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Versatile assembly of 5-aminothiazoles based on the Ugi four-component coupling

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ABSTRACT

A flexible route to novel 5-aminothiazoles has been developed based on cyclisation of diamide adducts, prepared using the Ugi reaction, in the presence of Lawesson's reagent. The Walborsky reagent (1,1,3,3-tetramethylbutyl isocyanide) was used as the isonitrile component, facilitating subsequent deprotection of the *N*-alkyl group to yield free 5-aminothiazoles, which were prepared with a variety of substituents at the 2- and 4-positions.

1. Introduction

The thiazole ring occurs widely in structures of pharmaceutical interest together with many natural products.[1] Of the amino-substituted derivatives, 2-aminothiazoles have been extensively studied due to their ease of synthesis, whereas the related 5-amino compounds remain comparatively unexplored.

Aside from our recent discovery of 2,4-diphenylthiazolyl-5-amides **1** as antiprion agents[2] (Fig. 1), only a handful of other libraries containing the 5-aminothiazole substructure have been reported. Compounds of type **2** displayed potential as novel antibacterial and antifungal agents through inhibition of methionine aminopeptidases,[3] and those of type **3** were investigated as thymidylate synthase inhibitors possessing antitumour activity.[4] Other than these small libraries, only a handful of other examples are to be found as members of wider-ranging screening sets. In order to progress our SAR studies with second-generation analogues of active compounds **1**, a synthetic route was required which would permit easy variation of the 2- and 4-substituents using readily available starting materials.

Our reported route[5] (Scheme 1) to 4-phenyl-5-aminothiazoles **6**, from N-acylated glycinamides **4** via trifluoroacetamides **5**, meets this requirement in terms of variation at the 2-position but is rather inflexible with regard to the 4-position, since differently substituted glycinamides are not easily available as building blocks.

To address this deficiency, we assumed that precursors to general 5-aminothiazoles **7** (Scheme 2) could readily be accessed via

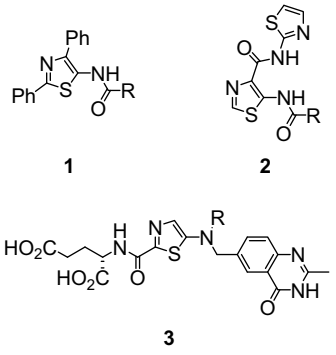
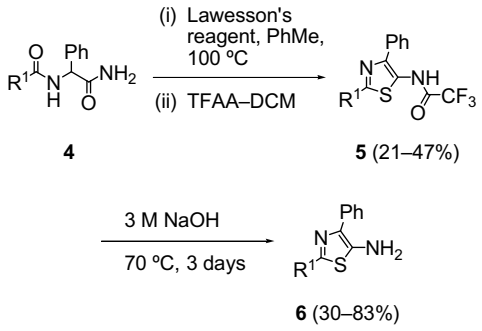


Figure 1. Biologically active 5-aminothiazoles.



Scheme 1. Synthesis of 4-phenyl-5-aminothiazoles from N-acylated phenylglycinamide derivatives.[5]

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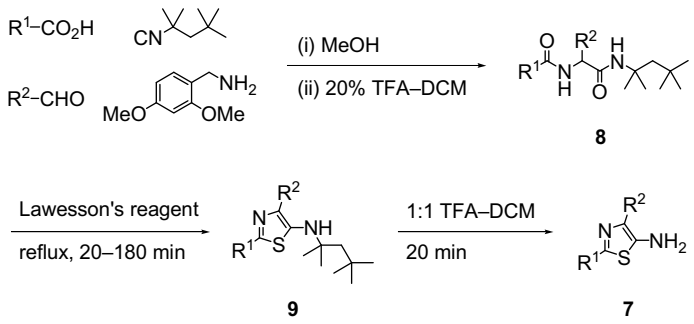


Scheme 2. Synthesis of 2,4-disubstituted 5-aminothiazoles from Ugi adducts **8**.[5]

the Ugi four-component coupling[6–8] (Ugi 4-CC) given a suitable protection strategy. The Walborsky reagent (1,1,3,3-tetramethylbutyl isocyanide) was chosen as the isonitrile component since the *N*-alkyl group is easily removable from the penultimate product, as demonstrated by the successful application of this reagent in a related multicomponent synthesis of 3-aminoimidazo-[1,2-a]pyridines.[9–11] It was also used as a cleavable isonitrile in the synthesis of α-aminomethyl tetrazoles.[12] Since an ammonia equivalent was also required,[13] 2,4-dimethoxybenzylamine was employed for this purpose.[14] In this case the 2,4-dimethoxybenzyl (DMB) group is straightforward to remove after the Ugi 4-CC by treatment with TFA. Thus, a one-pot route to diamide intermediates **8** with considerable scope for variation of substitution was realised.

Cyclisation to *N*-protected 5-aminothiazoles **9** was then addressed. Optimisation reactions were carried out using **8a** as substrate (R^1 = Ph; R^2 = thiophen-2-yl, Table 1). Refluxing with Lawesson's reagent in toluene resulted in efficient thionation but little formation of the thiazole. In line with Lawesson's brief initial studies on glycine derivatives,[15] we found that a higher temperature reflux in *m*-xylene was required to drive the cyclisation, conversion to **9a** being essentially complete in 1 h.

As in our earlier work, we found that incorporation of an aqueous work-up prior to column chromatography markedly improved the isolated yield. Extending the reaction time offered little advantage. Finally, we observed that using a larger excess of Lawesson's reagent had a negative effect upon the yield. Thus, the optimum protocol for conversion of **8a** to **9a** was established as a one hour reflux in *m*-xylene, using 1.2 equiv of Lawesson's reagent and incorporating an aqueous workup before purification by column chromatography.

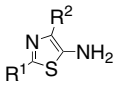
Deprotection of the *N*-(1,1,3,3-tetramethylbutyl) group proceeded rapidly in the presence of TFA to give the desired 5-amino-

Table 1
Optimisation results for cyclisation of diamide **8a** (R^1 = Ph, R^2 = thiophen-2-yl) to thiazole **9a**

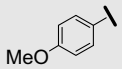
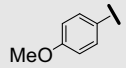
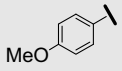
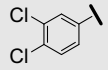
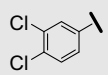
Solvent[a]	*t*, min	Aqueous work-up[c]	Thiazole **9a**, %	Thioamide, %
Toluene	20	N	8	70
m-Xylene	20	N	39	29
m-Xylene	60	N	37	6
m-Xylene	60	Y	52	n.d.
m-Xylene	180	N	55	n.d.
m-Xylene	180	Y	59	n.d.
m-Xylene[b]	180	Y	49	n.d.

[a] All reactions carried out with 1 mmol **8a** and 1.2 mmol Lawesson's reagent at reflux, under N_2, in the solvent stated (20 mL).
[b] 1.6 mmol Lawesson's reagent used.
[c] Refers to partitioning of crude product between DCM and satd $NaHCO_3$ followed by separation and drying of organic extract.

Table 2
Isolated yields obtained for the three-step synthesis shown in Scheme 2 with differing substituents R^1 and R^2



7a–m

	R^1	R^2	8, %	9, % (*t*, h)	7, %
a			45	59 (3) 55 (1)	50
b			75	32 (3)	46
c			40	54 (3)	42
d			57	28[b] (1)	30
e			76	21 (3) 32 (1)	69
f			74	48 (3)	36
g			69	30 (3)	51
h			89	31 (3)	41
i			29[a]	36 (3)	55
j			45	72 (3) 15 (1)	40[c]
k			44	36 (3) 15 (1)	47
l			74	32 (3)	46
m			41	38 (1)	30

[a] Synthesised using PMB protection.
[b] No aqueous work-up, as hydrolysis of the furan was observed in this case.
[c] 52% yield based on recovered starting material (incomplete conversion).

thiazole **7a**. A range of aromatic and aliphatic substituents at the R^1 and R^2 positions were then investigated in order to evaluate the scope of our synthetic procedure (Table 2).

Ugi 4-CC products **8a**–**m** were produced smoothly in moderate to good isolated yields, mostly being recovered without the need for chromatography. Compound **8i** was not directly accessible by this method, however, as it was isolated still in DMB-protected form. The presence of the 3-pyridyl substituent arrested the TFA-mediated deprotection in this case, and neither could removal of the DMB group be achieved using buffered potassium persulfate in aqueous media.[16] Instead, the Ugi 4-CC was repeated with 4-methoxybenzylamine and the PMB protecting group was cleaved successfully using CAN to afford **8i** in 29% overall yield.

The cyclisation step appears to be quite general, though further investigation of optimum heating time with other examples (**9j**–**k**) revealed the longer 3 h reflux to be advantageous. The exception to this was when the product bore an aliphatic substituent (**9e**), presumably due to thermal instability of this particular compound under extended heating. Indeed, no obvious trend was identifiable in the isolated yields with respect to electron donating or withdrawing characteristics of the 2- and 4-substituents (R^1 and R^2) being introduced. It is thus probable that the cyclisation yields are primarily dictated by the thermal stability of each individual compound at the high temperature necessary to drive the reaction.

Deprotection of cyclised products **9a**–**m** to the corresponding free 5-aminothiazoles **7a**–**m** was achieved using a short (20 min) treatment with 50% TFA in DCM, resulting in acceptable yields in most cases. One notable exception was **7d**, isolated in low yield as might be expected given the acid sensitivity of the 2-furyl group. Though both aliphatic and aromatic substituents are well-tolerated at the 2-position (R^1), only aryl groups may be reliably introduced at the 4-position (R^2). When we tried to incorporate an aliphatic group at this position (R^2 = cyclohexyl or 2-phenylethyl), deprotection of intermediates **9** gave very low crude yields (<20%) of impure 5-amino compounds **7**, and any further attempted purification resulted in decomposition. We therefore concluded that free 5-aminothiazoles **7** bearing an aliphatic substituent at the 4-position (R^2) are unstable, even though their *N*-protected counterparts **9** may be isolated successfully.

Nonetheless, despite modest yields in most cases, we found that this new synthetic method offered a viable route to a range of novel 2,4-disubstituted 5-aminothiazoles in sufficient quantities to be carried forward as building blocks in parallel library synthesis. By way of example, scale-up of the preparation of **7a** and **7e** proved quite practicable.

Though a one-pot, multicomponent-based assembly of thiazole libraries was previously developed by Dömling,[17] this approach focused upon varying the substituent at the 2-position only. Thus, the strategy reported herein builds upon previously documented multicomponent approaches to the thiazole ring by allowing a novel entry to 5-aminothiazoles with full control over substitution at the 2- and 4-positions. The substituents introduced at these positions are derived from simple and widely variable building blocks. Though yields are modest, the route offers access to a large number of diverse new compounds, based around this pharmaceutically relevant substructure, which would otherwise be considerably more difficult to prepare by alternative routes.

2. Experimental

2.1. Representative Ugi procedure

2,4-Dimethoxybenzylamine (751 μL, 836 mg, 5 mmol) was added to a solution of thiophene-2-carboxaldehyde (467 μL, 561 mg, 5 mmol) in methanol (2 mL). After stirring for 30 min, additional methanol (2 mL) was added followed by 4-fluorobenzoic acid (700 mg, 5 mmol) and finally 1,1,3,3-tetramethylbutyl isocyanide (877 μL, 696 mg, 5 mmol). The reaction mixture was stirred at room temperature overnight, then evaporated to dryness. The crude intermediate so obtained was stirred in TFA/DCM (1:4, 10 mL) for 1 h, then evaporated, and the sticky residue was triturated with satd aq $NaHCO_3$. A small amount of ether (approximately 5 mL) was added to the mixture and trituration continued until the initially sticky gum had precipitated as a solid, which was collected by filtration and washed successively with satd aq $NaHCO_3$ (×3), water (×2), then ether (2 × 10 mL). Pure product was isolated by washing through the sinter slowly with chloroform (4 × 30 mL) and drying the solution over $MgSO_4$, then evaporating to afford **8c**[18] as an off-white solid (0.78 g, 40%).

2.2. Representative cyclisation procedure

The diamide starting material **8c** (0.75 g, 1.92 mmol) was suspended in anhydrous *m*-xylene (40 mL) under N_2, together with Lawesson's reagent (0.93 g, 2.30 mmol). The mixture was heated at reflux for 3 h, then the solvent was removed by rotary evaporation and the residue taken up in DCM, washed with satd aq $NaHCO_3$, dried over $MgSO_4$ and evaporated once more. The crude product was purified by flash column chromatography on silica gel, eluted with 2% then 4% ethyl acetate–hexane, yielding thiazole **9c**[19] as a thick, bright yellow oil (0.40 g, 54%) which slowly crystallised on standing to give a pale yellow solid.

2.3. Representative deprotection procedure

The *N*-(1,1,3,3-tetramethylbutyl)amine **9c** (0.38 g, 0.98 mmol) was dissolved in 1:1 TFA/DCM (8 mL) and stirred for 20 min at room temperature, then the reaction mixture was evaporated. The residue was taken up in DCM and washed with satd aq $NaHCO_3$, then the organic layer was dried over $MgSO_4$ and evaporated. Following column chromatography on basic alumina, eluted with 20% then 33% then 50% ethyl acetate–hexane, free amine **7c**[20] was isolated as a pale brown powder (114 mg, 42%).

Acknowledgement

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Supplementary data

Supplementary data associated with this article (full experimental details, together with characterisation data and NMR spectra for all compounds) can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.067.

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13. On the suggestion of a reviewer, we attempted direct synthesis of **8a** by an Ugi 4-CC using ammonia as the amine component. The desired product was obtained in a modest 36% yield, but this single step method did not prove general. Attempted preparation of **8e** and **8k** by the same procedure resulted in the formation of product mixtures, necessitating separation by column chromatography. After purification, **8e** and **8k** were isolated only in rather low yields (26% and 16%, respectively). For example uses of ammonia in the Ugi reaction, see: (a) Pick, R.; Bauer, M.; Kazmaier, U.; Hebach, C. *Synlett* **2005**, 757–760; (b) Banfi, L.; Basso, A.; Damonte, G.; De Pellegrini, F.; Galatini, A.; Guanti, G.; Monfardini, I.; Riva, R.; Scapolla, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1341–1345; (c) Simoneau, C. A.; George, E. A.; Ganem, B. *Tetrahedron Lett.* **2007**, *47*, 1205–1207.
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18. ^{1}H NMR (400 MHz, $CDCl_3$) 7.90–7.83 (m, 2H), 7.61 (d, 1H, J = 6.5 Hz), 7.29–7.27 (m, 1H), 7.18 (d, 1H, J = 3.0 Hz), 7.12 (t, 2H, J = 8.6 Hz), 6.98 (dd, 1H, J = 3.5 Hz, 5.0 Hz), 5.96 (s, 1H), 5.86 (d, 1H, J = 6.5 Hz), 1.79–1.60 (m, 2H), 1.43–1.41 (m, 6H), 0.91 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) 167.5, 165.5, 165.0 (d, J = 251 Hz), 141.0, 129.9, 129.6, 129.5, 126.9, 126.6, 125.9, 115.6 (d, J = 22.0 Hz), 56.1, 53.4, 52.2, 31.5, 31.2, 28.9, 28.4. ν_{max} (solid)/cm^{-1} 3280, 2957, 1632, 1547, 1502, 1226, 848, 693. m/z (ES), 397 ([M+H]$^+$); HRMS, found 391.1864 ($C_{21}H_{28}FN_2O_2S$, [M+H]$^+$, requires 391.1856).
19. ^{1}H NMR (400 MHz, $CDCl_3$) 7.94–7.89 (m, 2 H), 7.51 (d, 1H, J = 3.5 Hz), 7.31–7.28 (m, 1H), 7.16–7.09 (m, 3H), 3.96 (s, 1H), 1.76 (s, 2H), 1.45 (s, 6H), 1.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) 163.3 (d, J = 248 Hz), 154.5, 140.2, 138.0, 135.5, 130.4, 127.5, 127.4, 127.2, 123.9, 123.8, 115.8 (d, J = 22.0 Hz), 57.3, 53.1, 31.7, 31.6, 29.5. ν_{max} (solid)/cm^{-1} 3293, 2952, 1226, 1150, 831, 698. m/z (ES), 389 ([M+H]$^+$); HRMS, found 389.1510 ($C_{21}H_{26}N_2FS_2$, [M+H]$^+$, requires 389.1521).
20. ^{1}H NMR (250 MHz, $CDCl_3$) 7.88–7.79 (m, 2H), 7.38 (dd, 1H, J = 1.5 Hz, 4.0 Hz), 7.31 (dd, 1H, J = 1.5 Hz, 5.5 Hz), 7.17–7.05 (m, 3H), 3.76 (s, 2H). ^{13}C NMR (62.8 MHz, $CDCl_3$) 163.4 (d, J = 249 Hz), 152.6, 140.3, 137.7, 132.4, 130.1, 128.4, 127.6, 127.5, 124.1, 123.3, 115.9 (d, J = 22.0 Hz). ν_{max} (solid)/cm^{-1} 3276, 1605, 1502, 1434, 1224, 972, 834, 694. m/z (ES), 277 ([M+H]$^+$); HRMS, found 277.0272 ($C_{13}H_{10}FN_2S_2$, [M+H]$^+$, requires 277.0269).