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Synthesis of 5-aminothiazoles as building blocks for library synthesis

Mark J. Thompson, William Heal and Beining Chen*

Department of Chemistry, University of Sheffield, Brook Hill, Sheffield S3 7HF, UK

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Abstract—A convenient route to 4-phenyl-5-aminothiazoles is described, which offers control over substitution at the 2-position. 2-*N*-Acylglycinamides were dithionated and a subsequent TFAA-mediated cyclisation step was followed by removal of the 5-*N*-trifluoroacetyl group providing the free amines. Though applicable generally the method was found to be most effective when introducing aromatic substituents at the 2-position, whereupon moderate overall yields of the 5-amino compounds were obtained.

Thiazoles are amongst the most frequently encountered heterocycles in compounds of biological interest, along with many other applications. Whilst syntheses of thiazoles and 2-aminothiazoles have been studied extensively, the preparation of 5-aminothiazoles has not been so widely reported. This class of compounds has received attention in a range of applications from antibiotics[1] to photosensitisers;[2] however, searching the literature for a general approach allowing structural variation and based on readily available starting materials gave limited results. Known routes[3–5] to 5-aminothiazoles are narrow in scope with regard to substituents at the 2- and 4-positions, sometimes involving many synthetic steps.

We were looking for a convenient route to a series of differently 2-substituted 4-phenyl-5-aminothiazoles **1** (Fig. 1), and since we required access to moderate quantities of compounds of this type for subsequent library synthesis, the development of a more flexible approach to such structures was therefore investigated. This letter reports a convenient route to synthesise this class of compounds.

Our initial approach was based on the results of Barrett,[6] who reported conversion of 2-*N*-(thiobenzoyl)acetamides into 5-(trifluoroacetylamino)thiazoles in good yields upon treatment with neat TFAA. However, in our hands, the analogous reaction of 2-phenyl-2-(thiobenzoylamino)acetamide **2**—not a substrate investigated by Barrett—was found to result in the formation of an approximately equal mixture of thiazole **3** and oxazole **4** (Scheme 1). This problem of mixed product formation was overcome by reaction of **2** with Lawesson's reagent prior to treatment with TFAA, resulting in exclusive formation of the desired thiazole product **3**.

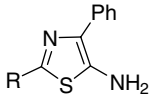

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Figure 1. General structure of 2-substituted-4-phenyl-5-aminothiazoles **1**.

Based upon these observations, a general route to 5-(trifluoroacetylamino)thiazoles **8** was devised (Scheme 2). 2-*N*-Acylglycinamides **6a**–**e**, prepared by reaction of D-(−)-phenylglycinamide **5** with various acid chlorides (R = alkyl, aryl) in the presence of *N*-ethylmorpholine (NEM), were dithionated to provide bis(thioamide) intermediates of type **7**. These compounds were not sufficiently stable to allow their isolation and were consequently treated with TFAA directly to give products **8a**–**e** via a two-step, one-pot procedure.

As a modification of Barrett's procedure, use of DCM as a co-solvent in the cyclisation reactions was found

Keywords: Thiazoles; Thionation reactions; Lawesson's reagent; Belleau's reagent; Cyclisation reactions.
* Corresponding author. Fax: +44 (0)114 222 9346; e-mail: b.chen@shef.ac.uk

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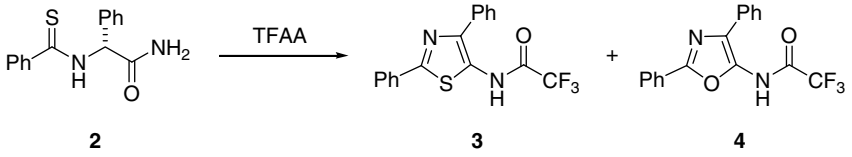
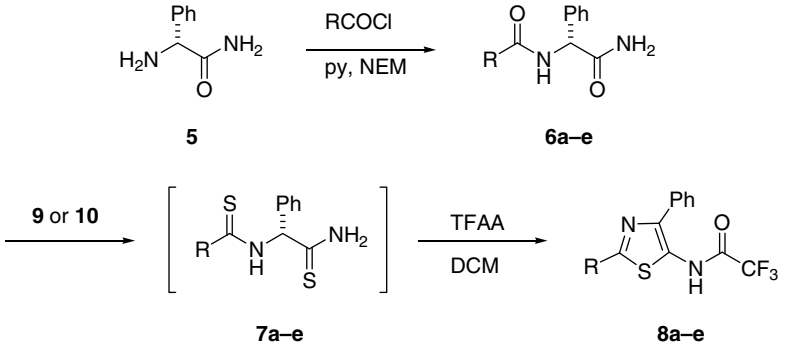


Scheme 1. No regioselectivity was seen in the TFAA-mediated cyclisation of **2**.



Scheme 2. Preparation of 5-(trifluoroacetylamino)thiazoles **8a–e** based on an initial thionation step ensuring formation of a single cyclisation product.

to improve the efficiency of these steps by ensuring dissolution of the otherwise sparingly soluble material. Furthermore, in contrast to the limited accessibility of thioamides of type **2**, use of intermediates of general structure **6** as a starting point in thiazole formation permits a wide variety of substituents derived from commercially available acid chlorides to be introduced at the 2-position.

The thionation step was explored using both Lawesson's reagent **9** and Belleau's reagent[7,8] **10** (Fig. 2) to establish whether any advantage could be gained from the milder conditions offered in utilising the latter. Reactions of the 2-*N*-acylglycinamide intermediates **6** were thus carried out both with Lawesson's reagent **9** in toluene at 100 °C for 35–60 min (Method A, with the duration of heating dependent upon the solubility of the starting material), and with Belleau's reagent **10** in THF at 50 °C overnight (Method B)—although thionation of the primary amide group of **6** was complete in 1–2 h at room temperature, extended reaction times with heating were found to be necessary to effect any significant conversion of the less reactive secondary amide function. In each case, the crude thionated product **7** was subsequently treated with TFAA for 45 min to afford the corresponding trifluoroacetamide **8**, which was isolated by column chromatography.

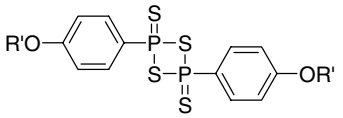
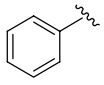
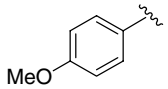
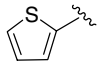
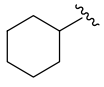


Figure 2. Structures of the thionating reagents used: Lawesson's reagent **9** and Belleau's reagent **10**.

Table 1. Comparative yields of differently 2-substituted 4-phenyl-5-(trifluoroacetylamino)thiazoles **8a–e** prepared as outlined in Scheme 2

Entry	R	Product	Yield, % (Method A)	Yield, % (Method B)
1		**8a**	47	40
2		**8b**	41	33
3		**8c**	46	28[a]
4		**8d**	21	22
5		**8e**	30	35

Reactions were performed on a 2 mmol scale.

[a] Reaction was carried out on a 1 mmol scale. A 20% yield of the oxazole product was isolated in addition to the thiazole.

The results so obtained, summarised in Table 1, show that where aryl groups were introduced at the 2-position (entries 1–3), moderate overall yields of **8a–c** were obtained for the two-step procedure. Where an alkyl group was introduced, however, notably lower yields were obtained (**8d–e**; entries 4–5). It is thought that the limiting factor in the yields obtained by this route is the stability of the bis(thioamide) intermediates **7**, and that the presence of an aryl group (i.e., R = Ar) confers additional stability upon these intermediates leading to the higher yields observed.

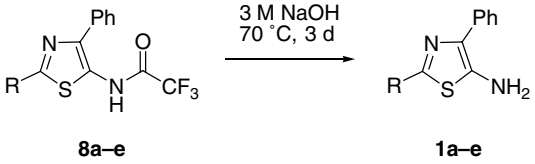
Unexpectedly, the use of Belleau's reagent under milder conditions offered no discernable advantage in the pres-

ent work. It seems the harsher conditions required for the use of Lawesson's reagent are necessary to drive the dithionation step to completion. In particular, formation of the 2-thienyl product **8c** (entry 3) required these more vigorous conditions: when Belleau's reagent was used, an almost equal amount of the corresponding oxazole product was isolated, indicating particularly low reactivity of the secondary amide in this case.

Deprotection of trifluoroacetamides **8a–e** to the desired free amines of general structure **1** was achieved by heating in 3 M NaOH[9] (Scheme 3): such concentrated hydroxide was required given the ready formation of the trifluoroacetamide anion of these compounds.

The hydrolysis reliably reached completion at 70 °C and for **8a–c**, containing two aromatic substituents (R = Ar), provided the corresponding free amines in good yields after a simple workup procedure (Table 2, entries 1–3). However, under these conditions the trifluoroacetamides containing an aliphatic substituent gave mixed results (entries 4–5): whereas the 2-cyclohexyl compound **1d** was obtained in good yield, 2-isopropyl derivative **1e** was only isolated in low yield. Hydrolysis of the trifluoroacetyl group of **8e** was explored using 3 M NaOH in ^{i}PrOH–H_2O (1:1) to improve solubility in an attempt to overcome this problem. Though a homogeneous reaction solution resulted, hydrolysis of the trifluoroacetamide was found to be considerably slower in this solvent mixture and no improvement in yield over the original conditions could be achieved.

In conclusion, we have described a general synthesis of 4-phenyl-5-aminothiazoles of type **1**, which offers a wide range of diversity in 2-substitution using readily available acid chlorides. The fact that compounds of type **6** are much more accessible than those of type **2** offers improvement over reported procedures and allows for greater structural diversity in the 5-aminothiazole products **1**. These themselves serve as versatile building blocks through subsequent derivatisation of the 5-amino group. Furthermore, scale-up of our thionation–cyclisation procedure proved to be especially valuable: compound **8a** was prepared from **6a** in 65% yield on a 15 mmol scale.



8a–e **1a–e**

Scheme 3. Hydrolysis of the 5-trifluoroacetyl group provided the desired free amines **1a–e** (see Table 2 for further structural information).

Table 2. Yields of free amines **1a–e** prepared as illustrated in Scheme 3

Entry	Substrate	Amine	Yield (%)
1	**8a**	**1a**	83
2	**8b**	**1b**	77
3	**8c**	**1c**	81
4	**8d**	**1d**	76
5	**8e**	**1e**	30

The synthetic route we have detailed proved most effective for the preparation of products containing an aromatic group at the 2-position of the thiazole ring. Introduction of an aliphatic group was found to be possible, but at the expense of substantially compromising the overall yield.

Diversity at the 4-position could easily be achieved by use of differently substituted glycinamides **5**, either commercially available or synthesised using a literature procedure,[10,11] as starting materials to prepare the 2-*N*-acylglycinamides prior to cyclisation. Full library synthesis and biological activities of 2,4,5-substituted thiazoles based on this work will be reported elsewhere.

Representative thionation–cyclisation procedure (*Table 1, entry 3, product* **8c**): D-2-Phenyl-2-(thiophene-2-carbonylamino)acetamide (**6c**; R = 2-thienyl; 0.52 g, 2.0 mmol) and Lawesson's reagent (0.97 g, 2.4 mmol) were suspended in toluene (50 mL) and the mixture heated to 100 °C under N_2. Once a homogeneous solution was obtained (after ~20 min), heating was continued for a further 20 min followed by cooling to rt and evaporation of the solvent. TFAA (10 mL) was added, followed by DCM (10 mL) 3 min later to affect dissolution, thus ensuring efficient mixing of the thick, sticky residue with the anhydride. The resultant mixture was stirred at rt for an additional 45 min and evaporated to dryness. The residue was taken up in DCM (100 mL) and washed with PBS buffer pH 7.4 (2 × 100 mL) and the organic layer dried over $MgSO_4$, filtered and evaporated. Flash column chromatography on silica gel, eluted with 40–50–60% DCM–hexane, afforded 2-thienyl-4-phenyl-5-(trifluoroacetylamino)thiazole **8c** as a yellowish solid (324 mg, 46%).[12]

Representative deprotection procedure (*product* **1c**): Compound **8c** (296 mg, 0.84 mmol) was stirred in 3 M NaOH (15 mL) at 70 °C for 3 d. The reaction mixture was diluted with water then extracted into ethyl acetate (2 × 30 mL) and the combined organic extracts washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. 2-Thienyl-4-phenyl-5-aminothiazole **1c** was obtained as a brownish solid (174 mg, 81%).[13]

Acknowledgements

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12. Analytical data for compound **8c**: ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.13 (br s, 1H), 7.82–7.69 (m, 4H), 7.54–7.37 (m, 3H), 7.19 (dd, 1H, $^{3}J_{H-H} = 3.7$ Hz, 4.9 Hz). ^{19}F NMR (235 MHz, DMSO-d_6): δ −72.9. ^{13}C NMR (125 MHz, DMSO-d_6): δ 156.6, 156.0 (q, $^{2}J_{C-F} = 37.6$ Hz), 146.3, 136.3, 132.9, 129.4, 128.7, 128.6, 128.5, 127.8, 127.6, 115.7 (q, $^{1}J_{C-F} = 286$ Hz). HRMS (ES+) m/z calcd for $C_{15}H_{10}F_3N_2OS_2$ $[M+H]^+$ 355.0187, obs. 355.0170.
13. Analytical data for compound **1c**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.77–7.71 (m, 2H), 7.48–7.40 (m, 2H), 7.35–7.28 (m, 3H), 7.03 (dd, 1H, $^{3}J_{H-H} = 3.7$ Hz, 4.9 Hz), 3.66 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.2, 140.9, 137.8, 135.7, 134.2, 128.8, 127.6, 127.3, 127.1, 126.4, 124.9. HRMS (ES+) m/z calcd for $C_{13}H_{11}N_2S_2$ $[M+H]^+$ 259.0364, obs. 259.0356.