether/petroleum spirit; 1:3) affording the title compound (66 mg, 62%) as a white solid, after sublimation (115 °C/0.05 mmHg), mp 118-119 °C. ^{1}H nmr: δ 1.32 (t, 3H, J 7.14); 1.60-1.73 (bm, 6H); 1.95-2.05 (bm, 6H); 2.08-2.20 (bm, 3H); 4.28 (q, 2H, J 7.14); 6.56 (bs, NH); 7.77 (s, 1H). ^{13}C nmr: δ 14.4; 29.3; 36.0; 40.9; 53.6; 61.0; 116.2; 144.4; 161.7; 169.8. Mass spectrum m/z (EI) 306 ($M^{+\bullet}$, 26%), 261 (3), 221 (2), 185 (2), 172 (4), 169 (1), 157 (3), 135 (100), 107 (7).

Anal. Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.72; H, 7.24; N, 9.14; $M^{+\bullet}$ 306.1402. Found: C, 62.96; H, 7.46; N, 9.10; 306.1402.

Ethyl *R*-(+)-2-*N*-(1-Methylbenzylamino)-1,3-thiazole-5-carboxylate (**6**).

R-(+)-1-Methylbenzylamine (327 µL, 311 mg, 2.57 mmol) and ethyl 2-bromothiazole-5-carboxylate (202 mg, 0.856 mmol) in 1,4-dioxane (0.5 ml) were heated at 105 °C for 10 h. Work-up as above afforded a residue which was subjected to column chromatography (diethyl ether/petroleum spirit; 1:1) affording the title compound (191 mg, 80%) as pale yellow crystals after recrystallisation (diethyl ether/petroleum spirit), mp 118-119 °C. ^{1}H nmr: δ 1.27 (t, 3H, J 7.16); 1.63 (d, 3H, J 6.76); 4.22 (q, 2H, J 7.16); 4.46 (q, 1H, J 6.76); 7.26-7.36 (m, 5H); 7.72 (s, 1H). ^{13}C nmr: δ 14.3; 23.8; 56.6; 60.9; 116.4; 126.2; 127.9; 128.9; 141.6; 145.3; 161.8; 173.5. Mass spectrum m/z (EI) 276 ($M^{+\bullet}$, 83%), 261 (10), 242 (9), 225 (5), 199 (8), 172 (82), 171 (5), 144 (7), 127 (22), 105 (100), 77 (16).

Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14; $M^{+\bullet}$ 276.0933. Found: C, 60.80; H, 5.92; N, 10.00; 276.0925.

Ethyl 2-*N*-(2-Hydroxyethylamino)-1,3-thiazole-5-carboxylate (**7**).

Ethyl 2-bromothiazole-5-carboxylate (116 mg, 0.492 mmol) and ethanolamine (94 mg, 1.54 mmol) in 1,4-dioxane (0.5 mL) were heated at 95 °C for 19 h. Column chromatography (diethyl ether) afforded the title compound (64 mg, 60%) as fine white crystals, mp 136-137 °C. ^{1}H nmr: δ 1.31 (t, 3H, J 7.14); 3.03 (bs, OH), 3.46 (m, 2H); 3.86 (m, 2H), 4.28 (q, 2H, J 7.14); 6.42 (bs, NH), 7.76 (s, 1H); ^{13}C nmr: δ 14.3; 48.5; 60.6; 61.2; 116.5; 144.9; 161.6; 173.7. Mass spectrum m/z (EI) 216 ($M^{+\bullet}$, 25%), 185 (46), 172 (50), 157 (68).

Anal. Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95; $M^{+\bullet}$ 216.0569. Found: C, 44.55; H, 5.65; N, 12.96; 216.0570.

Ethyl 2-*N*-Valinol-1,3-thiazole-5-carboxylate (**8**).

Ethyl 2-bromothiazole-5-carboxylate (150 mg, 0.636 mmol) and valinol (196 mg, 1.91 mmol) in 1,4-dioxane (0.5 ml) was heated at 105 °C for 24 h. Work-up as above afforded a residue which was subjected to column chromatography (diethyl ether/petroleum spirit, 3:1) affording the title compound (143 mg, 73%) as a yellow oil. Attempts to prepare microanalytical samples resulted in decomposition. ^{1}H nmr: δ 0.99 (dd, 6H, J 6.73, 1.1); 1.3 (t, 3H, J 7.08); 1.98 (sextet, 1H, J 6.73); 2.9 (bs, 1H); 3.25 (m, 1H); 3.73 (m, 2H); 4.26 (q, 2H, J 7.08); 7.72 (s, 1H). ^{13}C nmr: δ 14.3; 18.9; 19.4; 29.7; 61.2; 62.6; 66.2; 115.6; 144.0; 161.4; 174.2. Mass spectrum m/z (EI) 258 ($M^{+\bullet}$, 14%), 227 (100), 216 (50), 199 (54), 187 (36), 183 (25), 172 (52), 169 (71), 137 (46), 69 (94), 55 (54), 44 (67).

Anal. Calcd for $C_{11}H_{18}N_2O_3S$: $M^{+\bullet}$, 258.1038. Found: $M^{+\bullet}$, 258.1038.

Ethyl 2-*N*-Dibutylamino-1,3-thiazole-5-carboxylate (**9**).

(i) Ethyl 2-bromothiazole-5-carboxylate (175 mg, 0.441mmol) and di-*n*-butylamine (0.375 mL, 288 mg, 2.23 mmol) in 1,4-dioxane (0.5 ml) were sonicated at room temperature for 4 h. Work up as above afforded a residue which was subjected to column chromatography (diethyl ether/petroleum spirit, 1:9) affording the title compound (159 mg, 76%) as a yellow oil.

(ii) Ethyl 2-bromothiazole-5-carboxylate (104 mg, 0.742 mmol) and di-*n*-butylamine (0.39 mL, 2.2 mmol) in 1,4-dioxane (0.5 mL) were heated at 105 °C for 20 mins. Work up as above afforded a residue which was subjected to column chromatography (diethyl ether/petroleum spirit, 1:9) affording the title compound (117 mg, 93%) as a yellow oil. ^{1}H nmr: δ 0.92 (t, 6H, J 7.2); 1.30 (t, 3H, J 7.2); 1.30 (m, 4H); 1.6 (m, 4H); 3.41 (t, 4H, J 7.6); 4.25 (q, 2H, J 7.2); 7.82 (s, 1H). ^{13}C nmr: δ 13.8; 14.4; 20.1; 29.1; 51.5; 60.5; 115.1; 148.3; 162.4; 173.7. Mass spectruum m/z (EI) 284 ($M^{+\bullet}$, 30%), 255 (9), 241 (38), 227 (19), 210 (53), 199 (88), 185 (100), 171 (18), 157 (54), 139 (5).

Anal. Calcd for $C_{14}H_{24}N_2O_2S$: C, 59.12; H, 8.51; N, 9.85; $M^{+\bullet}$, 284.1558. Found: C, 59.35; H, 8.77; N, 9.83; $M^{+\bullet}$, 284.1559.

Ethyl 2-*N*-Morpholino-1,3-thiazole-5-carboxylate (**10**).

(i) Ethyl 2-bromothiazole-5-carboxylate (156 mg, 0.66 mmol) and morpholine (0.173 mL, 173 mg, 1.98 mmol) in 1,4-dioxane (0.5 ml) were sonicated at room temperature for 1 h. Work up as above afforded a residue which was subjected to column chromatography (diethyl ether/petroleum spirit, 1:1) affording the title compound (159 mg, 76%) as a white solid after sublimation (95°/0.01 mmHg).

(ii) Ethyl 2-bromothiazole-5-carboxylate (76 mg, 0.322 mmol) and morpholine (0.14 mL, 1.15 mmol) in 1,4-dioxane (0.5 mL) were heated at 105 °C for 15 mins. Work up as above afforded a residue, which was subjected to column chromatography (diethyl ether/petroleum spirit, 1:1) affording the title compound (56 mg, 73%) as a white solid after sublimation (95 °C/0.01 mmHg), mp 113-115 °C. ^{1}H nmr: δ 1.32 (t, 3H, J 7.08); 3.54 (m, 4H); 3.80 (m, 4H); 4.28 (q, 2H, J 7.08); 7.86 (s, 1H). ^{13}C nmr: δ 14.3; 48.6; 61.2; 65.8; 117.1; 145.5; 161.5; 173.8. Mass spectrum m/z (EI) 242 ($M^{+\bullet}$, 100%), 227 (2), 211 (16), 197 (47), 185 (93), 169 (16), 157 (36), 139 (28).

Anal. Calcd for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56; $M^{+\bullet}$ 242.0725. Found: C, 49.67; H, 5.86; N, 11.36; 242.0721.

Ethyl 2-*N*-Prolinol-1,3-thiazole-5-carboxylate (**11**).

(i) Ethyl 2-bromothiazole-5-carboxylate (114 mg, 0.483 mmol) and prolinol (214 mg, 2.10 mmol) in 1,2-dichloroethane (1 mL) were sonicated for 70 mins. Work up as above and column chromatography (ethyl acetate/dichloromethane; 6:4) afforded the title compound (96 mg, 78 %) as a brown oil.

(ii) Ethyl 2-bromothiazole-5-carboxylate (56 mg, 0.237 mmol) and prolinol (100 mg, 0.980 mmol) in 1,4-dioxane (0.5 mL) were heated at 100 °C for 40 mins. Work up and chromatography as above afforded the title compound (44 mg, 74%) as a brown oil. ^{1}H nmr: δ 1.31 (t, 3H, J 7.32); 1.67-1.84 (m, 1H); 1.92-2.28 (m, 3H); 3.24-3.54 (m, 2H) 3.59-3.80 (m, 2H); 4.13-4.30 (m, 1H); 4.27 (q, 2H, J 7.32); 4.6 (bs, OH); 7.80 (s, 1H). ^{13}C nmr: δ 14.3; 24.0; 29.4; 52.4; 61.2; 65.2; 65.7; 116.4; 144.0; 161.3; 171.0. Mass spectrum m/z (EI) 256 ($M^{+\bullet}$, 10%), 225 (100), 197 (38), 185 (20), 44 (38).

Anal. Calcd for $C_{11}H_{16}N_2O_3S$: C, 51.55; H, 6.29; N, 10.93; $M^{+\bullet}$, 256.0882. Found: C, 51.50; H, 6.38; N, 10.88; $M^{+\bullet}$, 256.0877.

Ethyl 2-*N*-Anilino-1,3-thiazole-5-carboxylate (**12**).

Ethyl 2-bromothiazole-5-carboxylate (168 mg, 0.712 mmol) and aniline (0.195 mL, 199 mg 2.14 mmol) and in 1,4-dioxane (0.5 mL) were heated at 105 °C for 8 h. Work up as above afforded a residue which was subjected to column chromatography (diethyl ether/petroleum spirit, 1:3) affording the title compound as a pale yellow solid (143 mg, 81%) after sublimation (170 °C/0.01 mmHg), mp 188-189 °C. ^{1}H nmr: δ 1.34 (t, 3H, J 7.20); 4.34 (q, 2H, J 7.20); 6.30 (bs, NH), 7.4 (m, 5H, Ar); 7.88

(s, 1H); ^{13}C nmr: δ 14.4; 61.2; 116.4; 119.5; 124.8; 129.8; 139.1; 145.0; 161.6; 170.4. Mass spectrum m/z (EI) 248 ($M^{+\bullet}$, 100%), 219 (27), 203 (22), 174 (59), 135 (26), 119 (60), 91 (42).

Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28; $M^{+\bullet}$ 248.06198. Found: C, 58.10; H, 4.81; N, 11.26; 248.0617.

Ethyl 2-*N*-1-Napthylamino-1,3-thiazole-5-carboxylate (**13**).

Ethyl 2-bromothiazole-5-carboxylate (128 mg, 0.542 mmol) and 1-napthylamine (233 mg, 1.63 mmol) in 1,4-dioxane (0.5 mL) were heated at 105 °C for 20 h. Work up as above afforded a residue which was subjected to column chromatography (diethyl ether/petroleum spirit, 1:3) affording the title compound as a pale brown solid (118 mg, 73%) after sublimation (180 °C/0.01 mmHg), mp 186.5-187.5 °C. ^{1}H nmr: δ 1.24 (t, 3H, J 6.96); 4.21 (q, 2H, J 6.96); 7.46-7.64 (m, 3H); 7.71-7.85 (m, 3H), 7.87-7.98 (m, 1H); 8.10-8.24 (m, 1H), 10.3 (bs, NH). ^{13}C nmr: δ 14.3; 60.9; 116.4; 120.3; 121.8; 125.8; 126.9; 127.1; 128.2; 128.7; 134.7; 135.7; 146.8; 161.9; 173.9. Mass spectrum m/z (EI) 298 ($M^{+\bullet}$, 100%), 269 (31), 253 (10), 224 (32), 197 (6), 185 (6), 179 (4), 169 (28), 153 (20), 140 (20), 127 (21), 115 (16), 84 (19).

Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; $M^{+\bullet}$ 298.0775. Found: C, 64.29; H, 4.65; N, 9.12; 298.0774.

REFERENCES AND NOTES

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[1a] J. Pratt, H.-S. Lae, S. Rosenberg, K. Spina, M. Winn, S. Buckner, E. Novosad, D. Kerkman, K. Shiosaki, T. Opgenorth and J. DeBernardis, *Bioorg. Med. Chem. Lett.*, **4**, 169 (1994); [b] B. Plouvier, C. Bailly, R. Houssin and J.-P. Hénichart, *Heterocycles*, **32**, 693 (1991); [c] P. R. Marsham, L. R. Hughes, A. L. Jackman, A. J. Hayter, J. Oldfield, J. M. Wardleworth, J. A. M. Bishop, B. M. O'Connor and A. H. Calvert, *J. Med. Chem*., **34**, 1594 (1991).

[2a] D. H. Nguyen, J. W. Szewczyk, E. E. Baird, and P. B. Dervan, *Bioorg. Med. Chem*., **9**, 7 (2001); [b] Y. Sakai, T. Matsumoto, A. Tanaka and M. Shibuya, *Heterocycles*, **36**, 565 (1993); [c] T. E. Lehmann, W. A. Greenberg, D. A. Liberles, C. K. Wada and P. B. Dervan, *Helv. Chim. Acta*, **80**, 2002 (1997); [d] K. E. Rao, Y. Bathini and J. W. Lown, *J. Org. Chem*., **55**, 728 (1990); [e] J. Kosáry, E. Kasztreiner, G. Rablóczky and B. Vitális, *Pharmazie*, **42**, 373 (1987).

[3a] D. Brickute, F. A. Sløk, C. Rømming and A. Sackus, *J. Chem. Soc., Perkin Trans. 1*, 652 (2002); [b] R. Zhao, S. Gove, J. E. Sundeen and B.-C. Chen, *Tetrahedron Lett.*, **42**, 2101 (2001); [c] T. Masquelin and D. Obrecht, *Tetrahedron*, **57**, 153 (2001); [d] H.-O. Kim and M. Kahn, *Synlett*, 1239 (1999); [d] M. Romero-Ortega, A. Aviles, R. Cruz, A. Fuentes, R. M. Gómez and A. Plata, *J. Org. Chem*., **65**, 7244 (2000); [e] P. D. Dey, A. K. Sharma, J. S. Mahajan and M. P. Mahajan, *Indian J. Chem.*, **41B**, 1286 (2002).

[4a] R. Barone, M. Chanon and R. Gallo, 'Thiazole and its Derivatives' Part 2, pp. 9, Ed. J. V. Metzger, in 'The Chemistry of Heterocyclic Compounds', Eds. A. Wiessberger and E. C. Taylor, John Wiley & Sons, New York, 1979; [b] J. V. Metzger, in 'Comprehensive Heterocyclic Chemistry', Eds. A.R. Katritzky & C.W. Rees, Vol. 6, Part 4B, pp.235, Pergamon Press, Oxford, 1984.

[5] Alcoholysis and thioalcoholysis has been reported, L. F. Lee, F. M. Schleppnik and R. K. Howe, *J. Heterocyclic Chem*., **22**, 1621 (1985).

[6] See for example: [a] L. M. Werbel and J. R. Battaglia, *J. Med. Chem*., **14**, 10 (1971); [b] L. M. Werbel, E. F. Elslager, A. A. Phillips, D. F. Worth, P. J. Islip and M. C. Neville, *J. Med. Chem*., **12**, 521 (1969).

[7] B. Prijs, W. Mengisen, S. Fallab and H. Erlenmeyer, *Helv. Chim. Acta*, **35**, 187 (1952).

[8] R. A. LeMahieu, M. Carson, A. F. Welton, H. W. Baruth and B. Yaremko, *J. Med. Chem*., **26**, 107 (1983).

[9] 2,4-Dichloro-1,3-thiazole-5-carboxaldehydes have been investigated, N. Debski, W. Hanefeld and M. Schlitzer, *J. Heterocyclic Chem*., **34**, 1427 (1997).

[10] Table 1 reflects optimised reaction duration (hr) and yields (%). Thermal reaction times are derived from complete consumption of starting material.

[11a] T. J. Mason, *Chem. Soc. Rev.*, **26**, 443 (1997); [b] C. Einhorn, J. Einhorn and J. L. Luche, *Synthesis*, 787 (1989).

[12a] H. H. Lee, B. D. Palmer, M. Boyd and W. A. Denny, *J. Heterocyclic Chem*., **33**, 1191 (1996); [b] A. O. Ilvespää, *Helv. Chim. Acta*, **51**, 1723 (1968).