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

 Sophie Pate, Joshua Taujanskas, Robyn Wells, Craig M. Robertson, Paul M. O'Neill and Andrew V. Stachulski \*

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>

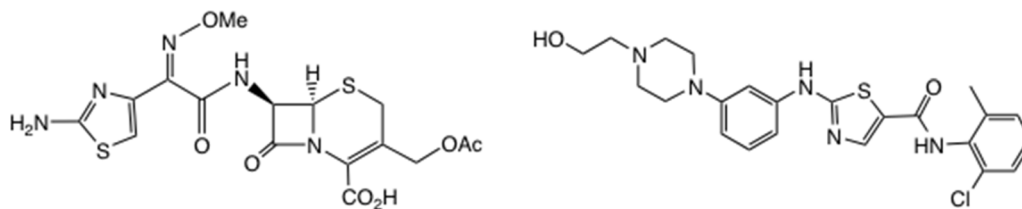
In general, 5-substituted thiazolides such as **1a/1b** are the easiest to obtain. The natural position of electrophilic substitution of a 2-aminothiazole is at position 5, even when the 2-amine is acylated. In order to synthesise thiazolides with a 4-substituent, including 4-halo examples, various methods 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

Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK. E-mail: [stachuls@liv.ac.uk](mailto:stachuls@liv.ac.uk); Fax: +44-(0)151-794-3482; Tel: +44-(0)151-794-3482

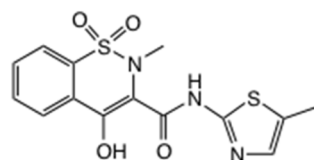
† Electronic supplementary information (ESI) available. CCDC 2330479, 2330480 and 2362657. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4ra04959d>





**Cefotaxime**  
*Broad spectrum antibiotic*

**Dasatinib**  
*Kinase inhibitor/ Anticancer*



**Meloxicam**  
*Non-steroidal antiinflammatory*

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

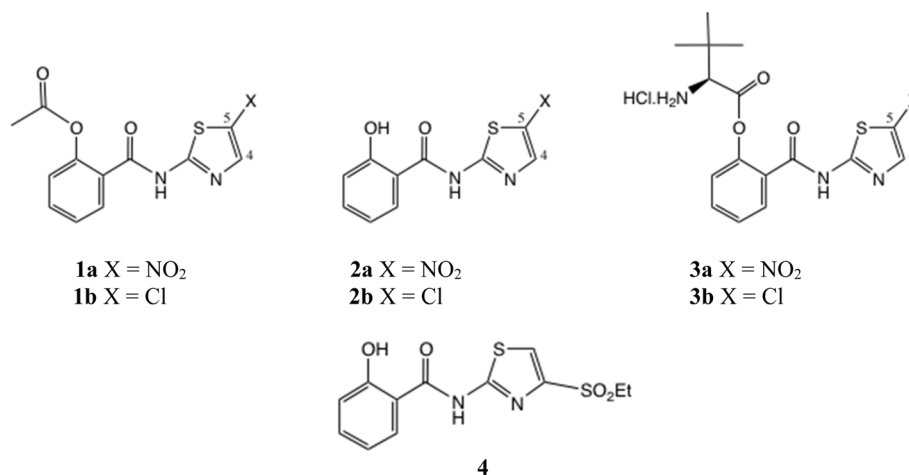
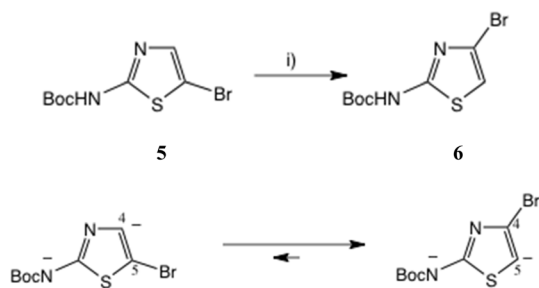


Fig. 2 Thiazolide structures.



Scheme 1 Synthesis of 2-Boc-amino, 4-bromothiazole by halogen rearrangement. Conditions: (i) LiNPr<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

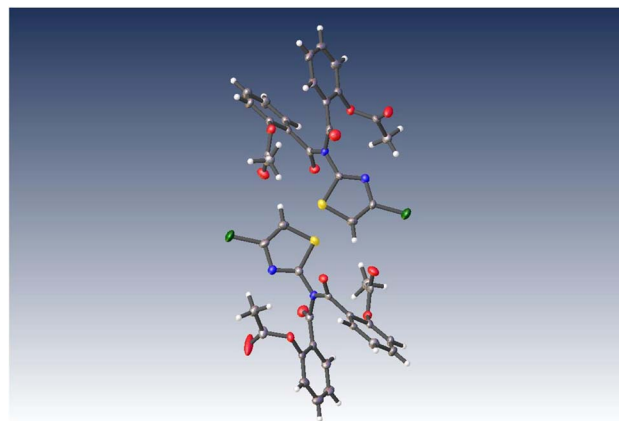
### Acylation of 2-amino-4-bromo and 2-amino-4-chlorothiazole

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 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 **8**<sup>21</sup> 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,

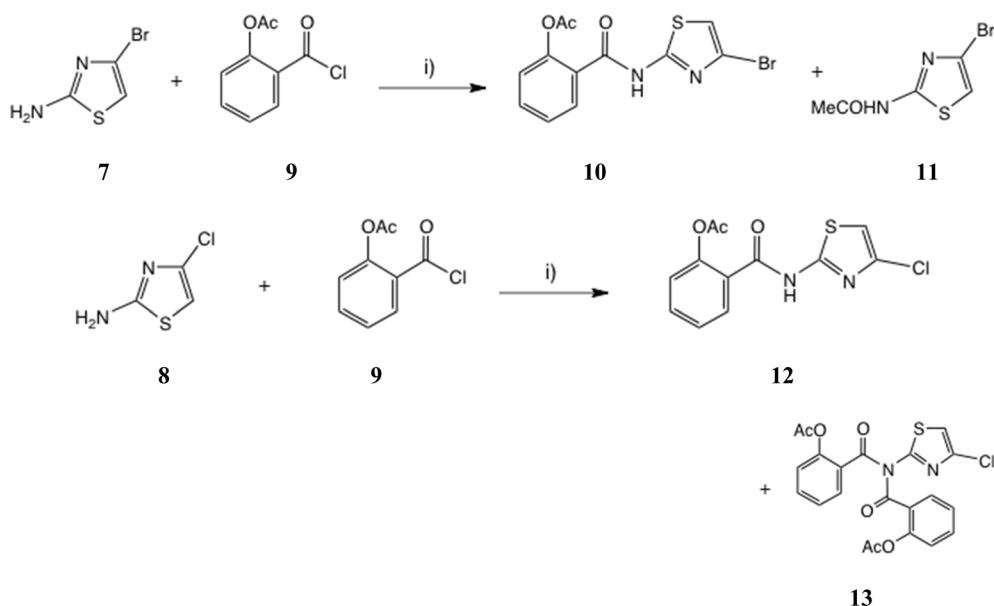


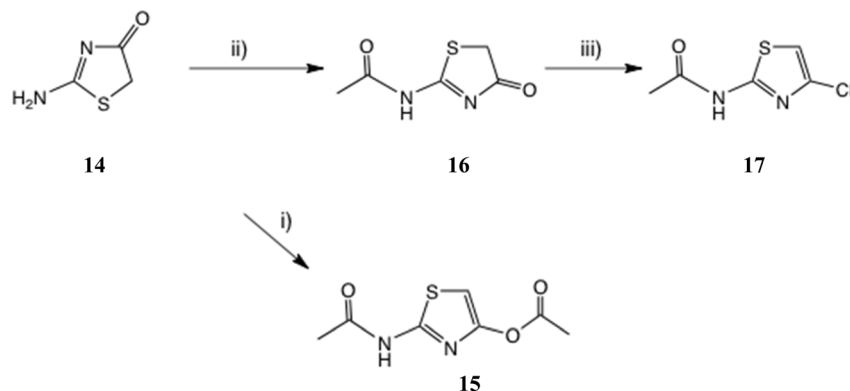
13

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

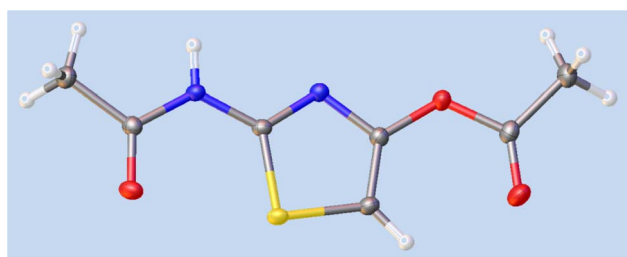
is commercially available or easily prepared from thiourea and bromoacetic acid in a typical Hantzsch synthesis,<sup>23</sup> and carries built-in 4-substitution. As noted above, heating **14** with excess POCl<sub>3</sub><sup>21</sup> gave a very low yield of 2-amino-4-chlorothiazole **8**.

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.

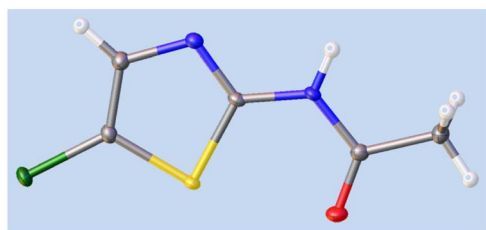
Scheme 2 Acylation of 2-amino-4-bromo and 2-amino-4-chlorothiazole. Conditions: (i) THF, Et<sub>3</sub>N, 0 °C–20 °C.



**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%.



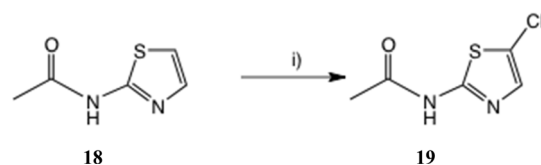
**15**



**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%.

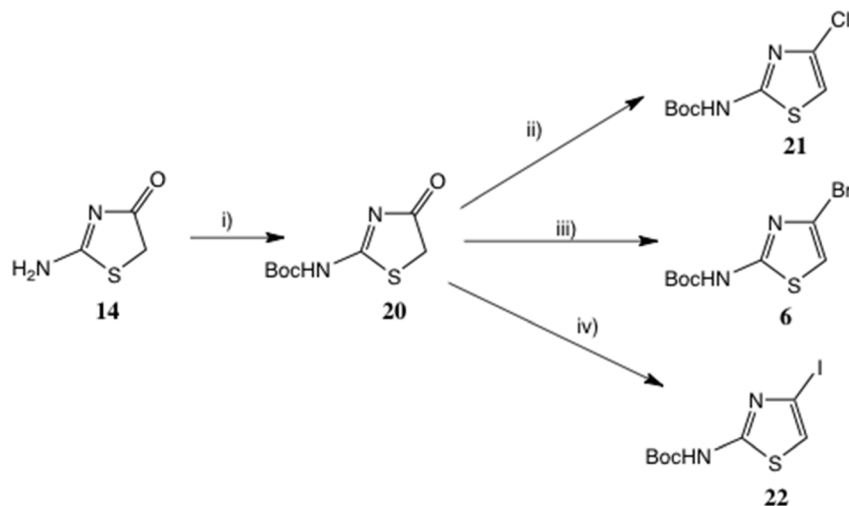
To seek reassurance on the regiochemical point, we studied the direct chlorination of 2-acetamidothiazole **18** with NCS in MeCN, Scheme 4. We used a similar procedure once before on a thiazolidine.<sup>11</sup> In fact this chlorination proceeded smoothly, using mild acid catalysis with Amberlyst A-15 ( $\text{H}^+$ ) 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)  $\text{Ph}_3\text{P}$ ,  $\text{Cl}_3\text{C}\cdot\text{CN}$ ,  $\text{CH}_2\text{Cl}_2$ , 73%; (iii)  $\text{Ph}_3\text{P}$ , NBS, MeCN, 63%; (iv)  $\text{Ph}_3\text{P}$ , NIS, MeCN, 28%. Alternative conditions discussed in text.

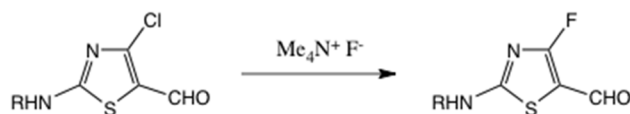
been described. Here,  $\text{Ph}_3\text{P}$  in conjunction with  $\text{CCl}_4$ <sup>31</sup> (or preformed  $\text{Ph}_3\text{PCl}_2$ <sup>32</sup>), *N*-chlorosuccinimide<sup>33</sup> or trichloroacetonitrile<sup>34</sup> all converted **20** into **21**. THF,  $\text{CH}_2\text{Cl}_2$  and MeCN 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>

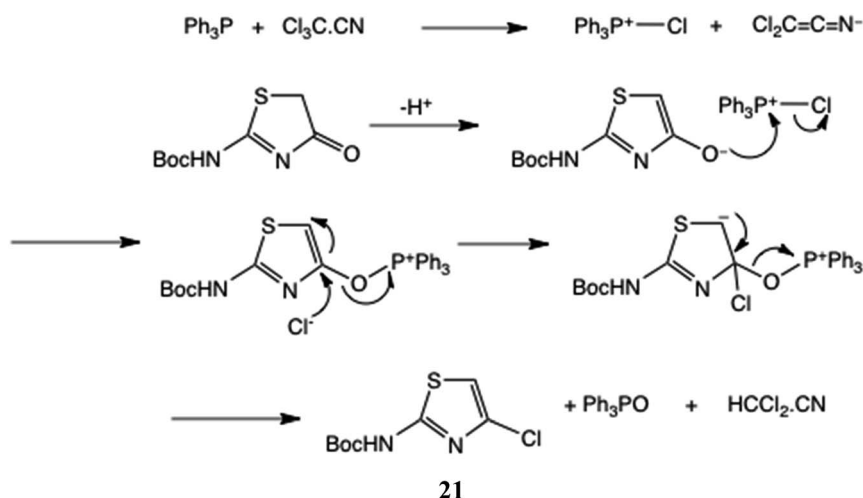
2-Boc-amino-4-iodothiazole **22** was disclosed in a patent<sup>40</sup> as a useful intermediate for Suzuki couplings, but with no preparative detail. We obtained this compound in an unoptimised 28% yield by treatment of **20** with  $\text{Ph}_3\text{P}$  and *N*-iodosuccinimide at 0–20 °C; a little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

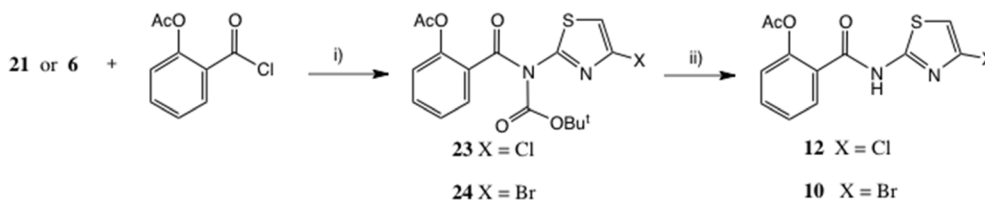


**Scheme 7** Synthesis of a 4-fluorothiazole by nucleophilic halogen substitution; R=Ac or Boc.



**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;  $\delta_{\text{H}}$  ( $d_6$ -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);  $\delta_{\text{C}}$  ( $d_6$ -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;  $\delta_{\text{H}}$  ( $d_6$ -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);  $\delta_{\text{C}}$  ( $d_6$ -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;  $\delta_{\text{H}}$  ( $d_6$ -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);  $\delta_{\text{C}}$  ( $d_6$ -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>SNa (MNa<sup>+</sup>) requires *m/z*, 239.0461; δ<sub>H</sub> (CDCl<sub>3</sub>) δ 1.55 (s, 9H), 3.80 (s, 2H) and 9.61 (br s, 1H, NH); δ<sub>C</sub> (CDCl<sub>3</sub>) 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 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>SNa (MNa<sup>+</sup>) requires *m/z*, 257.0122; δ<sub>H</sub> (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); δ<sub>C</sub> (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; 1H NMR δ<sub>H</sub> (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); δ<sub>C</sub> (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>SNa (MNa<sup>+</sup>) requires *m/z*, 348.9478; δ<sub>H</sub> (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); δ<sub>C</sub> (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>SNa (MNa<sup>+</sup>) requires *m/z*, 419.0439; δ<sub>H</sub> (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); δ<sub>C</sub> (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>SNa (MNa<sup>+</sup>) requires *m/z*, 462.9939; δ<sub>H</sub> (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, ArH), 7.36 (1H, t, ArH), 7.58 (1H, t, ArH) and 7.68 (1H, d, ArH); δ<sub>C</sub> (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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