Unexpected synthesis of 3-(2-aminothiazol-5-yl)-3-arylpropanoates through a one-pot four-component procedure

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The novel one-pot four-component reactions of 2-aminothiazole, aldehydes, Meldrum's acid and aliphatic alcohols were investigated, and a series of unexpected compounds, 3-(2-aminothiazol-5-yl)-3-arylpropanoates, were synthesised under catalyst-free conditions. The protocol has advantages of mild conditions, high yield and simple work-up procedure. Thiazoles are important in the field of organic and medicinal chemistry.

Keywords: 2-aminothiazole, 3-(2-aminothiazol-5-yl)-3-arylpropanoate, heterocycles, Meldrum's acid, multi-component synthesis, organic and medicinal chemistry

Aminothiazoles are known to be ligands of estrogen receptors[1] as well as a novel class of adenosine receptor antagonists.[2] Compounds including an aminothiazole moiety have been found to possess antidegenerative,[3] hypolipidemic[4] and hypoglycemic[5] activities. Metal complexes bearing aminothiazole ligands have antitumour activity.[6–7] In addition, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds. Thus, the thiazole nucleus is of importance in the field of organic and medicinal chemistry.

Multi-component reactions (MCRs) are more and more popular and effective. Recently MCRs have emerged as a highly valuable synthetic tool in the context of modern drug discovery. The atom economical and convergent character, the simplicity of a one-pot procedure, the possible structural variations, the accessible complexity of the molecules, as well as the very large number of accessible compounds are among the advantages of MCRs.[8,9] Thus, they are perfectly amenable to automation for combinatorial synthesis.[10,11]

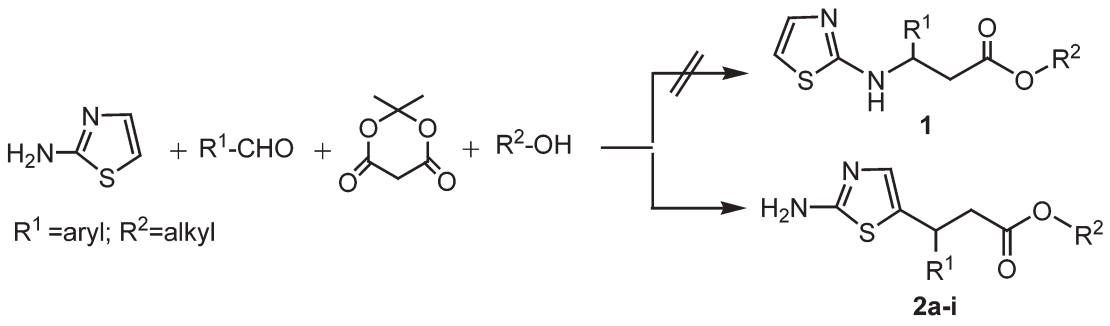
In continuation of our ongoing program to synthesise biologically active compounds and develop one-pot multi-component synthetic strategies for important organic compounds,[12–15] we now report an efficient, unexpected route to prepare 3-(2-aminothiazol-5-yl)-3-arylpropanoates by condensation of 2-aminothiazoles, aldehydes, Meldrum's acid and aliphatic alcohols under catalyst-free conditions.

Results and discussion

In our previous work,[16] 2-amino-1,3,4-thiadiazoles, aldehydes, Meldrum's acid and aliphatic alcohols underwent a one-pot four-component reaction to give 3-(1,3,4-thiadiazol-2-ylamino)-3-arylpropanoates. In these reactions, the amino groups of the heteroaryl amine participated in the four-component reaction to form a C–N bond in the final products. However, in later research to extend this synthetic method using 2-aminothiazole instead of 2-amino-1,3,4-thiadiazole as a substrate under similar conditions, a series of unexpected novel compounds were obtained, in which the amino group of thiazole was compatible to the reaction systems, and the formation of C–N bonds was not observed. Instead, the reactions took place at the 5-position of the thiazole ring, and very different compounds, 3-(2-aminothiazol-5-yl)-3-arylpropanoates **2a–i**, were readily formed in high yield (Scheme 1). Although the reactions could, potentially, proceed at the 4-position of the thiazole ring, the ^{1}H NMR data ($\delta_{H\text{-}4}$ = 6.64–6.87) of compounds **2a–i** are in full accord with the C-5 substitution products. For example, in 2-amino-5-methylthiazole $\delta_{H\text{-}4}$ = 6.68 whereas in 2-amino-4-methylthiazole H-5 is much less deshielded $\delta_{H\text{-}5}$ = 6.01.[17]

In order to explore the generality and scope of these promising findings, 2-aminothiazole, various aldehydes, Meldrum's acid and aliphatic alcohols were selected as model substrates to carry out the reactions by a one-pot procedure under catalyst-free conditions. It was found that all of these four-component reactions proceeded smoothly to give 3-(2-aminothiazol-5-yl)-3-arylpropanoates **2a–i** in high yield under reflux conditions and none of the expected 3-aryl-3-(thiazol-2-ylamino)propanoates **1** were observed. In these reactions, various aromatic aldehydes were all suitable substrates, and the different substituents on aromatic rings have no obvious effect on the yield of the reactions. Aliphatic alcohols, such as ethanol and methanol, acted both as reactants and solvents. The influence of catalytic systems, such as Lewis acids and Lewis bases, were investigated for the reactions, however, no significant effects were observed (Table 1).

A plausible mechanism for these four-component reactions is shown in Scheme 2. The Knoevenagel condensation of aldehydes with Meldrum's acid first gives the α,β-unsaturated intermediate **A**. The latter undergoes Michael addition with 2-aminothiazole to yield intermediates **B**. One carbonyl group



Scheme 1 Synthesis of 3-(2-aminothiazol-5-yl)-3-arylpropanoates.

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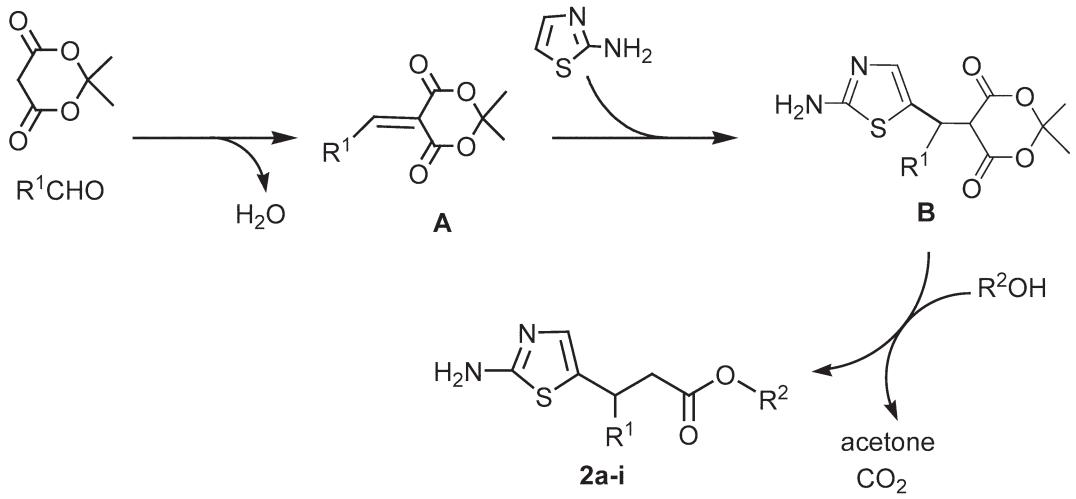

Scheme 2 The proposed mechanism for four-component synthesis of 3-(2-aminothiazol-5-yl)-3-arylpropanoates.

of **B** is then subjected to nucleophilic attack by the aliphatic alcohol and this is followed by elimination of acetone and decarboxylation to afford 3-(2-aminothiazol-5-yl)-3-arylpropanoates **2a–i** as the final products.

Conclusion

In summary, an efficient synthetic method to access 3-(2-aminothiazol-5-yl)-3-arylpropanoates by a catalyst-free, one-pot four-component reaction of 2-aminothiazole, aldehydes, Meldrum's acid and aliphatic alcohols has developed. This protocol has the advantages of mild conditions, high yield and a simple work-up procedure.

Experimental

IR spectra were recorded using KBr pellets on a Digilab FTS 3000 FTIR spectrophotometer, and ^{1}H NMR, ^{13}C NMR spectra on a Varian Mercury Plus-400 instrument using $CDCl_3$ or DMSO-d_6 as solvent and Me_4Si as internal standard. Elemental analyses were performed on a Vario E1 Elemental Analysis instrument. Melting points were determined using an Electrothermal apparatus.

Synthesis of 3-(2-aminothiazol-5-yl)-3-arylpropanoates; general procedure

A mixture of 2-aminothiazole (2.0 mmol), an appropriate aldehyde (2.2 mmol) and Meldrum's acid (2.0 mmol) in ethanol or methanol (5 mL) was stirred under reflux for the time indicated in Table 1. After completion of reaction (TLC), the solvent was removed under reduced pressure, and the residue was subjected to column chromatography using petroleum ether (b.p. 60–90 °C) and ethyl acetate (1:1) as eluent to give pure product. The analytical data for the products are given below.

Ethyl 3-(2-aminothiazol-5-yl)-3-phenylpropanoate (**2a**): White solid, m.p. 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.20 (m, 5H, Ph-H), 6.77 (s, 1H, Th-H), 5.20 (brs, 2H, NH_2), 4.57–4.53 (t, J = 8.0 Hz, 1H, CH), 4.09–4.03 (q, J = 7.2 Hz, 2H, CH_2), 3.03–2.89 (m, 2H, CH_2), 1.16–1.13 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.09, 167.73, 142.30, 134.31, 131.15, 128.58, 127.28, 127.07, 60.61, 41.39, 40.52, 13.98. IR (KBr, v, cm^{-1}): 3368 (NH), 3295 (NH), 1714 (C=O). Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.77; H, 5.83; N, 10.11%.

Ethyl 3-(2-aminothiazol-4-yl)-3-(2-chlorophenyl)propanoate (**2b**): White solid, m.p. 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.15 (m, 4H, Ph-H), 6.79 (s, 1H, Th-H), 5.27 (brs, 2H, NH_2), 5.11–5.07 (t, J = 8.0 Hz, 1H, CH), 4.11–4.05 (q, J = 7.2 Hz, 2H, CH_2), 3.30–2.97 (d, J = 8.4 Hz, 2H, CH_2), 1.18–1.14 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.69, 167.65, 139.62, 135.08, 133.45, 129.83, 129.38, 128.24, 127.97, 127.11, 60.72, 40.37, 36.57, 13.98. IR (KBr, v, cm^{-1}): 3390 (NH), 3281 (NH), 1721(C=O). Anal. Calcd for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.86; N, 9.01. Found: C, 54.21; H, 4.87; N, 8.99%.

Ethyl 3-(2-aminothiazol-4-yl)-3-(4-chlorophenyl)propanoate (**2c**): White solid, m.p. 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.18 (m, 4H, Ph-H), 6.76 (s, 1H, Th-H), 5.13 (brs, 2H, NH_2), 4.55–4.51 (t, J = 7.8 Hz, 1H, CH), 4.10–4.04 (q, J = 7.2 Hz, 2H, CH_2), 3.02–2.86 (m, 2H, CH_2), 1.18–1.14 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.83, 167.62, 140.83, 134.64, 132.89, 130.82, 128.78, 128.75, 60.76, 41.28, 39.93, 14.04. IR (KBr, v, cm^{-1}): 3366 (NH), 3296 (NH), 1714 (C=O). Anal. Calcd for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.86; N, 9.01. Found: C, 54.04; H, 4.86; N, 8.98%.

Ethyl 3-(2-aminothiazol-4-yl)-3-(2,4-dichlorophenyl)propanoate (**2d**): White solid, m.p. 86–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (s, 1H, Ph-H), 7.20–7.18 (d, J = 8.4 Hz, 2H, Ph-H), 6.78 (s, 1H, Th-H), 5.39 (brs, 2H, NH_2), 5.05–5.01 (t, J = 7.8 Hz, 1H, CH), 4.11–4.06 (q, J = 7.2 Hz, 2H, CH_2), 2.97–2.95 (d, J = 8.0 Hz, 2H, CH_2), 1.19–1.15 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.45, 167.86, 138.30, 135.15, 134.11, 133.30, 129.57, 128.88, 128.62, 127.41, 60.82, 40.16, 36.16, 13.97. IR (KBr, v, cm^{-1}): 3355 (NH), 3199 (NH), 1726 (C=O). Anal. Calcd for $C_{14}H_{14}Cl_2N_2O_2S$: C, 48.70; H, 4.09; N, 8.11. Found: C, 48.65; H, 4.08; N, 8.13%.

Ethyl 3-(2-aminothiazol-4-yl)-3-(2-nitrophenyl)propanoate (**2e**): White solid, m.p. 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.36 (m, 4H, Ph-H), 6.87 (s, 1H, Th-H), 5.24–5.20 (t, J = 8.0 Hz, 1H, CH), 5.13 (brs, 2H, NH_2), 4.06–4.03 (q, J = 7.0 Hz, 2H, CH_2), 3.08–3.06 (d, J = 8.8 Hz, 2H, CH_2), 1.15–1.12 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.11, 167.96, 149.30, 136.76, 135.01, 133.01, 129.14, 129.04, 127.95, 124.52, 60.97, 40.84, 34.50, 13.94. IR (KBr, v, cm^{-1}): 3383 (NH), 3274 (NH), 1715 (C=O). Anal. Calcd for $C_{14}H_{15}N_3O_4S$: C, 52.33; H, 4.70; N, 13.08. Found: C, 52.40; H, 4.71; N, 13.05%.

Ethyl 3-(2-aminothiazol-4-yl)-3-(4-nitrophenyl)propanoate (**2f**): White solid, m.p. 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19–8.16 (m, 2H, Ph-H), 7.46–7.42 (m, 2H, Ph-H), 6.82 (s, 1H, Th-H), 5.05 (brs, 2H, NH_2), 4.70–4.66 (t, J = 7.6 Hz, 1H, CH), 4.12–4.04 (q, J = 8.0 Hz, 2H, CH_2), 3.09–2.93 (m, 2H, CH_2), 1.20–1.16 (t, J = 8.0 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.41, 167.68, 149.70, 147.04, 135.22, 129.53, 128.40, 123.98, 60.00, 40.90, 40.28, 14.06. IR (KBr, v, cm^{-1}): 3363 (NH), 3299 (NH), 1712 (C=O). Anal.

Table 1 Synthesis of 3-(2-aminothiazol-5-yl)-3-arylpropanoates

Compd	R^1	R^2	Time/h	M.p./°C	Yield/%[a]
2a	C_6H_5	C_2H_5	10	110–112	80
2b	2-ClC_6H_4	C_2H_5	15	110–111	82
2c	4-ClC_6H_4	C_2H_5	11	113–115	72
2d	2,4-$Cl_2C_6H_3$	C_2H_5	14	86–88	73
2e	2-$O_2NC_6H_4$	C_2H_5	12	116–118	77
2f	4-$O_2NC_6H_4$	C_2H_5	9	114–116	83
2g	4-$CH_3OC_6H_4$	C_2H_5	15	84–86	85
2h	4-HOC_6H_4	C_2H_5	13	180–181	75
2i	C_6H_5	CH_3	11	108–110	79

[a]Yields refer to the isolated products.

Calcd for $C_{14}H_{15N_3O_4}S$: C, 52.33; H, 4.70; N, 13.08. Found: C, 52.43; H, 4.71; N, 13.04%.

Ethyl 3-(2-aminothiazol-4-yl)-3-(4-methoxyphenyl)propanoate (**2g**): White solid, m.p. 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18–7.14 (m, 2H, Ph-H), 6.85–6.81 (m, 2H, Ph-H), 6.75 (s, 1H, Th-H), 5.14 (brs, 2H, NH_2), 4.52–4.48 (t, *J* = 7.8 Hz, 1H, CH), 4.09–4.02 (q, *J* = 7.6 Hz, 2H, CH_2), 3.76 (s, 3H, CH_3), 3.00–2.86 (m, 2H, CH_2), 1.17–1.14 (t, *J*=7.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.15, 167.53, 158.51, 134.47, 134.22, 131.89, 128.33, 113.91, 60.58, 55.14, 41.59, 39.76, 14.02. IR (KBr, *v*, cm^{-1}): 3369 (NH), 3295 (NH), 1714 (C=O). Anal. Calcd for $C_{15}H_{18N_2O_3}S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.71; H, 5.93; N, 9.13%.

Ethyl 3-(2-aminothiazol-4-yl)-3-(4-hydroxyphenyl)propanoate (**2h**): White solid, m.p. 180–181 °C; ^{1}H NMR (400 MHz, DMSO–d_6): δ 9.29 (s, 1H, OH), 7.05 (s, 2H, NH_2), 6.69–6.64 (m, 5H, Ph-H, Th-H), 4.32–4.28 (t, *J* = 7.8 Hz, 1H, CH), 4.02–3.94 (m, 2H, CH_2), 2.97–2.81 (m, 2H, CH_2), 1.09–1.06 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.82, 167.04, 156.04, 133.95, 133.93, 133.37, 129.21, 128.21, 115.09, 59.86, 40.95, 14.01. IR (KBr, *v*, cm^{-1}): 3449 (OH), 3331 (NH), 3201 (NH), 1723 (C=O). Anal. Calcd for $C_{14}H_{16N_2O_3}S$: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.42; H, 5.53; N, 9.60%.

Methyl 3-(2-aminothiazol-4-yl)-3-phenylpropanoate (**2i**): White solid, m.p. 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.21 (m, 5H, Ph-H), 6.76 (s, 1H, Th-H), 5.17 (brs, 2H, NH_2), 4.57–4.53 (t, *J* = 7.8 Hz, 1H, CH), 3.61 (s, 3H, CH_3), 3.05–2.91 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.56, 167.79, 142.26, 134.19, 131.12, 128.65, 127.25, 127.15, 51.80, 41.14, 40.44. IR (KBr, *v*, cm^{-1}): 3348 (NH), 3168 (NH), 1732 (C=O). Anal. Calcd for $C_{13}H_{14N_2O_2}S$: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.65; H, 5.39; N, 10.65%.

Electronic supplementary information

IR and ^{1}H and ^{13}C NMR spectra of compounds **2a–i** have been deposited in the ESI available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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