RESEARCH FRONT

CSIRO PUBLISHING

Aust. J. Chem. **2014**, *67*, 1217–1221
http://dx.doi.org/10.1071/CH14055

Full Paper

Annulation of Eight- to Ten-Membered Oxaza Rings to the Benzo[*b*]thiophene System by Intramolecular Nucleophilic Displacement

John B. Bremner[A,C] *and Zemin Wu*[A,B]

[A]School of Chemistry, University of Wollongong, Wollongong, NSW 2522, Australia.
[B]Current address: Avipep Pty Ltd, 343 Royal Parade, Parkville, Vic. 3052, Australia.
[C]Corresponding author. Email: john_bremner@uow.edu.au

Concise synthetic routes to 2*H*-benzo[*b*]thieno[3,2-*b*][1,5]oxazocin-6(3*H*)-one, and the new benzo[*b*]thieno[3,2-*b*][1,5]oxazonin-7(2*H*)-one and 2*H*-benzo[*b*]thieno[3,2-*b*][1,5]oxazecin-8(3*H*)-one systems, have been developed based on intramolecular nucleophilic displacement in the key ring forming step.

Manuscript received: 5 February 2014.
Manuscript accepted: 28 March 2014.
Published online: 22 April 2014.

Introduction

Although much progress has been made in the synthesis of N, O-containing fused medium ring systems, many opportunities for new systems remain.[1] Such compounds are of inherent chemical interest and are also of significance as novel scaffolds for pharmaceutical development,[2–4] particularly eight-membered systems.[5–9]

As part of some structure–pharmacological activity studies on benzo[*b*]thiophene-based potentiators of the action of serotonin, we required systems in which amide functionality at the 2-position of the benzo[*b*]thiophene was incorporated in a semi-flexible ring system, while retaining an electronegative group at the 3-position. Fused medium-sized [1,5]-oxaza systems **1** (Scheme 1) were thus considered as synthetic targets.

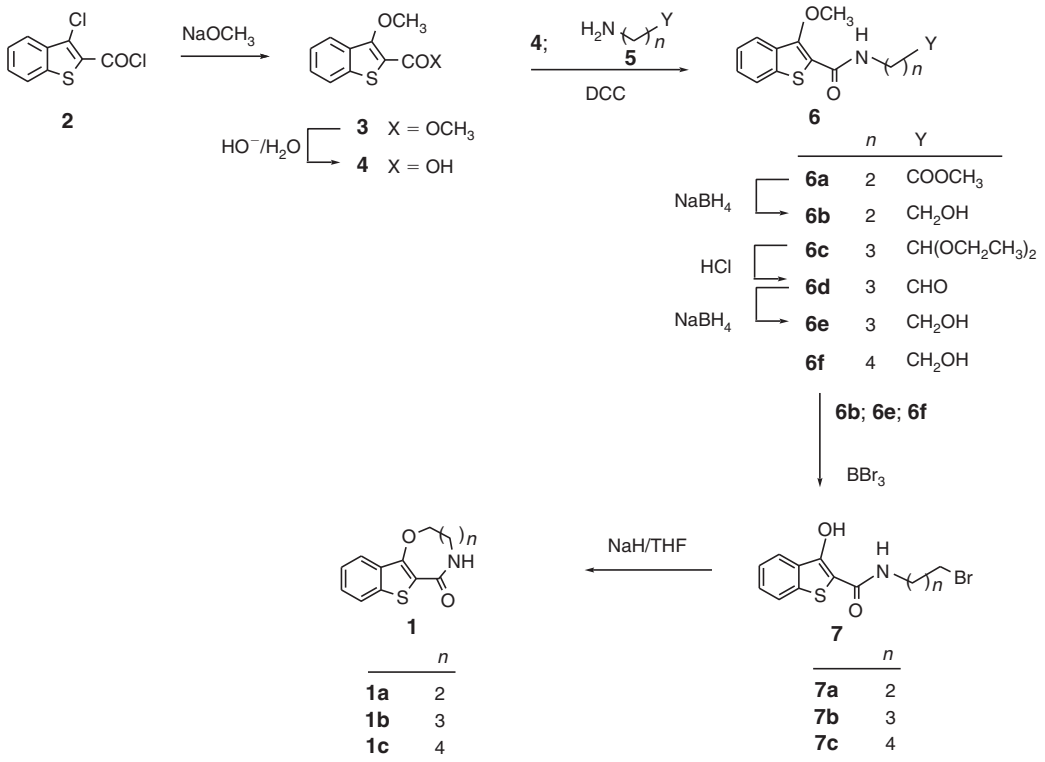
N-Substituted 3-hydroxy derivatives of the fused eight-membered ring system **1a** are known (although not the parent lactam **1a** itself), and were made by lactamisation in the final medium ring forming step.[10] Lactam formation also featured in approaches to the recently described 10-methoxy and 10-benzyloxy derivatives of **1a** which had some inhibitory activity against protein kinase D, an enzyme involved in several important cellular processes.[11] The fused nine- and ten-membered ring systems **1b** and **1c** respectively have not been described previously, although representatives with isomeric [1,4]- and [1,5]-oxaza fused skeletons have been reported.[12] It is of interest to note that the fused seven-membered ring analogue **1** ($n = 1$) and bio-active derivatives (cell adhesion and HIV inhibitors) have been reported and were accessed by lactamisation at the final step.[13,14]

Our new ring construction approach to the systems of type **1a**–**c** involved an alternative and versatile O–CH_2 bond formation by nucleophilic displacement at saturated carbon in the final cyclisation step. The results of this work are presented in this paper.

Results and Discussion

The essential precursors for the ultimate cyclisation reaction were the bromo amides **7a**–**c**, which could be accessed by the alcohols **6b**, **6e**, and **6f** in a series of steps from the readily available acid chloride **2**, prepared in turn from the reaction of cinnamic acid with thionyl chloride in the presence of pyridine[15] (Scheme 1). Substitution of the 3-chloro group in acid chlorides of type **2** is readily achieved by a nucleophilic addition–elimination sequence.[16] Thus reaction of **2** with sodium methoxide gave the 3-methoxy substituted methyl ester **3**,[17] from which the corresponding acid **4**[17] could be obtained by standard alkaline hydrolysis. Amide derivatisation was then achieved by dicyclohexylcarbodiimide-mediated reaction of methyl β-alinate **5** ($Y = COOCH_3$, $n = 2$) with the acid **4** in the case of **6a**, and with the commercially available acetal **5** ($Y = CH(OCH_2CH_3)_2$, $n = 3$) or the alcohol **5** ($Y = CH_2OH$, $n = 4$), to afford **6c** and **6f** respectively. These transformations proceeded in good yield and structural assignments followed from the spectroscopic data and methods of preparation.

With the procedure for the $n = 2$ series further terminal functional group manipulation by hydride reduction of **6a** to the primary alcohol **6b** was necessary, while in the $n = 3$ series, the acetal intermediate **6c** was hydrolysed to the aldehyde **6d** and then reduced to the required alcohol precursor **6e**. In the case of **6a** an uncommon reduction of the ester functionality with sodium borohydride was involved leaving the amide group intact. There is some precedent for such reductions (see, for example, Saeed and Ashraf[18] and Boechat et al.[19]) and in this case there may be some increased susceptibility of the ester carbonyl group to hydride attack as a result of intramolecular H-bonding of the amide N–H group. Reaction of the alcohols **6b**, **6e**, and **6f** with boron tribromide resulted in *O*-demethylation with a concomitant primary alcohol to bromide transformation to give the respective bromides **7a**–**c** in good yields.



Scheme 1. Synthesis of the fused medium ring derivatives **1a**–**c**.

The key intramolecular nucleophilic displacement reaction to realise the fused medium ring derivatives **1a**–**c** then proceeded smoothly on treatment of **7a**–**c** in each case with sodium hydride in THF to generate the active 3-oxide nucleophile followed by bromide ion loss. Structural confirmation of the annulated eight- to ten-membered ring products rested on high resolution mass spectroscopic data and the ^{1}H and ^{13}C NMR spectra. In the ^{13}C NMR spectra the presence of the lactam carbonyl group was consistent with signals in the region of δ161–163. Stereochemically stable rotational isomers in the medium ring products are possible by analogy with the related bioisosteric naphthalene-ring fused oxaza systems,[7–9] and some tentative evidence was seen for these in **1a**–**c** on the basis of the NMR spectra.

Although somewhat more severe conditions were required to form the eight- and ten-membered fused lactams compared with the nine-membered congener, yields were still good. In all cases, delocalisation of the negative charge on the 3-oxide through the 2,3-benzo[*b*]thiophene bond to the amide carbonyl group would presumably weaken the C=N resonance contribution to the amide and allow for rotation to the *cisoid* amide form. Suitable positioning of the CH_2–Br moiety would thus be realised for a subsequent favourable *exo-tet* intramolecular nucleophilic displacement process. In no case was evidence seen for competing macro ring formation (16-, 18-, and 20-membered rings) through dimerisation, nor for any smaller ring products which could result from amide anion formation; the preferential formation of the oxide anion would be expected based on the likely greater acidity of the 3-OH group. An analogous ring formation strategy, but involving chloride ion displacement by a phenoxide ion, was employed to access the benz-fused eight-membered ring derivative, 8-chloro-4,5-dihydro-2*H*-1,5-benzoxazocin-6(3*H*)-one.[20]

Conclusion

A concise and efficient route based on O–CH_2 bond formation in the final ring forming step allowed smooth access to benzo[*b*]thiophene-fused [1,5]-N,O containing medium ring systems. Extension of this methodology to prepare a range of heteroaromatic and aromatic ring fused, medium-sized oxaza heterocyclic systems should be feasible.

Experimental

Methods and Materials

All melting points (uncorrected) were determined on a Reichert hot stage apparatus. Infrared spectra were recorded on a Bio Rad Fourier Transform Infrared Spectrometer FTS-7 as mulls in Nujol unless otherwise stated and the absorption bands are described as strong (s), medium (m), or weak (w).

^{1}H and ^{13}C NMR spectra were determined at 399.9 and 100.1 MHz, respectively, with a Varian Unity-400 spectrometer. All the spectra were measured in $CDC1_3$ unless otherwise stated. Mass spectra were obtained using Vacuum General 12–12, Vacuum General Quattro and MAT-44 spectrometers by the direct insertion technique with an electron beam energy of 70 eV and a source temperature of 200°C. The peak intensities, in parentheses, are expressed as the percentage abundance. High resolution mass spectra were run by Dr X. Song of the School of Chemistry, University of Sydney, or Dr N. Davies, Central Science Laboratory, University of Tasmania. Elemental microanalyses of samples were performed by the Queensland Microanalytical Service, Department of Chemistry, University of Queensland. Analytical TLC was performed on Merck silica gel F_{254} silica on aluminium sheets. Column chromatography was performed under medium pressure using Merck silica gel unless otherwise indicated. All solvent ratios are v/v.

All extracts were dried over anhydrous sodium sulfate before being evaporated under reduced pressure. THF was freshly distilled from sodium wire in the presence of benzophenone under nitrogen. Other commercial chemicals and reagents were used as received.

Synthesis

3-Chloro-benzo[b]thiophene-2-carbonyl Chloride (**2**)

Thionyl chloride (11.1 mL, 90 mmol) was added to a solution of (*E*)-cinnamic acid (4.5 g, 30 mmol) in toluene (50 mL) containing pyridine (0.5 mL, 3 mmol). After addition, the mixture was heated at reflux for 60 h. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was chromatographed on a short column (2 % ethyl acetate/hexane) to give a crude product, which was recrystallised from CH_2Cl_2 to afford the acid chloride **2** (4.5 g, 64 %) as yellow needles, mp 114–116°C (lit.[15] mp 114–116°C).

Methyl 3-Methoxy-benzo[b]thiophene-2-carboxylate (**3**)

Methanol (0.9 mL, 22.2 mmol) was added dropwise to a suspension of sodium hydride (860 mg, 60 % content, 21.5 mmol) in THF (15 mL) at room temperature under nitrogen. After stirring for 1 h, a solution of the acid chloride **2** (1.7 g, 7.4 mmol) in THF (15 mL) was added dropwise. The reaction mixture was heated at reflux overnight and then allowed to cool to room temperature before being quenched with a saturated NH_4Cl solution. The mixture was extracted with ethyl acetate (3×30 mL). The combined extracts were washed with brine (20 mL) and dried. Removal of the solvent afforded the ester **3** (1.46 g, 89 %) as colourless crystals, mp 110–112°C (lit.[17] mp 64.5–65.5°C). ν_{max} /cm^{-1} 1718 (s, C=O), 1593 (m). δ_H 8.08 (m, 1H), 7.92 (m, 1H), 7.60 (m, 2H), 4.10 (s, 3H), 3.9 (s, 3H). *m/z* (EI$^+$) 222 (100 %, M$^+\cdot$), 207 (10), 191 (60), 176 (45).

3-Methoxy-benzo[b]thiophene-2-carboxylic Acid (**4**)

A mixture of the ester **3** (1 g, 4.5 mmol) and sodium hydroxide (1 M, 5 mL) in methanol (25 mL) was stirred overnight. The solvent was removed and the residue dissolved in water (5 mL) and neutralised with hydrochloric acid (1 M) to give a precipitate. Filtration under vacuum afforded the acid **4** (0.9 g, 97 %) as colourless crystals, mp 250°C (dec.) (lit.[17] mp 176–177°C). ν_{max} /cm^{-1} 1686 (m, C=O). δ_H 8.08 (m, 1H), 7.92 (m, 1H), 7.60 (m, 2H), 4.10 (s, 3H). *m/z* (EI$^+$) 208 (97 %, M$^{+\bullet}$), 164 (15), 149 (40).

N-(3-Methoxy-benzo[b]thien-2-oyl)-β-alanine Methyl Ester (**6a**)

A solution of β-alanine methyl ester (**5**, Y = $COOCH_3$, $n = 2$; 150 mg, 1.4 mmol) in DMF (10 mL) was added to a solution of the acid **4** (208 mg, 1 mmol), 1,3-dicyclohexylcarbodiimide (206 mg, 1 mmol), and 1-hydroxybenzotriazole (150 mg, 1.1 mmol) in DMF (10 mL). The reaction mixture was stirred overnight. The solvent was removed under vacuum and the residue was column chromatographed (20 % and then 40 % ethyl acetate/hexane) to give the ester **6a** (230 mg, 79 %) as colourless crystals, mp 61–62°C. ν_{max} (film)/cm^{-1} 3387 (m, NH), 1732 (s, *CO*OCH$_3$), 1641 (s, Ar*CO*NH), 1535 (s). δ_H 8.10 (br s, 1H), 7.82–7.80 (m, 2H), 7.43–7.39 (m, 2H), 4.10 (s, 3H), 3.75 (dt, *J* 6.0, 6.8, 2H), 3.72 (s, 3H), 2.68 (t, *J* 6.0, 2H). δ_C 172.9, 161.6, 150.5, 137.8, 132.4, 126.6, 124.3, 123.6, 123.5, 122.0, 61.9, 51.7, 48.8, 34.8. *m/z* (ESI$^+$) 316 (100 %, [M + Na]$^+$), 294 (10, [M + H]$^+$). *m/z* (HRMS, EI$^+$) Calc. for $C_{14}H_{15}NO_4S$: 293.0722. Found 293.0728.

N-(3′-Hydroxypropyl)-3-methoxy-benzo[b]thiophene-2-carboxamide (**6b**)

An excess of sodium borohydride (20 mg, 0.8 mmol) was added to a solution of the methyl ester **6a** (140 mg, 0.48 mmol) in ethanol (5 mL) and the mixture was stirred overnight. A saturated ammonium chloride solution was added and the aqueous mixture was extracted with ethyl acetate (3×10 mL). The extract was washed with brine (10 mL), dried, and evaporated to afford a crude product, which was chromatographed (60 % ethyl acetate/hexane) to yield the alcohol **6b** (125 mg, 98 %) as colourless crystals, mp 64–66°C. ν_{max} (film)/cm^{-1} 3379 (br s, OH, NH), 3060 (w), 2878 (w). 1626 (s, C=O), 1542 (s). δ_H 7.84–7.80 (m, 3H), 7.46–7.41 (m, 2H), 4.13 (s, 3H), 3.74 (t, *J* 5.6, 2H), 3.67 (dt, J_1 6.4, J_2 6.0, 2H), 1.85–1.82 (m, 2H). δ_C 162.8, 150.7, 137.8, 132.3, 126.7, 124.4, 123.5, 122.9, 122.0, 61.9, 59.5, 36.5, 32.1. *m/z* (ESI$^+$) 266 (100, [M + H]$^+$). *m/z* (HRMS, EI$^+$) Calc. for $C_{13}H_{15}NO_3S$: 265.0773. Found 265.0776.

N-(3′-Bromopropyl)-3-hydroxy-benzo[b]thiophene-2-carboxamide (**7a**)

An excess of boron tribromide (0.25 mL) was added dropwise to a solution of the alcohol **6b** (100 mg, 0.38 mmol) in CH_2Cl_2 (5 mL) at −78°C under nitrogen. The dry-ice bath was then removed and the reaction mixture stirred overnight. The reaction was quenched with water and the reaction mixture extracted with CH_2Cl_2 (3×15 mL). The combined extracts were washed with brine (10 mL), dried, and evaporated. Column chromatography of the residue (60 % ethyl acetate/hexane) afforded the bromo derivative **7a** (80 mg, 69 %) as a white powder, mp 135–136°C. ν_{max} /cm^{-1} 3349 (w, NH), 1611 (m, C=O). δ_H 7.94 (d, *J* 8.0, 1H), 7.71 (d, *J* 8.0, 1H), 7.48 (dt, J_1 1.2, J_2 8.0, 1H), 7.42 (dt, J_1 1.2, J_2 8.0, 1H), 5.78 (br s, 1H), 3.63 (dt, J_1 6.4, J_2 6.4, 2H, $NHCH_2$), 3.50 (t, *J* 6.4, 2H), 2.21 (quint., *J* 6.4, 2H). δ_C 167.1, 158.9, 136.2, 131.2, 128.5, 124.7, 123.0, 122.9, 102.1, 38.2, 32.1, 30.7. *m/z* (EI$^+$) 315, 313 (10 %, M$^{+\bullet}$), 297, 295 (5). *m/z* (HRMS, EI$^+$) Calc. for $C_{12}H_{12}{}^{79}BrNO_2S$: 312.9772. Found 312.9771.

4,5-Dihydro-2H-benzo[b]thieno[3,2-b][1,5]oxazocin-6(3H)-one (**1a**)

Sodium hydride (10 mg, 0.4 mmol) was added to a solution of the bromide **7a** (30 mg, 0.1 mmol) in THF (10 mL) under nitrogen. After stirring for 2 h, no reaction was observed by TLC analysis (20 % ethyl acetate/hexane). The reaction mixture was then heated at reflux for 2 h and quenched with water. The mixture was extracted with ethyl acetate (3×15 mL) and the combined extracts were washed with brine (10 mL) and dried. The solvent was evaporated to furnish a crude product, which was subjected to column chromatography (methanol/ethyl acetate/hexane, 10 : 80 : 100) to give the cyclised compound **1a** (15 mg, 68 %) as a yellow powder, mp 196–197°C. ν_{max} /cm^{-1} 1626 (s, C=O). δ_H 7.98–7.94 (m, 1H), 7.62–7.59 (m, 1H), 7.42 (dt, J_1 1.2, J_2 8.0, 1H), 7.28 (dt, J_1 1.2, J_2 8.0, 1H), 4.49–4.40 (m, 2H), 3.60–3.56 (m, 2H), 2.22–2.16 (m, 2H). δ_C 178.5, 162.8, 140.6, 134.7, 129.6, 124.2, 123.5, 123.3, 90.0, 66.3, 37.5, 21.2. *m/z* (EI$^+$) 233 (55, M$^{+\bullet}$). *m/z* (HRMS; EI$^+$) Calc. for $C_{12}H_{11}NO_2S$: 233.0511. Found 233.0479. Anal. Calc. for

$C_{12}H_{11}NO_2S{\cdot}H_2O$: C 57.36, H 5.21, N 5.57. Found: C 57.59, H 4.66, N 5.67 %.

N-*(3′-Methoxy-benzo[*b*]thien-2′-oy1)-4-aminobutanal (**6d**)*

A mixture of the acid **4** (208 mg, 1 mmol), 1,3-dicyclohexylcarbodiimide (206 mg, 1 mmol), 1-hydroxybenzotriazole (150 mg, 1.1 mmol), and 4-aminobutanal diethyl acetal **5** (Y = CH(OCH_2CH_3)$_2$, $n = 3$; 0.3 mL, 1.74 mmol) in THF (15 mL) was stirred overnight. The reaction was quenched with water and the aqueous mixture extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed with brine and dried. Removal of the solvent gave a residue, which was chromatographed (20 % ethyl acetate/hexane) to give the partially characterised acetal intermediate **6c** (300 mg, 85 %) as colourless crystals, mp 110–111°C. ν_{max} /cm^{-1} 3387 (m, NH), 3065 (w), 1648 (s), 1534. δ_H 7.80–7.78 (m, 2H), 7.54 (br s, 1H), 7.43–7.40 (m, 2H), 4.53 (t, *J* 4.8 Hz, 1H), 4.10 (s, 3H), 3.65 (q, *J* 7.2, 4H), 3.55–3.48 (m, 4H), 1.74–1.72 (m, 2H), 1.21 (t, *J* 7.2, 6H). *m/z* (EI) 322 (<1 %, [M − CH_2CH_3]$^+$), 305 (3), 259 (20), 224 (30), 191(100), 176 (60). *m/z* (HRMS, EI$^+$) 351.1489. $C_{18}H_{25}NO_4S$ requires 351.1504. The acetal **6c** (70 mg, 0.2 mmol) in acetone (10 mL) was then treated with a few drops of 1 M hydrochloric acid at room temperature and stirred overnight. The solvent was removed and the residue was chromatographed (40 % ethyl acetate/hexane) to give the aldehyde **6d** (55 mg, 100 %) as an oil. ν_{max} /cm^{-1} 3387 (s, NH), 3060 (w), 1725 (s, CHO), 1641 (s, Ar*CO*NH), 1527 (s). δ_H 9.80 (t, *J* 0.8, 1H), 7.82–7.80 (m, 2H), 7.60 (br s, 1H), 7.43–7.40 (m, 2H), 4.10 (s, 3H), 3.50 (dt, J_1 7.2, J_2 6.8, 2H), 2.60 (t, *J* 6.8, 2H), 2.02 (t, *J* 6.8, 2H), 1.98 (t, *J* 6.8, 2H). δ_C 201.6, 162.1, 150.4, 137.9, 132.4, 126.7, 124.5, 123.7, 122.1, 108.3, 61.97, 41.4, 38.9, 29.7. *m/z* (EI) 277 (8, M$^{+\bullet}$), 249 (5), 191 (100). *m/z* (HRMS, EI$^+$) 277.0769. $C_{14}H_{15}NO_3S$ requires 277.0773.

N-*(4′-Hydroxybuty1)-3-methoxy-benzo[*b*]thiophene)-2-carboxamide (**6e**)*

An excess of sodium borohydride (20 mg, 0.8 mmol) was added to a solution of the aldehyde **6d** (55 mg, 0.2 mmol) in ethanol (10 mL) and the mixture was allowed to stir overnight. The reaction was quenched with a saturated NH_4Cl solution and the mixture extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried. Removal of the solvent gave the alcohol **6e** (55 mg, 100 %) as colourless crystals, mp 139–140°C. ν_{max} (film)/cm^{-1} 3243 (br s, OH), 1641 (s, C=O), 1535 (s). δ_H 7.82 (dd, J_1 2, J_2 6.8, 2H), 7.59 (br s, 1H), 7.42–7.40 (m, 2H), 4.10 (s, 3H), 3.74 (t, *J* 6.0, 2H), 3.55 (dt, J_1 6.8, J_2 6.4, 2H), 1.73–1.70 (m, 4H). δ_C 162.0, 151.0, 139.1, 132.5, 126.7, 124.5, 124.0, 123.7, 122.0, 62.3, 61.9, 39.0, 30.1, 26.50. *m/z* (ESI$^+$) 280 (100 %, [M + H]$^+$), 191 (10). *m/z* (HRMS, EI$^+$) 279.0929. $C_{14}H_{17}NO_3S$ requires 279.0929.

N-*(4′-Bromobuty1)-3-hydroxy-benzo[*b*]thiophene-2-carboxamide (**7b**)*

Boron tribromide (0.2 mL) was added dropwise to a solution of the alcohol **6e** (100 mg, 0.36 mmol) in CH_2Cl_2 (10 mL) at −78°C under nitrogen. The dry ice bath was then removed and the reaction mixture stirred overnight. The reaction was quenched with water and the mixture extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried. Chromatography of the residue (10 % ethyl acetate/hexane) afforded the bromide **7b** (105 mg, 90 %) as a grey powder, mp 87–88°C. ν_{max} /cm^{-1} 3354 (w, NH), 1626 (m, C=O), 1586 (s). δ_H 7.94 (dd, J_1 0.8, J_2 8.0, 1H), 7.72 (dd, J_1 0.8, J_2 8.0, 1H), 7.49 (dt, J_1 1.2, J_2 8.0, 1H), 7.42 (dt, J_1 1.2, J_2 8.0, 1H), 5.60 (br s, 1H), 3.5 (dt, J_1 7.2, J_2 6.8, 2H), 3.47 (t, *J* 6.4, 2H), 1.99–1.95 (m, 2H), 1.85–1.81 (m, 2H). δ_C 166.9, 158.9, 136.1, 131.2, 128.5, 124.7, 122.9, 122.8, 102.5, 38.6, 33.1, 29.8, 28.3. *m/z* (EI$^+$) 327, 329 (15 %, M$^{+\bullet}$). *m/z* (HRMS, EI$^+$) 326.9926. $C_{13}H_{14}{}^{79}BrNO_2S$ requires 326.9929.

*3,4,5,6-Tetrahydro-benzo[*b*]thieno[3,2-*b*][1,5]oxazonin-7(2*H*)-one (**1b**)*

Sodium hydride (10 mg, 0.4 mmol) was added to a solution of the bromide **7b** (40 mg, 0.12 mmol) in THF (20 mL) under nitrogen. After stirring overnight, water was added to stop the reaction. The reaction mixture was extracted with ethyl acetate (3 × 15 mL). The extracts were washed with brine (10 mL) and dried. The solvent was evaporated to furnish, after column chromatography (15 % ethyl acetate/hexane) of the residue, the cyclised compound **1b** (28 mg, 70 %) as colourless crystals, mp 95–96°C. ν_{max} /cm^{-1} 1621 (w, C=O), 1565 (s). δ_H 7.99–7.96 (m, 1H), 7.75–7.73 (m, 1H), 7.48 (dt, J_1 1.2, J_2 8.0, 1H), 7.41 (dt, J_1 1.2, J_2 8.0, 1H), 3.84–3.80 (m, 4H), 2.01–1.98 (m, 4H). δ_C 166.6, 160.9, 137.9, 130.8, 128.1, 124.3, 122.8, 122.4, 101.6, 76.6, 47.0 (C3,4,5). *m/z* (EI$^+$) 247 (M$^{+\bullet}$, 69). *m/z* (HRMS, EI$^+$) 247.0670. $C_{13}H_{13}NO_2S$ requires 247.0667. Anal. Calc. for $C_{13}H_{13}NO_2S$: C 63.14, H 5.30, N 5.66. Found: C 63.55, H 5.80, N 5.19 %.

N-*(5′-Hydroxypenty1)-3-methoxy-benzo[*b*]thiophene-2-carboxamide (**6f**)*

A mixture of the acid **4** (208 mg, 1 mmol), 1,3-dicyclohexylcarbodiimide (206 mg, 1 mmol), 1-hydroxybenzotriazole (150 mg, 1.1 mmol), and 5-aminopentan-l-ol in DMF (10 mL) was stirred overnight. The solvent was removed under high vacuum, and the residue was chromatographed (30 % ethyl acetate/hexane) to afford the alcohol **6f** (240 mg, 80 %) as colourless crystals, mp 68–69°C. ν_{max} (film)/cm^{-1} 3463 (m, OH), 3387 (m, NH), 1634 (s, C=O), 1535 (s). δ_H 7.83–7.80 (m, 2H), 7.53 (br s, 1H), 7.42–7.39 (m, 2H), 4.1 (s, 3H), 3.67 (t, *J* 6.4, 2H), 3.50 (dt, J_1 7.2, J_2 6.8, 2H), 1.76 (br s, 1H), 1.66–1.68 (m, 4H), 1.52–1.49 (m, 2H). δ_C 161.8, 150.0, 137.7, 132.4, 126.6, 124.4, 123.6, 121.9, 124.2, 62.5, 61.9, 39.3, 32.3, 29.6, 23.1. *m/z* (ESI$^-$) 292 (65 %, [M − H]$^-$); (ESI$^+$) 316 (100 %, [M + Na]$^+$), 294 (22, [M + H]$^+$). *m/z* (HRMS, EI$^+$) 293.1090. $C_{15}H_{19}NO_3S$ requires 293.1086.

N-*(5′-Bromopenty1)-3-hydroxy-benzo[*b*]thiophene-2-carboxamide (**7c**)*

An excess of boron tribromide (0.2 mL) was added dropwise to a solution of the alcohol **6f** (100 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) at −78°C under nitrogen. After addition, the dry ice bath was removed and the reaction mixture stirred overnight. The reaction was quenched with water and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried. Chromatography of the residue (15 % ethyl acetate/hexane) yielded the bromide **7c** (100 mg, 86 %) as pink crystals, mp 94–95°C. ν_{max} /cm^{-1} 3356 (m, NH), 1610 (s, C=O), 1550 (m). δ_H 7.93 (dd, J_1 0.8, J_2 8.0, 1H), 7.71 (dd, J_1 0.8, J_2 8.0, 1H), 7.48 (dt, J_1 1.2, J_2 8.0, 1H), 7.40 (dt, J_1 1.2, J_2 8.0, 1H), 5.60 (br s, 1H), 3.46 (dt, J_1 7.2, J_2 6.8, 2H), 3.42 (t, *J* 6.4, 2H), 1.95–1.49 (m, 6H). δ_C 166.9, 158.7, 136.1, 131.2, 128.4, 124.6, 122.9, 122.8, 102.4, 39.3, 33.5, 32.1,

28.9, 25.3. *m/z* (ESI^-) 340, 342 (95%, $[M-H]^-$), 79, 81 (89). *m/z* (HRMS, EI^+) 341.0079. $C_{14}H_{16}{}^{79}BrNO_2S$ requires 341.0085.

*4,5,6,7-Tetrahydro-2H-benzo[b]thieno[3,2-b][1,5]oxazecin-8(3H)-one (**1c**)*

An excess of sodium hydride (10 mg, 0.4 mmol) was added to a solution of the bromide **7c** (68 mg, 0.2 mmol) in THF (20 mL). After stirring for 1 h, no reaction occurred. The reaction mixture was heated at reflux for 1 h, and then quenched with water. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried. The solvent was evaporated and the residue was chromatographed (15% ethyl acetate/hexane) to give the cyclised compound **1c** (42 mg, 81%) as pink crystals, mp 69–70°C. ν_{max} /cm^{-1} 1573 (m), 1527 (m). δ_H 7.98–7.96 (m, 1H), 7.72–7.70 (m, 1H), 7.47–7.45 (m, 1H), 7.42–7.39 (m, 1H), 3.86–3.83 (m, 4H), 2.08 (br s, 1H), 1.72–1.70 (m, 6H). δ_C 167.0, 161.8, 137.3, 130.8, 128.4, 124.4, 122.8, 122.1, 101.2, 46.1 (2C), 26.2 (2C), 24.5. *m/z* (EI^+) 261 ($M^{+\bullet}$, 65), 176 (94). *m/z* (HRMS, EI^+) $M^{+\bullet}$ 261.0787. $C_{14}H_{15}NO_2S$ requires 261.0824. Anal. Calc. for $C_{14}H_{15}NO_2S$: C 64.34, H 5.79, N 5.36. Found: C 64.15, H 5.97, N 5.36%.

Supplementary Material

NMR and mass spectra are available on the Journal's website.

Acknowledgements

The authors thank the Australian Research Council for financial support. They also thank Dr M. Song, University of Sydney, and Dr N. Davies, University of Tasmania, for the high resolution mass spectra, and Mr A. Shakoori for help with the manuscript. Assistance for this research from the University of Wollongong is also gratefully acknowledged, together with the valued friendship and support of the late Emeritus Professor Roger Brown.

References

[1] T. P. Majhi, B. Achari, P. Chattopadhyay, *Heterocycles* **2007**, *71*, 1011. doi:10.3987/REV-07-612

[2] D. B. Ramachary, V. V. Narayana, M. S. Prasad, K. Ramakumar, *Org. Biomol. Chem.* **2009**, *7*, 3372. doi:10.1039/B910397J

[3] V. V. Potapov, N. A. Fetisova, A. V. Nikitin, A. V. Ivachtchenko, *Mendeleev Commun.* **2009**, *19*, 287. doi:10.1016/J.MENCOM.2009.09.020

[4] B. Roy, R. N. De, S. Hazra, *Lett. Org. Chem.* **2011**, *8*, 391. doi:10.2174/157017811796064502

[5] G. Cirrincione, P. Diana, in *Comprehensive Heterocyclic Chemistry III* (Eds A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor) **2008**, Vol. 14, pp. 303–474 (Elsevier: Amsterdam, The Netherlands).

[6] S. Seto, A. Tanioka, M. Ikeda, S. Izawa, *Bioorg. Med. Chem.* **2005**, *13*, 5717. doi:10.1016/J.BMC.2005.06.015

[7] K. Ramig, *Tetrahedron* **2013**, *69*, 10783. doi:10.1016/J.TET.2013.10.023

[8] C. J. Ohnmacht, J. S. Albert, P. R. Bernstein, W. L. Rumsey, B. B. Masek, B. T. Dembofsky, G. M. Koether, D. W. Andisik, D. Aharony, *Bioorg. Med. Chem.* **2004**, *12*, 2653. doi:10.1016/J.BMC.2004.03.015

[9] J. S. Albert, C. Ohnmacht, P. R. Bernstein, W. L. Rumsey, D. Aharony, B. B. Masek, B. T. Dembofsky, G. M. Koether, W. Potts, J. L. Evenden, *Tetrahedron* **2004**, *60*, 4337. doi:10.1016/J.TET.2004.03.054

[10] S. Conde, C. Corral, J. Lissavetzky, *J. Heterocycl. Chem.* **1980**, *17*, 937. doi:10.1002/JHET.5570170518

[11] K. M. George, M.-C. Frantz, K. Bravo-Altamirano, C. R. LaValle, M. Tandon, S. Leimgruber, E. R. Sharlow, J. S. Lazo, Q. J. Wang, P. Wipf, *Pharmaceutics* **2011**, *3*, 186. doi:10.3390/PHARMACEUTICS3020186

[12] J. B. Bremner, E. J. Browne, L. M. Engelhardt, C. S. Greenwood, A. H. White, *Aust. J. Chem.* **1988**, *41*, 1815. doi:10.1071/CH9881815

[13] S. S. Khatana, D. H. Boschelli, J. B. Kramer, D. T. Connor, H. Barth, P. Stoss, *J. Org. Chem.* **1996**, *61*, 6060. doi:10.1021/JO960235M

[14] D. H. Boschelli, D. T. Connor, J. B. Kramer, P. C. Unangst, **1995**, (*Chem. Abstr.* **1996**, *124*, 117357s).

[15] W. B. Wright, Jr, H. J. Brabander, *J. Heterocycl. Chem.* **1971**, *8*, 711. doi:10.1002/JHET.5570080504

[16] D. T. Connor, W. A. Cetenko, M. D. Mullican, R. J. Sorenson, P. C. Unangst, R. J. Weikert, R. L. Adolphson, J. A. Kennedy, D. O. Thueson, C. D. Wright, M. C. Conroy, *J. Med. Chem.* **1992**, *35*, 958. doi:10.1021/JM00083A023

[17] Y. Matsuki, Y. Adachi, *Nippon Kagaku Zasshi* **1968**, *89*, 192 (*Chem. Abstr.* **1968**, *69*, 67165).

[18] A. Saeed, Z. Ashraf, *J. Chem. Sci.* **2006**, *118*, 419. doi:10.1007/BF02711452

[19] N. Boechat, J. C. S. Da Costa, J. S. Mendonça, K. C. Paes, E. L. Fernandes, P. S. M. De Oliveira, T. R. A. Vasconcelos, M. V. N. De Souza, *Synth. Commun.* **2005**, *35*, 3187. doi:10.1080/00397910500214482

[20] G. Orzalesi, R. Selleri, O. Caldini, *Boll. Chim. Farm.* **1972**, *111*, 749 (*Chem. Abstr.* **1973**, *78*, 147929).