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# Convenient syntheses of 2-acylamino-4-halothiazoles 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 anti-infective, 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.

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## Introduction

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

One important class of broad spectrum anti-infective 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).<sup>6</sup> To this day **1a** remains the antiparasitic agent of choice against *Cryptosporidium* spp.<sup>7</sup> It was later discovered that **1a** and other analogues, notably the 5-chloro analogue **1b**, were broad-spectrum antiviral agents,<sup>8–10</sup> dating from the use of **1a** in treating cryptosporidiosis in AIDS patients.

We have described the structure–activity relationships (SAR) of a wide range of thiazolides against hepatitis B, hepatitis C and influenza A viruses.<sup>11–13</sup> Against a typical H1N1 strain of influenza A virus, compound **1a** shows IC<sub>50</sub> = 3.3 μM and **1b** shows IC<sub>50</sub> = 3.4 μM.<sup>13b</sup> Clinical trials of **1a** have been performed against rotavirus<sup>14</sup> and acute uncomplicated influenza A.<sup>15a,b</sup> 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.<sup>16</sup> The active circulating metabolites of **1a/1b** *in vivo* are the free phenols **2a/2b**, of which the phenolic acetates are prodrugs.<sup>17</sup> Later we prepared more efficient, amino-acid ester prodrugs **3a/3b**, which were shown to offer greatly improved bioavailability compared to **1a/1b**.<sup>18</sup>

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.<sup>13b</sup>

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),<sup>19,20</sup> employing LiNPr<sub>2</sub><sup>i</sup> 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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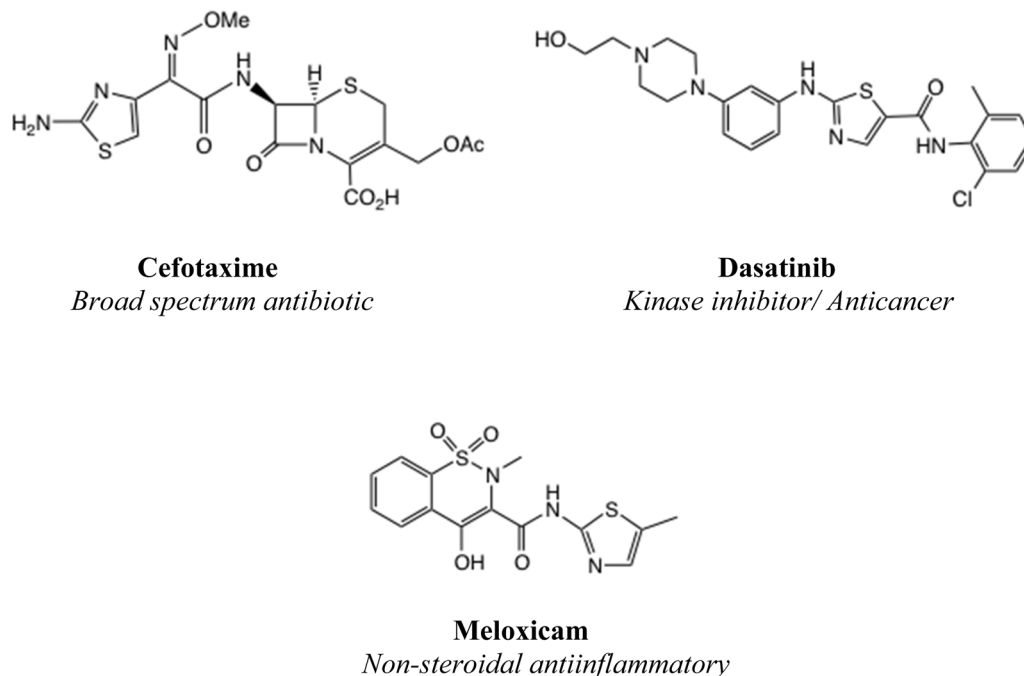


Fig. 1 Examples of (2-aminothiazole) containing drugs.

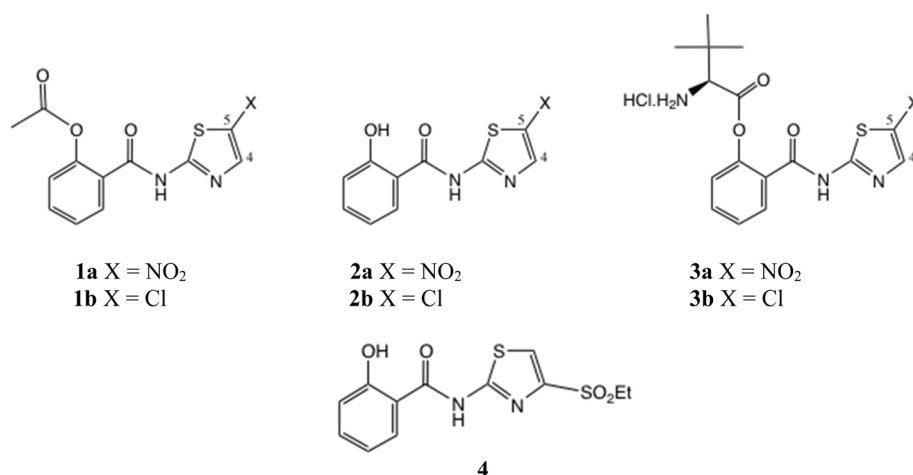
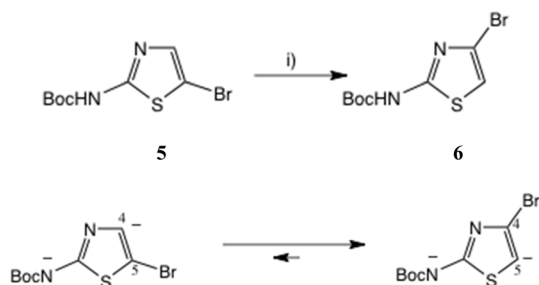


Fig. 2 Thiazolide structures.

Scheme 1 Synthesis of 2-Boc-amino, 4-bromothiazole by halogen rearrangement. Conditions: (i) LiNPr<sub>2</sub><sup>1</sup>, 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,<sup>21,22</sup> and here again, though we were able to reproduce one synthesis of this material in very low yield,<sup>21</sup> 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.



Fig. 3 2-Amino-4-halothiazoles.

## Discussion

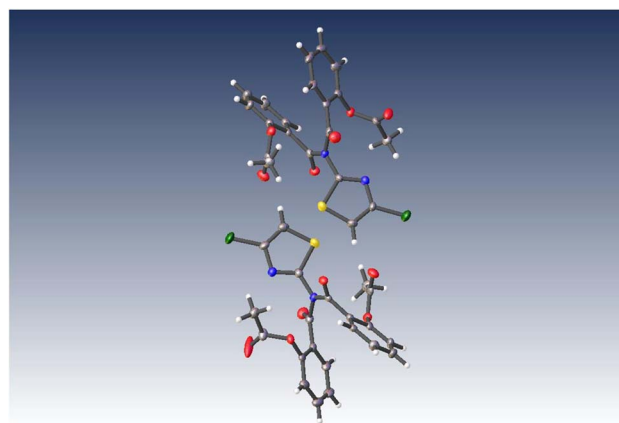
### Acylation of 2-amino-4-bromo and 2-amino-4-chlorothiazole

Treatment of Boc derivative **6**<sup>20</sup> with TFA in CH<sub>2</sub>Cl<sub>2</sub>, followed by basification with NaHCO<sub>3</sub> 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<sup>11,12</sup> was quite unsuccessful. Instead, anhydrous acylation in THF using Et<sub>3</sub>N as base gave a slow, complex reaction. Workup after 46 h at 20 °C gave two major products by chromatography, from which the desired thiazolidine **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 **8**<sup>21</sup> with **9** again gave a slow complex reaction. By chromatography, the desired thiazolidine **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,

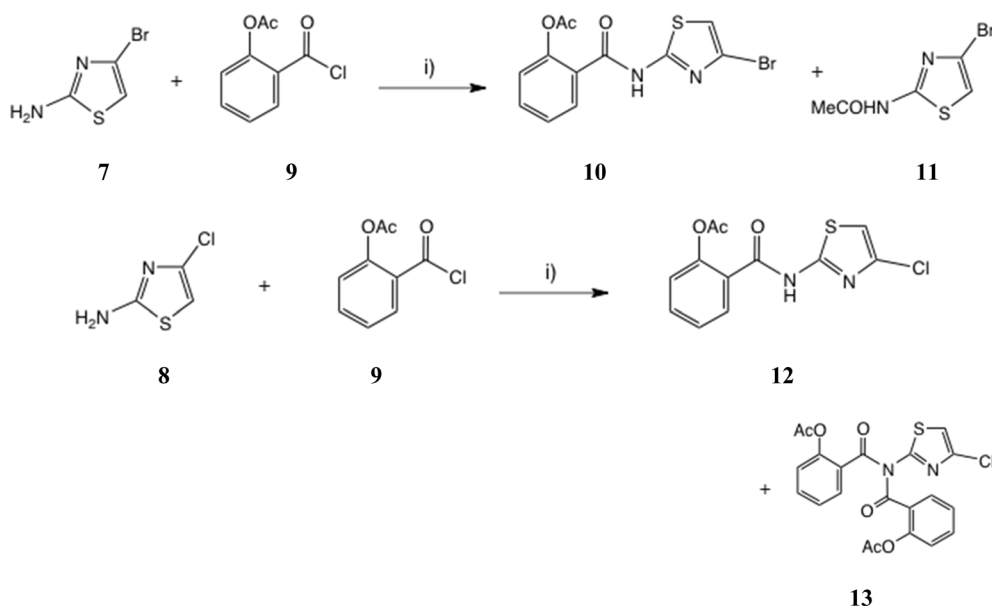


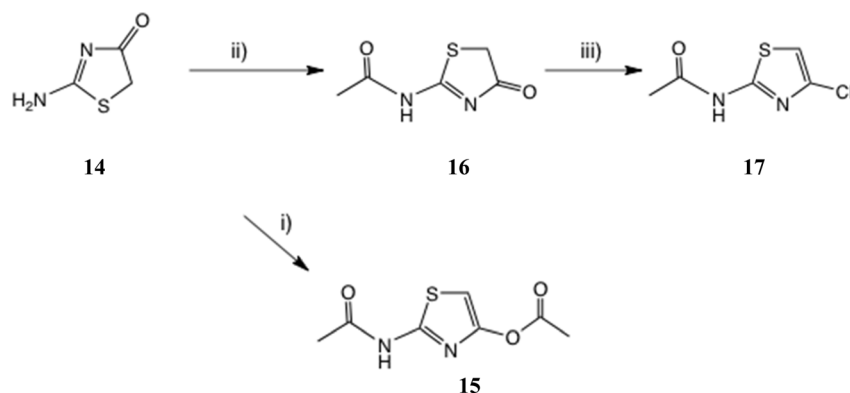
13

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

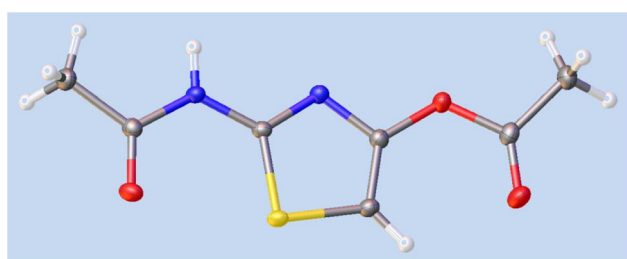
is commercially available or easily prepared from thiourea and bromoacetic acid in a typical Hantzsch synthesis,<sup>23</sup> and carries built-in 4-substitution. As noted above, heating **14** with excess POCl<sub>3</sub><sup>21</sup> gave a very low yield of 2-amino-4-chlorothiazole **8**.

We therefore studied *N*-protected versions of **14**, aiming first at the acetamide, Scheme 3. Heating **14** with Ac<sub>2</sub>O/AcOH<sup>24</sup> led to a very slow reaction, even at 100–105 °C, so we switched to amine bases. Treatment of **14** with Ac<sub>2</sub>O 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 Et<sub>3</sub>N gave a mixture of products including **15** and the desired monoacetamide.

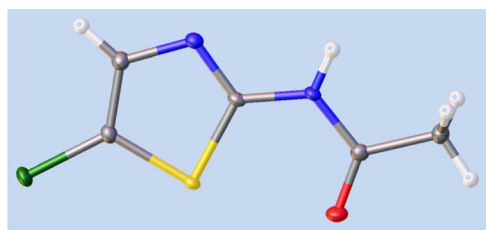
Scheme 2 Acylation of 2-amino-4-bromo and 2-amino-4-chlorothiazole. Conditions: (i) THF, Et<sub>3</sub>N, 0 °C–20 °C.



**Scheme 3** (2-Acetamido)thiazole intermediates. Conditions: (i)  $\text{Ac}_2\text{O}$ , DMAP, THF, 0–20 °C, 22 h, 81%; (ii)  $\text{Ac}_2\text{O}$ , *N*-Me morpholine, THF, 60 °C, 1.5 h, 83%; (iii)  $\text{POCl}_3$ , MeCN, 50 °C, 3 h, 57% or NCS,  $\text{Ph}_3\text{P}$ , MeCN, 20 °C, 5 h, 72%.



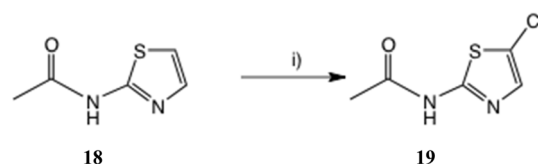
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19

**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  $\sigma^*$  orbital and O lone pair electrons.<sup>26</sup>

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  $\text{POCl}_3$  at 50 °C gave a very slow reaction until catalytic DMF was added; the 4-Cl compound **17**<sup>25a</sup> was then isolated in satisfactory yield. The same product was obtained in 72% yield by reaction of **16** with  $\text{Ph}_3\text{P}$  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,<sup>25b</sup> 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-one<sup>22</sup> was also stated to afford **17**.



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

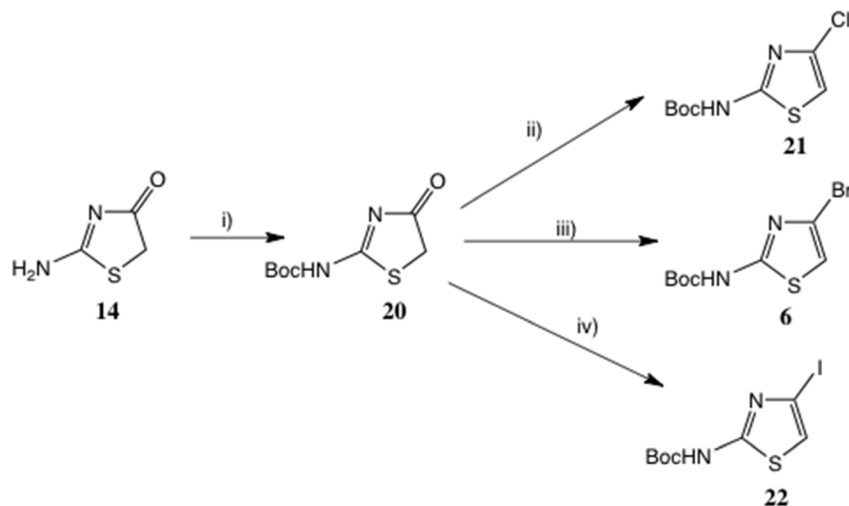
To seek reassurance on the regiochemical point, we studied the direct chlorination of 2-acetamidothiazole **18** with NCS in MeCN, Scheme 4. We used a similar procedure once before on a thiazolidine.<sup>11</sup> In fact this chlorination proceeded smoothly, using mild acid catalysis with Amberlyst A-15 ( $\text{H}^+$ ) 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  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of this material were identical with those reported<sup>25b</sup> 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,<sup>27a</sup> prepared by reaction of di-*t*-butyl pyrocarbonate ( $\text{Boc}_2\text{O}$ ) with **14** in 15% yield using DMAP catalysis. Instead, using THF-water at pH 10 with  $\text{Na}_2\text{CO}_3$  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  $\text{Boc}_2\text{O}$  is steadily hydrolysed. A later Pfizer patent<sup>27b</sup> cited a similar yield by heating **14** with two equivalents of  $\text{Boc}_2\text{O}$  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 Appel-type conditions<sup>28</sup> should be effective. More recently, variants of the original Appel method using catalytic  $\text{Ph}_3\text{PO}$ <sup>29</sup> and a sustainable procedure avoiding chlorinated solvents<sup>30</sup> have





**Scheme 5** Conversion of pseudothiohydantoin to 2-Boc-amino-4-halothiazoles. Conditions: (i)  $\text{Boc}_2\text{O}$ , aq. THF, pH10, 86%; (ii)  $\text{Ph}_3\text{P}$ ,  $\text{Cl}_3\text{CCN}$ ,  $\text{CH}_2\text{Cl}_2$ , 73%; (iii)  $\text{Ph}_3\text{P}$ , NBS, MeCN, 63%; (iv)  $\text{Ph}_3\text{P}$ , NIS, MeCN, 28%. Alternative conditions discussed in text.

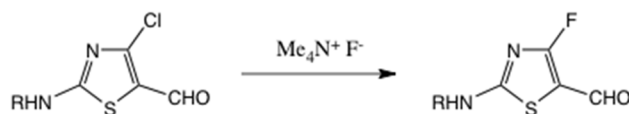
been described. Here,  $\text{Ph}_3\text{P}$  in conjunction with  $\text{CCl}_4$ <sup>31</sup> (or preformed  $\text{Ph}_3\text{PCl}_2$ <sup>32</sup>), *N*-chlorosuccinimide<sup>33</sup> or trichloroacetonitrile<sup>34</sup> all converted **20** into **21**. THF,  $\text{CH}_2\text{Cl}_2$  and MeCN were all adequate solvents; the best and mildest conditions proved to be  $\text{Ph}_3\text{P}$  and  $\text{Cl}_3\text{C}\cdot\text{CN}$  in  $\text{CH}_2\text{Cl}_2$  at 20 °C, affording **21** in 73% yield.

For the introduction of Br at C(4), as noted earlier, the Br rearrangement ('halogen dance')<sup>20a,b</sup> is feasible: the substrate (Scheme 1) is prepared from 2-amino-5-bromothiazole.<sup>35</sup> Here too, however, **20** proved a highly suitable intermediate, and on treatment with  $\text{Ph}_3\text{P}$  and *N*-bromosuccinimide<sup>33,34b</sup> **6** was readily obtained.<sup>36</sup> Here the solvent choice was significant, with MeCN definitely superior to  $\text{CH}_2\text{Cl}_2$ , giving **6** in 63% yield. Another good reagent proved to be ethyl tribromoacetate,<sup>34b,37</sup> 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 reaction<sup>38</sup> and may even divert the reaction to other products.<sup>39</sup>

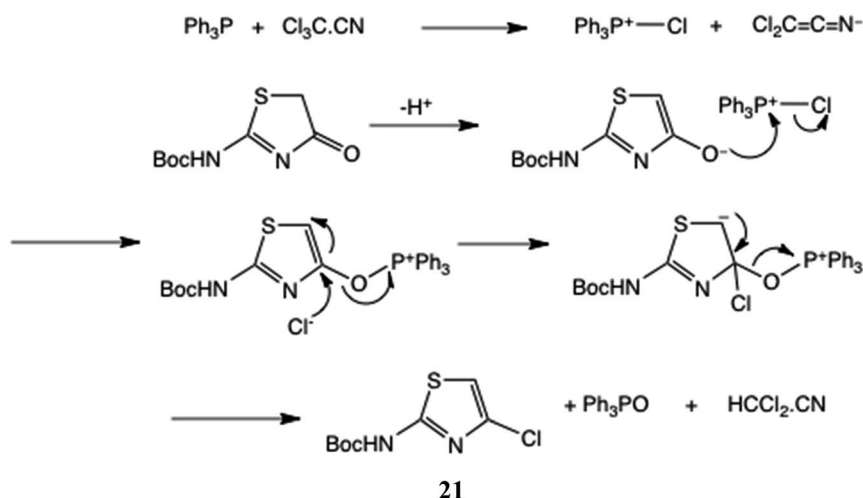
2-Boc-amino-4-iodothiazole **22** was disclosed in a patent<sup>40</sup> as a useful intermediate for Suzuki couplings, but with no preparative detail. We obtained this compound in an unoptimised 28% yield by treatment of **20** with  $\text{Ph}_3\text{P}$  and *N*-iodosuccinimide at 0–20 °C; a little free  $\text{I}_2$  was used to initiate the reaction.<sup>41</sup>

In Scheme 6 we give a mechanism for these halogenations, using  $\text{Cl}_3\text{C}\cdot\text{CN}$  as the example donor, generating **21**.

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

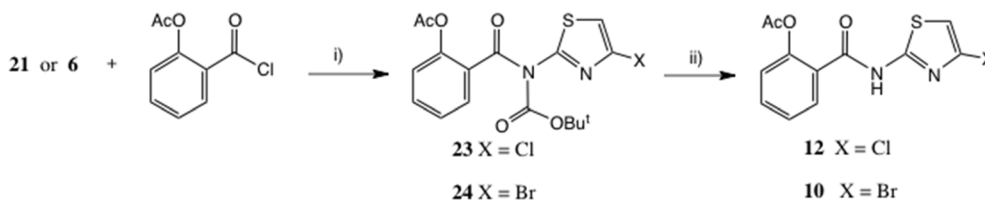


**Scheme 7** Synthesis of a 4-fluorothiazole by nucleophilic halogen substitution; R=Ac or Boc.



**Scheme 6** Proposed halogenation mechanism with  $\text{Cl}_3\text{C}\cdot\text{CN}$ .





Scheme 8 Thiazolide synthesis. Conditions: (i) Et<sub>3</sub>N, THF, 61% for **23**, 70% for **24**; (ii) dil. CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>, 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 obtained<sup>23</sup> by displacement from a 4-chlorothiazole using S<sub>N</sub>Ar reaction with anhydrous Me<sub>4</sub>N<sup>+</sup> F<sup>−</sup>, Scheme 7.

### Acylation of Boc intermediates and thiazolide synthesis

The NH of compounds such as **21** is considerably more acidic than a typical amide<sup>43</sup> or even acetanilide (pK<sub>a</sub> = 13),<sup>44</sup> and our previous experience had indeed shown that further *N*-acylation was possible. Using Et<sub>3</sub>N as base, acylation of **21** with *O*-acetylsalicyloyl chloride cleanly afforded a 70% yield of the Boc intermediate **23** (Scheme 8). Mild acidolysis (dilute CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>) 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 Ph<sub>3</sub>P under Appel-type conditions are effective reagents for the halogenation step, but Cl<sub>3</sub>CCN 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<sub>2</sub>SO<sub>4</sub> prior to rotary evaporation at <30 °C. Moisture sensitive reactions were carried out in anhydrous organic solvents (purchased from Sigma-Aldrich) under a N<sub>2</sub> or

Ar atmosphere. Reactions were monitored by analytical thin-layer chromatography using Merck Kieselgel 60 F<sub>254</sub> silica plates, and were viewed under UV or by staining with KMnO<sub>4</sub> 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. <sup>1</sup>H and <sup>13</sup>C 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 ppm (δ) relative to Me<sub>4</sub>Si. Coupling constants (*J*) are reported in Hz.

### 2-Amino-4-bromothiazole 7

A solution of *tert*-butyl (4-bromothiazol-2-yl)carbamate **6**<sup>20</sup> (0.56 g, 2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was stirred at 20 °C with CF<sub>3</sub>CO<sub>2</sub>H (5 mL). After 4 h, the solution was evaporated to dryness, azeotroped with CH<sub>2</sub>Cl<sub>2</sub> (2 × 5 mL) and the residue was partitioned between satd. aq. NaHCO<sub>3</sub> (20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (5 × 10 mL). Evaporation gave **7** as a white solid (0.336 g, 94%) which was progressed immediately; δ<sub>H</sub> (CDCl<sub>3</sub>) 5.32 (2H, br s, NH<sub>2</sub>) 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 N<sub>2</sub> at 0 °C and Et<sub>3</sub>N (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-*n*-hexane. Evaporation of early-eluting fractions afforded title compound **10** (0.133 g) which was recrystallised from EtOAc-*n*-hexane 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. C<sub>12</sub>H<sub>9</sub>BrN<sub>2</sub>O<sub>3</sub>S requires C, 42.25; H, 2.7; N, 8.2; S, 9.4%; *m/z*, 362.9415 (MNa<sup>+</sup>); δ<sub>H</sub> (CDCl<sub>3</sub>) 2.46 (3H, s, CH<sub>3</sub>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); δ<sub>C</sub> (CDCl<sub>3</sub>) 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



with the amide **11** plus other traces;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 2.33 (3H, s,  $\text{CH}_3\text{CO}$ ), 6.88 (1H, s, 5-H) and 10.65 (1H, br s, NH); found:  $m/z$  (CI, methane) 220.9387;  $\text{C}_5\text{H}_6^{79}\text{BrN}_2\text{OS}$  ( $\text{MH}^+$ ) requires  $m/z$ , 220.9379.

Method B: a solution of Boc derivative **24** (0.292 g, 0.64 mmol, v. i.) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was stirred at 20 °C and  $\text{CF}_3\text{CO}_2\text{H}$  (0.3 mL, 4 mmol) was added dropwise. After 3 h, the solution was diluted with EtOAc (20 mL) and cautiously washed with satd.  $\text{NaHCO}_3$  (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 **8**<sup>21</sup> (0.135 g, 1 mmol) was dissolved in anhydrous THF (4 mL) and stirred at 20 °C with *O*-acetylsalicyloyl chloride **9** (0.24 g, 1.2 mmol) under  $\text{N}_2$ . 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;  $\text{C}_{12}\text{H}_9\text{ClN}_2\text{O}_3\text{S}$  requires C, 48.6; H, 3.1; N, 9.4; S, 10.8%;  $\text{C}_{12}\text{H}_9^{35}\text{ClN}_2\text{O}_3\text{SNa}$  ( $\text{MNa}^+$ ) requires  $m/z$ , 318.9920;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 2.48 (3H, s,  $\text{CH}_3\text{CO}$ ), 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);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 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;  $\text{C}_{21}\text{H}_{15}\text{ClN}_2\text{O}_6\text{S}$  requires C, 55.0; H, 3.3; N, 6.1; S, 7.0%;  $\text{C}_{21}\text{H}_{15}^{35}\text{ClN}_2\text{O}_6\text{SNa}$  ( $\text{MNa}^+$ ) requires  $m/z$ , 481.0237;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 2.35 (3H, s,  $\text{CH}_3\text{CO}$ ), 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);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 21.1 ( $\times 2$ ), 113.7 ( $\times 2$ ), 123.4 ( $\times 2$ ), 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  $\text{CH}_2\text{Cl}_2$  (3 mL) and stirred at 20 °C, then  $\text{CF}_3\text{CO}_2\text{H}$  (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.  $\text{NaHCO}_3$  (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  $\text{Ac}_2\text{O}$  (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  $\text{Et}_2\text{O}$  (10 mL) and stored at 0 °C for 1 h, then filtered, washed with  $\text{Et}_2\text{O}$ , 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,  $\text{CH}_4$ ) 159.0228.  $\text{C}_5\text{H}_6\text{N}_2\text{O}_2\text{S}$  requires C, 38.0; H, 3.8; N, 17.7; S, 20.3%;  $\text{C}_5\text{H}_7\text{N}_2\text{O}_2\text{S}$  ( $\text{MH}^+$ ) requires  $m/z$ , 159.0223;  $\delta_{\text{H}}$  ( $\text{d}_6$ -DMSO)  $\delta$  2.19 (3H, s,  $\text{CH}_3\text{CO}$ ), 3.85 (2H, s,  $\text{CH}_2\text{CO}$ ) and 12.61 (1H, br s, NH);  $\delta_{\text{C}}$  ( $\text{d}_6$ -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  $\text{Ac}_2\text{O}$  (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,  $\text{CH}_4$ ) 201.033;  $\text{C}_7\text{H}_8\text{N}_2\text{O}_3\text{S}$  requires C, 42.0; H, 4.0; N, 14.0; S, 16.0%;  $\text{C}_7\text{H}_9\text{N}_2\text{O}_3\text{S}$  ( $\text{MH}^+$ ) requires  $m/z$ , 201.0328;  $\delta_{\text{H}}$  ( $\text{d}_6$ -DMSO)  $\delta$  2.14, 2.26 (6H, 2s, 2x $\text{CH}_3\text{CO}$ ), 6.73 (1H, 5-H) and 12.18 (1H, br s, NH);  $\delta_{\text{C}}$  ( $\text{d}_6$ -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  $\text{POCl}_3$  (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.  $\text{Na}_2\text{CO}_3$  which was added cautiously to give a pH of 8. The combined organic extracts were washed with  $\text{H}_2\text{O}$ , 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,  $\text{CH}_4$ ) 176.9892.  $\text{C}_5\text{H}_6^{35}\text{ClN}_2\text{OS}$  ( $\text{MH}^+$ ) requires  $m/z$ , 176.9884;  $\delta_{\text{H}}$  ( $\text{d}_6$ -DMSO)  $\delta$  2.15 (3H, s,  $\text{CH}_3\text{CO}$ ), 7.14 (1H, s, 5-H) and 12.36 (1H, br s, NH); ( $\text{CDCl}_3$ ) 2.35 (3H, s,  $\text{CH}_3\text{CO}$ ), 6.77 (1H, s, 5-H) and 10.93 (1H, br s, NH);  $\delta_{\text{C}}$  ( $\text{d}_6$ -DMSO) 22.9, 108.0, 133.8, 158.7 and 169.5; ( $\text{CDCl}_3$ ) 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*-chlorosuccinimide (0.27 g, 2.00 mmol) over Amberlite A-15 ( $\text{H}^+$ ) (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  $\text{Na}_2\text{SO}_4$  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.  $\text{C}_5\text{H}_5\text{ClN}_2\text{OS}$  requires C, 34.00; H, 2.85; N, 15.86%;  $\delta_{\text{H}}$  2.33 (3H, s,  $\text{CH}_3\text{CO}$ ), 7.27 (1H, s, 4-H) and 11.80 (1H, br s, NH);  $\delta_{\text{C}}$  22.9, 121.0, 133.5, 157.6 and 168.0.



***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 H<sub>2</sub>O : THF (15 mL) was added Boc<sub>2</sub>O (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 CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, 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. C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub>S requires C, 44.4; H, 5.6; N, 12.95; S, 14.8%; C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub>Na (MNa<sup>+</sup>) requires *m/z*, 239.0461;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>)  $\delta$  1.55 (s, 9H), 3.80 (s, 2H) and 9.61 (br s, 1H, NH);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>)  $\delta$  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 CH<sub>2</sub>Cl<sub>2</sub> (7.5 mL) was stirred at 20 °C under N<sub>2</sub> and trichloroacetonitrile (0.38 mL, 3.75 mmol) was added over one minute. After 40 h the mixture was diluted with Et<sub>2</sub>O (30 mL), washed with H<sub>2</sub>O (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. C<sub>8</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>2</sub>S requires C, 40.9; H, 4.7; N, 11.9; S, 13.7%; C<sub>8</sub>H<sub>11</sub><sup>35</sup>ClN<sub>2</sub>O<sub>2</sub>Na (MNa<sup>+</sup>) requires *m/z*, 257.0122;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.54 (9H, s, Me<sub>3</sub>C), 6.65 (1H, s, 5-H) and 9.20 (1H, br s, NH);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 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 N<sub>2</sub>, then the reaction was stirred at 20 °C overnight. The reaction was quenched with H<sub>2</sub>O (20 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with brine and dried over MgSO<sub>4</sub>. 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. C<sub>8</sub>H<sub>11</sub><sup>79</sup>BrN<sub>2</sub>NaO<sub>2</sub>S (MNa<sup>+</sup>) requires *m/z*, 300.9617; <sup>1</sup>H NMR  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.54 (9H, s, Me<sub>3</sub>C), 6.79 (1H, s, 5-H) and 9.50 (1H, br s, NH);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 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<sub>3</sub>P (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 I<sub>2</sub> (0.25 g, 1 mmol) and further Ph<sub>3</sub>P (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. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (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. C<sub>8</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub>SI requires C, 29.5; H, 3.4; N, 8.6; S, 9.8%; C<sub>8</sub>H<sub>11</sub>IN<sub>2</sub>O<sub>2</sub>Na (MNa<sup>+</sup>) requires *m/z*, 348.9478;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.55 (9H, s, Me<sub>3</sub>C), 7.01 (1H, s, 5-H) and 8.8–9.2 (1H, br, NH);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 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 N<sub>2</sub> 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. NaHCO<sub>3</sub> 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; C<sub>17</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>5</sub>S requires C, 51.45; H, 4.3; N, 7.1; S, 8.1%; C<sub>17</sub>H<sub>17</sub><sup>35</sup>ClN<sub>2</sub>O<sub>5</sub>Na (MNa<sup>+</sup>) requires *m/z*, 419.0439;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.22 (9H, s, Me<sub>3</sub>C), 2.24 (3H, s, CH<sub>3</sub>CO), 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);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 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 Et<sub>3</sub>N (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; C<sub>17</sub>H<sub>17</sub>BrN<sub>2</sub>O<sub>5</sub>Na (MNa<sup>+</sup>) requires *m/z*, 462.9939;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.32 (9H, s, Me<sub>3</sub>C), 2.34 (3H, s, CH<sub>3</sub>CO), 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);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 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<sub>21</sub>H<sub>15</sub>N<sub>2</sub>O<sub>6</sub>SCl **13**, C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>S **15** and C<sub>5</sub>H<sub>5</sub>-ClN<sub>2</sub>OS **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,<sup>45</sup> the structure was solved



with the ShelXT<sup>46</sup> structure solution program using Intrinsic Phasing and refined with the ShelXL<sup>47</sup> 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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