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Introduction

A 2-aminothiazole unit is a common feature of many biologically active molecular series,¹ such as cephalosporin antibiotics, kinase inhibitor anticancer agents and non-steroidal antiinflammatory drugs, Fig. 1. It has been suggested that 2-aminothiazole substitution favourably affects both the activity profile and absorption properties.^{2,3} Although a thiazole unsubstituted at both C(4) and C(5) is regarded as a metabolic risk,⁴ this danger is readily averted by appropriate substitution, especially with electron-withdrawing substituents.⁵

One important class of broad spectrum antiinfective 2-aminothiazole derivatives are the thiazolides, or [2-hydroxyaroyl-*N*-(thiazol-2-yl)-amides], typified by nitazoxanide **1a** which was first reported in 1975 (Fig. 2).⁶ To this day **1a** remains the antiparasitic agent of choice against *Cryptosporidium* spp.⁷ It was later discovered that **1a** and other analogues, notably the 5chloro analogue **1b**, were broad-spectrum antiviral agents,⁸⁻¹⁰ dating from the use of **1a** in treating cryptosporidiosis in AIDS patients.

Convenient syntheses of 2-acylamino-4halothiazoles and acylated derivatives using a versatile Boc-intermediate[†]

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The 2-aminothiazole grouping is a significant feature of many series of biologically active molecules, including antibiotics, anticancer agents and NSAIDs. We have a longstanding interest in the synthesis and biological evaluation of thiazolides, *viz.* [2-hydroxyaroyl-*N*-(thiazol-2-yl)-amides] which have broad spectrum antiinfective, especially antiviral, properties. However, 2-amino-4-substituted thiazoles, especially 4-halo examples, are not easily available. We now report practical, efficient syntheses of this class from readily available pseudothiohydantoin, or 2-aminothiazol-4(5*H*)-one: the key intermediate was its Boc derivative, from which, under Appel-related conditions, Br, Cl and I could all be introduced at C(4). Whereas 2-amino-4-Br/4-Cl thiazoles gave low yields of mixed products on acylation, including a bis-acyl product, further acylation of the Boc intermediates, with a final mild deprotection step, afforded the desired thiazolides cleanly and in good yields. In contrast, even mild hydrolysis of 2-acetamido-4-chlorothiazole led to decomposition with fast reversion to 2-aminothiazol-4(5*H*)-one. We also present a correction of a claimed synthesis of 2-acetamido-4-chlorothiazole, which in fact produces its 5-chloro isomer.

We have described the structure–activity relationships (SAR) of a wide range of thiazolides against hepatitis B, hepatitis C and influenza A viruses.^{11–13} Against a typical H1N1 strain of influenza A virus, compound **1a** shows $IC_{50} = 3.3 \mu M$ and **1b** shows $IC_{50} = 3.4 \mu M.^{13b}$ Clinical trials of **1a** have been performed against rotavirus¹⁴ and acute uncomplicated influenza A.^{15*a*,*b*} More recently, the SARS-CoV2 pandemic led to a strong resurgence of interest in small molecule antivirals, and NTZ has shown notable activity in trials against SARS-CoV2.¹⁶ The active circulating metabolites of **1a**/1b *in vivo* are the free phenols **2a**/**2b**, of which the phenolic acetates are prodrugs.¹⁷ Later we prepared more efficient, amino-acid ester prodrugs **3a**/3b, which were shown to offer greatly improved bioavailability compared to **1a**/1b.¹⁸

In general, 5-substituted thiazolides such as 1a/1b are the easiest to obtain. The natural position of electrophilic substitution of a 2-aminothiazole is at position 5, even when the 2-amine is acylated. In order to synthesise thiazolides with a 4-substituent, including 4-halo examples, various methods are possible: the 4-sulfonyl thiazolide 4 was synthesised from a thioester.^{13b}

One approach to a 2-amino-4-bromothiazole uses the halogen dance rearrangement from a protected 5-Br thiazole, as originally described by Stangeland and Stanetty (Scheme 1),^{19,20} employing LiNPr_2^{i} in THF. The rearrangement of 5 to 6 is considered to proceed *via* the *N*, *C*(5)-dianion which is thermodynamically preferred (Scheme 1, lower). This proved

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Cefotaxime *Broad spectrum antibiotic*

Dasatinib *Kinase inhibitor/ Anticancer*



Meloxicam Non-steroidal antiinflammatory

Fig. 1 Examples of (2-aminothiazole) containing drugs.



Fig. 2 Thiazolide structures.



Scheme 1 Synthesis of 2-Boc-amino, 4-bromothiazole by halogen rearrangement. Conditions: (i) $LiNPr_2^i$, THF, 0–10 °C, 20 min, 91%.

a robust procedure, but on removal of the Boc group the free amine 7, Fig. 3, proved rather unstable and difficult to acylate, in contrast to 2-amino-5-bromothiazole.

The literature on 2-amino-4-chlorothiazole **8** is limited,^{21,22} and here again, though we were able to reproduce one synthesis of this material in very low yield,²¹ we found **8** was unstable as the free base and difficult to acylate, giving mixed products.

The acidity of the amide NH in thiazolides such as **1a** and **1b** suggested an alternative route to 4'-substituted thiazolides, *viz.* further acylation of *N*-protected versions of **7** and **8**, followed by mild deprotection. We now report that *t*-butyl (4-*oxo*-4,5-dihydrothiazol-2-yl)carbamate is an ideal, versatile precursor for such derivatives.



Discussion

Acylation of 2-amino-4-bromo and 2-amino-4-chlorothiazole

Treatment of Boc derivative 6^{20} with TFA in CH₂Cl₂, followed by basification with NaHCO₃ and extraction, afforded the free amine 7 in 94% yield, which proved rather unstable on storage and was used immediately, Scheme 2. Reaction of 7 with *O*-acetylsalicyloyl chloride **9** using two-phase acylation conditions^{11,12} was quite unsuccessful. Instead, anhydrous acylation in THF using Et₃N as base gave a slow, complex reaction. Workup after 46 h at 20 °C gave two major products by chromatography, from which the desired thiazolide **10** was isolated in 17% yield and purified by recrystallisation. A major byproduct was apparently the acetamide **11** (*m*/*z* 221, 223) though this was difficult to purify fully.

Similarly, anhydrous acylation of 2-amino-4-chlorothiazole 8²¹ with 9 again gave a slow complex reaction. By chromatography, the desired thiazolide 12 was obtained in 19% yield and further purified by recrystallisation. A significant more polar product proved to be a bis-acylated derivative 13, which interestingly possessed a bis-acylamino rather than a tautomeric acylimino structure, as shown by single crystal X-ray analysis, Fig. 4. We therefore turned to alternative 2-aminothiazole intermediates.

Protected forms of pseudothiohydantoin

N-(4-*Oxo*-4,5-dihydrothiazol-2-yl)acetamide and its chlorination. Pseudothiohydantoin 14, sc. 2-aminothiazol-4(5*H*)-one,



Fig. 4 Single crystal X-ray structure of (((4-chlorothiazol-2-yl)azanediyl)bis(carbonyl))bis(2,1-phenylene) diacetate 13.

is commercially available or easily prepared from thiourea and bromoacetic acid in a typical Hantzsch synthesis,²³ and carries built-in 4-substitution. As noted above, heating 14 with excess $POCl_3^{21}$ gave a very low yield of 2-amino-4-chlorothiazole 8.

We therefore studied *N*-protected versions of **14**, aiming first at the acetamide, Scheme 3. Heating **14** with Ac₂O/AcOH²⁴ led to a very slow reaction, even at 100–105 °C, so we switched to amine bases. Treatment of **14** with Ac₂O and DMAP in THF at 20 °C gave a steady reaction and delivered very largely the previously unknown *N*, *O*-diacetate **15** in high yield; its structure was confirmed by a single crystal X-ray determination, Fig. 5, since other tautomeric products were possible. The use of Et₃N gave a mixture of products including **15** and the desired monoacetamide.



Scheme 2 Acylation of 2-amino-4-bromo and 2-amino-4-chlorothiazole. Conditions: (i) THF, Et₃N, 0 °C-20 °C.



Scheme 3 (2-Acetamido)thiazole intermediates. Conditions: (i) Ac₂O, DMAP, THF, 0–20 °C, 22 h, 81%; (ii) Ac₂O, *N*–Me morpholine, THF, 60 °C, 1.5 h, 83%; (iii) POCl₃, MeCN, 50 °C, 3 h, 57% or NCS, Ph₃P, MeCN, 20 °C, 5 h, 72%.



Fig. 5 Single crystal X-ray structures of 15 and 19. See ESI† for cif file data. The *syn*-orientation of the S atom and carbonyl oxygen in both cases results from nonbonding overlap between the C–S σ^* orbital and O lone pair electrons.²⁶

Use of the weaker base *N*-methylmorpholine at 60 °C gave a controlled reaction, which generated the desired acetamide **16** in very good yield with negligible diacetylation. Treatment of **16** with POCl₃ at 50 °C gave a very slow reaction until catalytic DMF was added; the 4-Cl compound **17**^{25*a*} was then isolated in satisfactory yield. The same product was obtained in 72% yield by reaction of **16** with Ph₃P and *N*-chlorosuccinimide (NCS) (1.5 eq. each; *cf.* next section) in MeCN at 20 °C. Another route claims chlorination of 2-acetamidothiazole using 'green' conditions, *viz.* NaCl and oxone,^{25*b*} but it is not clear whether the 4-Cl isomer **17** is the product since these authors' NMR data look significantly different from ours. The reaction of 2-aminothiazole with 1-chloro-1,2-benziodoxol-3-one²² was also stated to afford **17**.



Scheme 4 Synthesis of 2-acetamido-5-chlorothiazole. Conditions: (i) NCS, Amberlite A-15 (H⁺), 20 °C, 22 h, 65%.

To seek reassurance on the regiochemical point, we studied the direct chlorination of 2-acetamidothiazole **18** with NCS in MeCN, Scheme 4. We used a similar procedure once before on a thiazolide.¹¹ In fact this chlorination proceeded smoothly, using mild acid catalysis with Amberlyst A-15 (H^+) resin, and the product, isolated in unoptimised 65% yield, was shown to be the 5-Cl isomer **19** by a single crystal X-ray determination, Fig. 5. The ¹H and ¹³C NMR data of this material were identical with those reported^{25b} and claimed to be the 4-Cl isomer.

Under relatively mild conditions (HCl, aq. MeOH, 50 °C) we found that hydrolysis of 17 gave rapid decomposition with reversion to 14. This probably resulted from ring protonation at C(5) followed by attack of water at C(4).

Tert-Butyl (4-*oxo*-4,5-dihydrothiazol-2-yl)carbamate and its halogenation. We therefore switched to Boc protection, to allow for mild *anhydrous* acidolysis eventually. Boc pseudothiohydantoin is disclosed in the patent literature,^{27a} prepared by reaction of di-*t*-butyl pyrocarbonate (Boc₂O) with **14** in 15% yield using DMAP catalysis. Instead, using THF-water at pH 10 with Na₂CO₃ or NaOH, a clean conversion to the mono-Boc derivative was obtained: **20** was isolated in 86% yield, Scheme 5. Under these conditions, formation of any bis-adduct is minimal and excess Boc₂O is steadily hydrolysed. A later Pfizer patent^{27b} cited a similar yield by heating **14** with two equivalents of Boc₂O and no catalyst in THF at 60 °C for 48 h.

We anticipated that **20** would be readily enolised; hence reagents for the chlorination of other tautomeric hydroxy heterocycles such as 2-hydroxypyridine/2-pyridone under Appeltype conditions²⁸ should be effective. More recently, variants of the original Appel method using catalytic Ph_3PO^{29} and a sustainable procedure avoiding chlorinated solvents³⁰ have



Scheme 5 Conversion of pseudothiohydantoin to 2-Boc-amino-4-halothiazoles. Conditions: (i) Boc₂O, aq. THF, pH10, 86%; (ii) Ph₃P, Cl₃CCN, CH₂Cl₂, 73%; (iii) Ph₃P, NBS, MeCN, 63%; (iv) Ph₃P, NIS, MeCN, 28%. Alternative conditions discussed in text.

been described. Here, Ph_3P in conjunction with CCl_4^{31} (or preformed $Ph_3PCl_2^{32}$), *N*-chlorosuccinimide³³ or trichloroacetonitrile³⁴ all converted **20** into **21**. THF, CH_2Cl_2 and MeCN were all adequate solvents; the best and mildest conditions proved to be Ph_3P and $Cl_3C \cdot CN$ in CH_2Cl_2 at 20 °C, affording **21** in 73% yield.

For the introduction of Br at C(4), as noted earlier, the Br rearrangement ('halogen dance')^{20a,b} is feasible: the substrate (Scheme 1) is prepared from 2-amino-5-bromothiazole.³⁵ Here too, however, **20** proved a highly suitable intermediate, and on treatment with Ph₃P and *N*-bromosuccinimide^{33,34b} **6** was readily obtained.³⁶ Here the solvent choice was significant, with MeCN definitely superior to CH₂Cl₂, giving **6** in 63% yield. Another good reagent proved to be ethyl tribromoacetate,^{34b,37} again employing MeCN, which gave a virtually identical yield, though here purification was more difficult. It is noteworthy that MeCN often proves a superior solvent in the Appel-type halogenation reaction³⁸ and may even divert the reaction to other products.³⁹

2-Boc-amino-4-iodothiazole 22 was disclosed in a patent⁴⁰ as a useful intermediate for Suzuki couplings, but with no preparative detail. We obtained this compound in an unoptimised 28% yield by treatment of 20 with Ph_3P and *N*-iodosuccinimide at 0–20 °C; a little free I_2 was used to initiate the reaction.⁴¹

In Scheme 6 we give a mechanism for these halogenations, using $Cl_3C \cdot CN$ as the example donor, generating 21.

We also studied the reactions of both **16** and **20** with Middleton's DAST reagent,⁴² hoping to gain access to 4-fluoro derivatives: currently there is no reported preparation of







Scheme 6 Proposed halogenation mechanism with Cl₃C·CN.



Scheme 8 Thiazolide synthesis. Conditions: (i) Et₃N, THF, 61% for 23, 70% for 24; (ii) dil. CF₃CO₂H, CH₂Cl₂, 97% for 12, 65% for 10.

2-amino-4-fluorothiazole. Neither gave useful products; the reaction of **16** gave a low yield of a complex mixture and **20** gave rapid loss of the Boc group. A 4-fluorothiazole bearing a 5-formyl substituent was recently obtained²³ by displacement from a 4-chlorothiazole using S_NAr reaction with anhydrous Me_4N^+ F⁻, Scheme 7.

Acylation of Boc intermediates and thiazolide synthesis

The NH of compounds such as 21 is considerably more acidic than a typical amide⁴³ or even acetanilide ($pK_a = 13$),⁴⁴ and our previous experience had indeed shown that further *N*-acylation was possible. Using Et₃N as base, acylation of 21 with *O*-acetylsalicyloyl chloride cleanly afforded a 70% yield of the Boc intermediate 23 (Scheme 8). Mild acidolysis (dilute CF₃CO₂H, CH₂Cl₂) then delivered thiazolide 12 in near quantitative yield, identical to the product obtained in low yield by acylation of 8, Scheme 2.

This sequence was equally applicable to the bromo intermediate **6**, which *via* intermediate **24** gave **10**, *cf.* Scheme 2. Clearly this sequence represents the method of choice for the synthesis of **10** and **12**.

Conclusions

N-Boc protected forms of 2-amino-4-halothiazoles are readily available from Boc-pseudothiohydantoin, which is itself available from pseudothiohydantoin in high yield. The tendency of the heterocycle to exhibit tautomeric behaviour and to overreact with electrophiles is thus avoided. In general, N-halosuccinimides in conjunction with Ph₃P under Appel-type conditions are effective reagents for the halogenation step, but Cl₃CCN proved optimal for chlorination. Further acylation of these intermediates with O-acetylsalicyloyl chloride, followed by mild deprotection, offers high-yielding syntheses of 4-bromo and 4-chlorothiazolides. The relatively high acidity of amide NHs in derivatives such as 21 is significant: this bis-acylation/ mild deprotection sequence may well offer good alternative syntheses for other heterocyclic amides. Direct acylation of the corresponding free amines 7 and 8, by contrast, gave low yields of mixed products.

Experimental

General experimental procedures

Organic extracts were finally washed with saturated brine and dried over anhydrous Na_2SO_4 prior to rotary evaporation at <30 ° C. Moisture sensitive reactions were carried out in anhydrous organic solvents (purchased from Sigma-Aldrich) under a N_2 or

Ar atmosphere. Reactions were monitored by analytical thinlayer chromatography using Merck Kieselgel 60 F_{254} silica plates, and were viewed under UV or by staining with KMnO₄ or iodine. Preparative flash column chromatography was performed on either VWR Prolabo silica gel or Sigma-Aldrich silica gel (particle size 40–63 Å). Melting points were recorded using a Bibby-Sterlin Stuart SMP3 melting point apparatus and are uncorrected. Mass spectra were obtained in either electrospray mode (ES) with a Micromass LCT or chemical ionization (CI) mode with a Micromass Trio 1000 using ammonia. Elemental analyses were performed by Mrs Jean Ellis, University of Liverpool. ¹H and ¹³C NMR spectra were obtained using a Bruker Avance or a Bruker DPX 400 instrument operating at 400 and 100 MHz, respectively; chemical shifts are reported in Hz.

2-Amino-4-bromothiazole 7

A solution of *tert*-butyl (4-bromothiazol-2-yl)carbamate 6^{20} (0.56 g, 2 mmol) in CH₂Cl₂ (8 mL) was stirred at 20 °C with CF₃CO₂H (5 mL). After 4 h, the solution was evaporated to dryness, azeotroped with CH₂Cl₂ (2 × 5 mL) and the residue was partitioned between satd. aq. NaHCO₃ (20 mL) and CH₂Cl₂ (5 × 10 mL). Evaporation gave 7 as a white solid (0.336 g, 94%) which was progressed immediately; $\delta_{\rm H}$ (CDCl₃) 5.32 (2H, br s, NH₂) and 6.41 (1H, s, 5-H).

2-((4-Bromothiazol-2-yl)carbamoyl)phenyl acetate 10

Method A: a solution of 2-amino-4-bromothiazole 7 (0.42 g, 2.35 mmol) and O-acetylsalicyloyl chloride 9 (0.93 g, 4.69 mmol) in dry THF (10 mL) was stirred under N2 at 0 °C and Et3N (0.82 mL, 5.88 mmol) was added. The mixture was allowed to regain 20 °C, then after 23 h, 4- N,N-dimethylaminopyridine (0.12 g, 1 mmol) was added. After a total of 46 h, the mixture was diluted with EtOAc (20 mL) and worked up for a neutral product (0.93 g), which was chromatographed, eluting with a gradient of 30-50% EtOAc-nhexane. Evaporation of early-eluting fractions afforded title compound 10 (0.133 g) which was recrystallised from EtOAc-nhexane to afford pure product (0.100 g, 12.5%), m.p. 148-150 °C. Found: C, 42.3; H, 2.97; N, 7.96; S, 9.39; m/z, 362.9416. C₁₂H₉-BrN₂O₃S requires C, 42.25; H, 2.7; N, 8.2; S, 9.4%; m/z, 362.9415 $(MNa^{+}); \delta_{H} (CDCl_{3}) 2.46 (3H, s, CH_{3}CO), 6.92 (1H, s, thiazole 5-H),$ 7.40 (1H, d, Ar H), 7.63 (2H, m, Ar H), 8.04 (1H, d, Ar H) and 9.94 (1H, s, NH); $\delta_{\rm C}$ (CDCl₃) 21.3, 111.8, 121.3, 123.8, 124.4, 126.8, 130.9, 133.8, 148.5, 158.2, 162.4 and 168.3.

Later column fractions were pooled and evaporated to give a white solid (0.332 g) whose spectroscopic data were consistent Method B: a solution of Boc derivative **24** (0.292 g, 0.64 mmol, v. i.) in CH₂Cl₂ (2 mL) was stirred at 20 °C and CF₃CO₂H (0.3 mL, 4 mmol) was added dropwise. After 3 h, the solution was diluted with EtOAc (20 mL) and cautiously washed with satd. NaHCO₃ (10 mL). Standard workup afforded the title compound **10** as a white solid, essentially pure (0.147 g, 65%), m.p. 148–150 °C. Analytical and spectroscopic data were identical to those obtained by Method A.

2-((4-Chlorothiazol-2-yl)carbamoyl)phenyl acetate 12 and {[(4-chlorothiazol-2-yl)azanediyl]bis(carbonyl)]bis(2,1-phenylene} diacetate 13

Method A: 2-amino-4-chlorothiazole 8²¹ (0.135 g, 1 mmol) was dissolved in anhydrous THF (4 mL) and stirred at 20 °C with Oacetylsalicyloyl chloride 9 (0.24 g, 1.2 mmol) under N2. After addition of triethylamine (0.21 mL, 1.5 mmol), stirring was continued for 28 h then further acid chloride and triethylamine (1 mmol each) were added. After 96 h in all, the reaction was diluted with EtOAc (30 mL) and worked up for a neutral product, giving a pale orange gum (0.424 g). Chromatography, eluting with a gradient of 25-33% EtOAc in hexane, afforded firstly the mono-amide 12 (0.074 g, 25%), mp 148-149 °C. Found: C, 48.6; H, 3.0; N, 9.4; S, 10.6; m/z (ES +ve mode) 318.9918; C12H9ClN2O3S requires C, 48.6; H, 3.1; N, 9.4; S, 10.8%; $C_{12}H_9^{35}ClN_2O_3SNa$ (MNa⁺) requires m/z, 318.9920; δ_H (CDCl₃) 2.48 (3H, s, CH₃CO), 6.79 (1H, s, thiazole 5-H), 7.26 (1H, d, ArH), 7.42 (1H, t, ArH), 7.62 (1H, t, ArH), 8.07 (1H, d, ArH) and 9.92 (1H, br s, NH); $\delta_{\rm C}$ (CDCl₃) 21.3, 108.1, 123.8, 124.3, 126.8, 131.0, 133.9, 135.4, 148.4, 157.2, 162.3 and 168.2. Later column fractions were pooled and evaporated to afford the bis-amide 13 (0.077 g, 17%), m. p. 111-112 °C. Found: C, 55.0; H, 3.3; N, 6.1; S, 6.7; *m/z* (ES +ve mode) 481.0230; C₂₁H₁₅ClN₂O₆S requires C, 55.0; H, 3.3; N, 6.1; S, 7.0%; $C_{21}H_{15}^{35}ClN_2O_6SNa(MNa^+)$ requires m/z, 481.0237; $\delta_{\rm H}$ (CDCl₃) 2.35 (3H, s, CH₃CO), 7.07 (1H, s, thiazole 5-H), 7.08 (1H, d, ArH), 7.16 (1H, t, ArH), 7.42 (1H, t, ArH) and 7.57 (1H, d, ArH); $\delta_{\rm C}$ (CDCl₃) 21.1 (×2), 113.7 (×2), 123.4 (×2), 125.9, 126.8, 130.3, 133.5, 136.9, 148.5, 157.7, 167.2 and 168.7. Recrystallisation of 13 gave material of excellent crystalline form suitable for single crystal X-ray determination, q. v.

Method B: the *N*-Boc intermediate **23** (0.171 g, 0.43 mmol, v. i.) was dissolved in CH_2Cl_2 (3 mL) and stirred at 20 °C, then CF_3CO_2H (0.5 mL) was added over 1 min. Complete reaction was observed after 1 h; the solution was diluted with EtOAc (20 mL) and washed with satd. aq. NaHCO₃ (20 mL), giving an aq. pH~8, then the organic phase was further washed with water and evaporated to give the product **12** (0.124 g, 97%) as a white solid. Analytical and spectroscopic data were identical to those obtained by Method A.

N-(4-Oxo-4,5-dihydrothiazol-2-yl)acetamide 15

A suspension of pseudothiohydantoin 14 (0.50 g, 4.31 mmol) in THF (4 mL) and $Ac_2O(1 mL)$ was stirred at 20 °C during addition

of *N*-Me morpholine (1 mL), then heated at 65 °C for 1.5 h, when much solid had deposited. The mixture was cooled, treated with Et₂O (10 mL) and stored at 0 °C for 1 h, then filtered, washed with Et₂O, dried and evaporated to give essentially pure product **15** as a pale brown solid (0.565 g, 83%); an analytical sample was obtained by recrystallisation from MeOH-EtOAc. Found: C, 38.1; H, 3.8; N, 17.8; S, 20.15; *m/z* (CI, CH₄) 159.0228. C₅H₆N₂O₂S requires C, 38.0; H, 3.8; N, 17.7; S, 20.3%; C₅H₇N₂O₂S (MH⁺) requires *m/z*, 159.0223; $\delta_{\rm H}$ (d₆-DMSO) δ 2.19 (3H, s, CH₃CO), 3.85 (2H, s, CH₂CO) and 12.61 (1H, br s, NH); $\delta_{\rm C}$ (d₆-DMSO) 24.3, 37.1, 173.0, 182.6 and 188.2.

2-Acetamidothiazol-4-yl acetate 16

A suspension of pseudothiohydantoin 14 (0.5 g, 4.31 mmol) in THF (4 mL) and Ac₂O (1 mL) was stirred at 20 °C and *N*,*N*-dimethylaminopyridine (0.61 g, 5 mmol) was added. A yellow-orange solution gradually resulted, and after 6 h the mixture was stored at 0 °C for 16 h, then partitioned between EtOAc (30 mL + 10 mL) and 7% aq. citric acid (25 mL). The combined extracts were washed with brine, dried and evaporated to give the title compound 16 as a near-white solid (0.70 g, 81%). Found: C, 42.3; H, 4.0; N, 13.6; S, 15.8; *m*/*z* (CI, CH₄) 201.033; C₇H₈N₂O₃S requires C, 42.0; H, 4.0; N, 14.0; S, 16.0%; C₇H₉N₂O₃S (MH⁺) requires *m*/*z*, 201.0328; $\delta_{\rm H}$ (d₆-DMSO) δ 2.14, 2.26 (6H, 2s, 2xCH₃CO), 6.73 (1H, 5-H) and 12.18 (1H, br s, NH); $\delta_{\rm C}$ (d₆-DMSO) 21.1, 23.0, 97.1, 149.9, 156.2, 168.7 and 169.5.

N-(4-Chlorothiazol-2-yl)acetamide 17

A mixture of the acetamide **15** (0.40 g, 2.5 mmol) and POCl₃ (1 mL) in MeCN (4 mL) was heated with stirring at 50 °C; reaction was initiated by addition of DMF (3 drops). After 3 h, the mixture was cooled and partitioned between EtOAc (30 mL + 10 mL) and 10% aq. Na₂CO₃ which was added cautiously to give a pH of 8. The combined organic extracts were washed with H₂O, brine, dried and evaporated to give the title compound **17** (0.256 g, 57%) as a pale yellow solid, m. p. 144–145 °C (from EtOAc-hexane). Found: *m*/*z* (CI, CH₄) 176.9892. C₅H₆³⁵ClN₂OS (MH⁺) requires *m*/*z*, 176.9884; $\delta_{\rm H}$ (d₆-DMSO) δ 2.15 (3H, s, CH₃CO), 7.14 (1H, s, 5-H) and 12.36 (1H, br s, NH); (CDCl₃) 2.35 (3H, s, CH₃CO), 6.77 (1H, s, 5-H) and 10.93 (1H, br s, NH); $\delta_{\rm C}$ (d₆-DMSO) 22.9, 108.0, 133.8, 158.7 and 169.5; (CDCl₃) 23.4, 107.7, 134.1, 159.3 and 168.7.

N-(5-Chlorothiazol-2-yl)acetamide 19

A solution of 2-acetamidothiazole **18** (0.28 g, 2 mmol) in acetonitrile (5 mL) was stirred with *N*-chlorosuccimimide (0.27 g, 2.00 mmol) over Amberlite A-15 (H⁺) (0.5 g) at 20 °C. After 22 h, when much white solid had been deposited, EtOAc (40 mL) was added to give a clear solution which was decanted from the resin, washed with water and brine, dried over Na₂SO₄ and evaporated to give **19** as a white solid (0.229 g, 65%). Recrystallisation from EtOAc-hexane afforded material suitable for a single crystal X-ray structure determination, see Fig. 1, m. p. 200–202 °C (softened ~190 °C). Found: C, 33.9; H, 2.8; N, 15.8. C₅H₅ClN₂OS requires C, 34.00; H, 2.85; N, 15.86%; $\delta_{\rm H}$ 2.33 (3H, s, CH₃CO), 7.27 (1H, s, 4-H) and 11.80 (1H, br s, NH); $\delta_{\rm C}$ 22.9, 121.0, 133.5, 157.6 and 168.0.

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Tert-Butyl (4-oxo-4,5-dihydrothiazol-2-yl)carbamate 20

To a solution of pseudothiohydantoin 14 (1.0 g, 8.6 mmol) in 1 : 1 H₂O : THF (15 mL) was added Boc₂O (2.4 g, 11 mmol) followed by portionwise addition of NaOH (0.88 g, 22 mmol). The reaction mixture was stirred at 20 °C for 16 h, then partitioned between 7% aq. citric acid (30 mL) and CH₂Cl₂ (3 × 25 mL). The combined organic extracts were dried over MgSO₄, filtered and evaporated to dryness, to afford the title product **20** (1.60 g, 86%) as a pale-yellow solid which was sufficiently pure to progress directly; an analytical sample was obtained by recrystallisation from EtOAc-hexane, 1 : 1. Found: C, 44.5; H, 5.6; N, 12.9; S, 14.9; *m/z* (ES +ve mode), 239.0461. C₈H₁₂N₂O₅SN equires C, 44.4; H, 5.6; N, 12.95; S, 14.8%; C₈H₁₂N₂O₅SNa (MNa⁺) requires *m/z*, 239.0461; $\delta_{\rm H}$ (CDCl₃) δ 1.55 (s, 9H), 3.80 (s, 2H) and 9.61 (br s, 1H, NH); $\delta_{\rm C}$ (CDCl₃) δ 27.9, 36.4, 84.4, 153.6, 181.8 and 183.3.

tert-Butyl (4-chlorothiazol-2-yl)carbamate 21

A solution of carbamate **20** (0.54 g, 2.50 mmol) and triphenylphosphine (0.98 g, 3.75 mmol) in anhydrous CH₂Cl₂ (7.5 mL) was stirred at 20 °C under N₂ and trichloroacetonitrile (0.38 mL, 3.75 mmol) was added over one minute. After 40 h the mixture was diluted with Et₂O (30 mL), washed with H₂O (2×), brine, dried and evaporated to a clear gum. Chromatography, eluting with 20%EtOAc-hexane, afforded on evaporation of appropriate fractions the title compound **21** (0.425 g, 73%) as a white solid. Found: C, 41.0; H, 4.7; N, 11.9; S, 13.7; *m*/*z* (ES +ve mode), 257.0126. C₈H₁₁ClN₂O₂SN equires C, 40.9; H, 4.7; N, 11.9; S, 13.7%; C₈H₁₁³⁵ClN₂O₂SNa (MNa⁺) requires *m*/*z*, 257.0122; $\delta_{\rm H}$ (CDCl₃) 1.54 (9H, s, Me₃C), 6.65 (1H, s, 5-H) and 9.20 (1H, br s, NH); $\delta_{\rm C}$ (CDCl₃) 28.2, 83.0, 106.4, 134.4, 152.5 and 160.9.

tert-Butyl (4-bromothiazol-2-yl)carbamate 6 (ref. 20)

A solution of *N*-bromosuccinimide (0.32 g, 1.77 mmol, 1.5 eq.) in anhydrous MeCN (2.0 mL) was added dropwise to a suspension of the carbamate **20** (0.25 g, 1.17 mmol) and triphenylphosphine (0.46 g, 1.74 mmol) in the same solvent (3.0 mL) with stirring under N₂, then the reaction was stirred at 20 °C overnight. The reaction was quenched with H₂O (20 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with brine and dried over MgSO₄. Evaporation followed by column chromatography (5–10% ethyl acetate/hexane) afforded the title compound **6** as an off-white solid (0.20 g, 63% yield). Found: (ES +ve mode) *m/z*, 300.9618. C₈H₁₁⁷⁹BrN₂NaO₂S (MNa⁺) requires *m/z*, 300.9617; 1H NMR $\delta_{\rm H}$ (CDCl₃) 1.54 (9H, s, Me₃C), 6.79 (1H, s, 5-H) and 9.50 (1H, br s, NH); $\delta_{\rm C}$ (CDCl₃) 28.2, 83.2, 110.3, 120.4, 152.2 and 161.17.

tert-Butyl (4-iodothiazol-2-yl)carbamate 22

A solution of the carbamate **20** (0.22 g, 1 mmol) and Ph_3P (0.39 g, 1.5 mmol) in MeCN (5 mL) was treated with *N*-iodosuccinimide (0.34 g, 1.5 mmol) at 0 °C and allowed to warm to 20 °C. No reaction occurred until I₂ (0.25 g, 1 mmol) and further Ph_3P (0.26 g, 1 mmol) were added with continued stirring at 20 ° C. After a total of 22 h, EtOAc (30 mL) was added and the solution was washed with 5% aq. Na₂S₂O₃ (20 mL), water and brine, then dried and evaporated to a near colourless residue. Chromatography using 20% EtOAc-hexane afforded on evaporation of appropriate fractions the iodo compound **22** as a white crystalline solid (0.091 g, 28%). Recrystallisation from EtOAc-hexane afforded an analytical sample. Found: C, 29.7; H, 3.4; N, 8.8; S, 9.4. *m/z* (ES +ve mode): 348.9479. C₈H₁₁N₂O₂SI requires C, 29.5; H, 3.4; N, 8.6; S, 9.8%; C₈H₁₁IN₂O₂SNa (MNa⁺) requires *m/z*, 348.9478; $\delta_{\rm H}$ (CDCl₃). 1.55 (9H, s, Me₃C), 7.01 (1H, s, 5-H) and 8.8–9.2 (1H, br, NH); $\delta_{\rm C}$ (CDCl₃) 28.2, 83.3, 88.8, 117.6, 151.9 and 161.4.

2-[(*tert*-Butoxycarbonyl)(4-chlorothiazol-2-yl)carbamoyl] phenyl acetate 23

Compound 21 (0.175 g, 0.75 mmol) and O-acetylsalicyloyl chloride 9 (0.15 g, 0.75 mmol) were stirred in anhydrous THF (3 mL) under N₂ at 20 °C, then triethylamine (0.14 mL, 1 mmol) was added. After 22 h, when most 21 had reacted and some solid had been deposited, the mixture was diluted with EtOAc (20 mL) then washed successively with 7% aq. citric acid, satd. aq. NaHCO₃ and water, then evaporated to give a sticky solid (0.295 g). Chromatography, eluting with 20% EtOAc-hexane, afforded on evaporation of appropriate fractions the title compound 23 (0.181 g, 61%) as a white solid. Found: C, 51.3; H, 4.2; N, 6.9; S, 7.4; m/z (ES +ve mode) 419.0444; C₁₇H₁₇ClN₂O₅S requires C, 51.45; H, 4.3; N, 7.1; S, 8.1%; C₁₇H₁₇³⁵ClN₂O₅SNa (MNa⁺) requires m/z, 419.0439; δ_H (CDCl₃) 1.22 (9H, s, Me₃C), 2.24 (3H, s, CH₃CO), 6.94 (1H, s, thiazole 5-H), 7.14 (1H, dd, aryl H), 7.26 (1H, t, ArH), 7.49 (1H, t, ArH) and 7.63 (1H, dd, ArH); $\delta_{\rm C}$ (CDCl₃) 20.9, 27.4, 85.8, 112.7, 123.3, 126.1, 127.7, 130.3, 133.3, 136.4, 148.6, 150.2, 157.6, 166.6 and 168.8.

2-((4-Bromothiazol-2-yl)(*tert*-butoxycarbonyl)carbamoyl) phenyl acetate 24

2-(*t*-Butoxycarbonyl)amino-4-bromothiazole **6** (0.264 g, 0.95 mmol) was dissolved in THF (5 mL) with Et₃N (0.30 mL, 2.1 mmol) and treated with *O*-acetylsalicyloyl chloride **9** (0.35 g, 1.80 mmol) added portionwise at 20 °C with stirring. After 16 h, the reaction mixture was diluted with EtOAc (30 mL) and worked up for a neutral product, which was purified by chromatography, eluting with a gradient of 5 to 7.5% EtOAc in hexane to afford the title compound **24** (0.292 g, 70%). Found: *m*/*z* (ES +ve mode) 462.9937; C₁₇H₁₇BrN₂O₅SNa (MNa⁺) requires *m*/*z*, 462.9939; $\delta_{\rm H}$ (CDCl₃) 1.32 (9H, s, Me₃C), 2.34 (3H, s, CH₃CO), 7.19 (1H, s, thiazole 5-H), 7.24 (1H, d, Ar H), 7.36 (1H, t, Ar H), 7.58 (1H, t, Ar H) and 7.68 (1H, d, ArH); $\delta_{\rm C}$ (CDCl₃) 20.9, 27.4, 85.8, 116.5, 122.3, 123.2, 126.1, 127.8, 130.3, 133.2, 148.5, 150.2, 158.4, 166.6 and 168.8.

Crystallographic methods

Single crystals of $C_{21}H_{15}N_2O_6SCl$ **13**, $C_7H_8N_2O_3S$ **15** and C_5H_5 -ClN₂OS **19** were submitted for X-ray structural determination. A suitable crystal was selected and mounted on a MiTeGen tip using parabol oil and centred on a XtaLAB AFC12 (RCD3): Kappa single diffractometer. The crystal was kept at 100.01(10) K during data collection. Using Olex2,⁴⁵ the structure was solved with the ShelXT⁴⁶ structure solution program using Intrinsic Phasing and refined with the ShelXL⁴⁷ refinement package using Least Squares minimisation.

Crystallographic data

Cif files for compounds **13**, **15** and **19** have been deposited in the CCDC database, no. CCDC 2362657, CCDC 2330479 and CCDC 2330480, respectively. The full data files have been added to ESI.[†]

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts of interest to declare.

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