Tetrahedron 66 (2010) 3452–3456

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

S→N type Smiles rearrangement of the aminoethanethiol moiety attached to heterocyclic compounds

Simon J. Mountford [a], Eva M. Campi [a], Andrea J. Robinson [b], Milton T.W. Hearn [a,*]

[a] Centre for Green Chemistry, School of Chemistry, Monash University, Clayton 3800, Australia
[b] School of Chemistry, Monash University, Clayton 3800, Australia

ARTICLE INFO

Article history:
Received 5 January 2010
Received in revised form 19 February 2010
Accepted 8 March 2010
Available online 12 March 2010

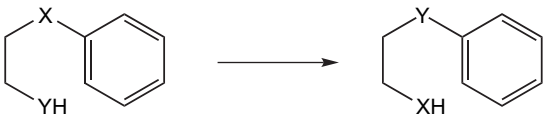
Keywords:
S→N type Smiles rearrangement
Aminoethanethiol heterocycles
Pyridine aminoalkylthiols
Pyridin-2-ylsulfanylalkylamines
Triazinylsulfanylalkylamines

ABSTRACT

Base catalysed S→N type Smiles rearrangement of aminoethanethiol-substituted pyridine and triazine compounds led to formation of the corresponding thiol or disulfide compounds. Prior to rearrangement, the heteroaryl sulfanylethylamines could be prepared in high yields as the hydrochloride or trifluoroacetate salts from the corresponding *tert*-BOC protected amine.

1. Introduction

Reactions that involve heteroatom migration as illustrated by the intramolecular nucleophilic substitution process shown in Scheme 1 are known as Smiles rearrangements. The rearrangement usually involves YH groups such as –OH, –SH, $-SO_2H$, $-NH_2$, or –NHacyl and X groups such as O, S, SO or SO_2.[1] Bunnett and Zahler have reviewed the early literature of this rearrangement and summarised various combinations of X and YH.[2]



Scheme 1. General representation of the Smiles rearrangement.

The rearrangement is usually base catalysed although acid[1,3] and heat[1,4] catalysed rearrangements have also been reported. The bridging carbon atoms between X and Y can be either saturated[5–7] or incorporated in an aromatic ring.[3,8–10] The rate of rearrangement is influenced by the nucleophilicity of Y, the acidity of the Y–H function, as well as the lability of X.[2] Although Warren and Smiles[11] first encountered this type of rearrangement in reactions involving unactivated naphthalene derivatives, many rearrangements involve aromatic rings activated by substituents such as *ortho*- and *para*-nitro groups[1,2,5,10,12] and occur with triazines[13,14] or heteroatom bridged pyridine systems.[1,4,12] Smiles type rearrangements have been proposed to occur with uracils,[8,9] thiadiazoles,[16] thiohydrazonates,[17] anilines[18] and pyrimidines.[19] They have also been reported to be involved in the synthesis of phenothiazines,[10,15] dipyridothiazines,[20] pyrido[1,4]-[21] and benzo[*b*][1,4]-thiazinones,[22] α-arylaminothiocarboxamides[23] and 2,4-disubstituted piperidines[24] A few of these rearrangements involve a saturated thioethylamine chain and have been reported in nitroarene,[5] aryl cytosine[6] and isocytosine[7] systems.

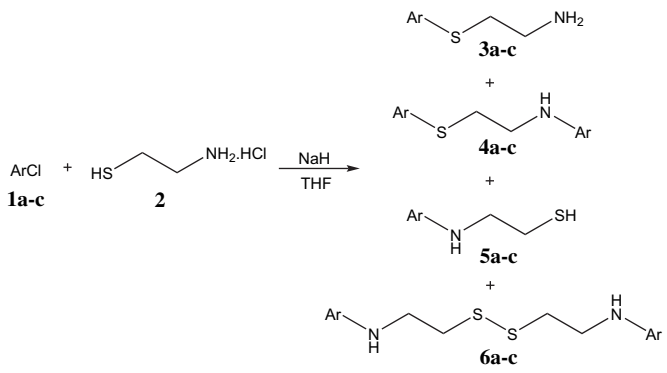
Herein we report a facile S→N type Smiles rearrangement that also occurs when an aminoethanethiol group is attached to substituted pyridine and triazine compounds.

2. Results and discussion

As part of our investigations into the preparation of chemical libraries involving a substituted pyridine core structure for use in the capture and isotopic tag labelling of monoclonal antibodies, the preparation of a variety of aryl sulfanylethylamines **3** was attempted using standard reaction protocols with limited success (Scheme 2). Reactions using NaH in dry THF at ambient temperature gave crude products, which when analysed by ^{1}H NMR spectroscopy were shown to contain a mixture of the desired ethylamine **3** and products **4**, **5** and **6** resulting from a Smiles rearrangement. Table 1 summarises these results.

* Corresponding author. Tel.: +61 3 9905 4547; fax: +61 3 9905 8501; e-mail address: milton.hearn@sci.monash.edu.au.

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.03.027

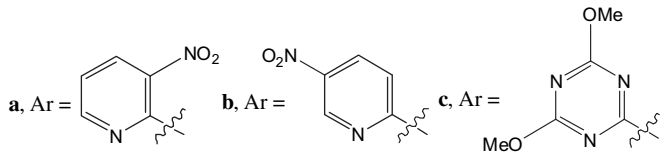


Scheme 2. General procedure (A) for the preparation of heteroaryl sulfanylethylamines and derived Smiles rearrangement products.

Table 1
Ratio of products (determined by ^{1}H NMR. spectroscopy) observed from reactions of aryl chloride **1** with cysteamine hydrochloride **2** at ambient temperature

Entry	1	Time	Product ratio[a] %			
			3	4	5	6
i	Ar=a	3 h	70 (Trace)	—	—	30 (Trace)
ii	Ar=b	3 h	5	20 (Trace)	60	15 (Trace)
iii	Ar=c	6 h	25	31	—	44
iv[b]	Ar=c	6 h	6 (0)	17 (38)	71 (13)	6 (10)

[a] Purified yield in brackets.
[b] K_2CO_3 substituted for NaH.

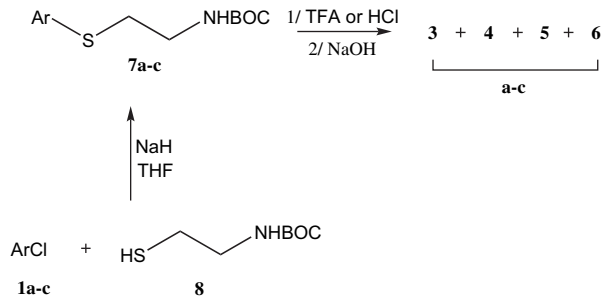


For example, reaction of 2-chloro-3-nitropyridine **1a** initially gave **3a** and the disulfide **6a** in a 70:30 ratio (Table 1, entry i), with the product **6a** presumably resulting from the oxidation of the rearranged thiol **5a**. Attempted purification on silica led to isolation of **3a** and **6a** in low yield. In contrast, reaction of the 5-nitropyridine analogue **1b** gave mainly the rearranged thiol **5b** as well as **4b** and the disulfide **6b** (ratio 60:20:15) and only ca. 5% of **3b** (Table 1, entry ii). None of the thiol **5b** was isolated after chromatography, with only small amounts of **4b** and **6b** recovered.

Similarly, reaction of 2-chloro-4,6-dimethoxytriazine **1c** gave the desired ethylamine **3c** as well as **4c** and the disulfide **6c** in a ratio of 25:31:44 (Table 1, entry iii). None of the thiol **5c** was detected. In contrast, a reaction using K_2CO_3 as base gave mainly this thiol **5c** with small amounts of **3c**, **4c** and **6c** (Table 1, entry iv). Chromatography gave the pure **4c** in 38% yield as well as ca. 10% of the thiol **5c** and the disulfide **6c**. Although ^{1}H NMR spectroscopy of the crude product indicated that the yield of **4c** was only ca. 17%, the compound was isolated as a pure sample in ca. twice this yield, suggesting that a S→N rearrangement had occurred during synthesis and work-up.

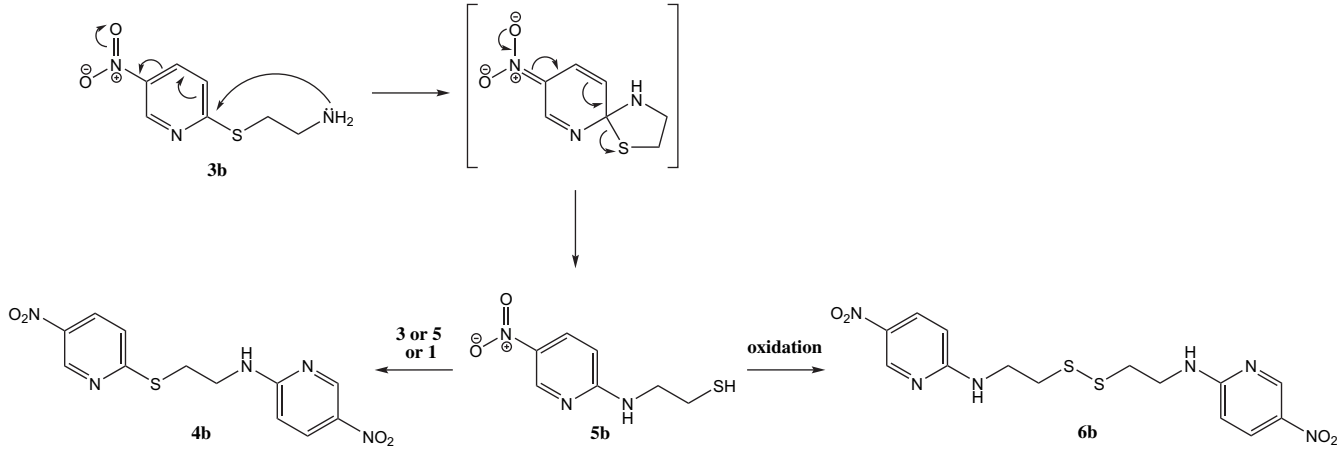
Scheme 3 (for the 5-nitropyridine analogue **3b**) shows a possible mechanism for the conversion of **3** into **5**. This outcome is in accord with recent studies on the mechanism of formation of thiazinone-fused pyridines, which occurs via an *ipso*-Smiles rearrangement,[24] or heterocycle-fused[1,4]oxazine derivatives involving the participation of five-membered spiro-intermediates.[25,26] Compound **4** can result from a reaction, on a 1:1 molar ratio, of the thiol **5** with either itself or the amine **3** during the synthesis of **3** or during isolation and/or purification of reaction products. It can also be formed by reaction of **5** with the starting aryl chloride **1** during the initial synthesis process.

An alternative route to the sulfanylethylamines **3** was investigated via the *tert*-BOC protected analogues **7**. These compounds were readily prepared (Scheme 4) in good to excellent yield (**7a** 99%; **7b** 100%; **7c** 79%) from the reaction of the *tert*-BOC protected thioethylamine **8** with aryl chlorides **1**.



Scheme 4. General procedure (B) for the preparation of heteroaryl sulfanylethylamines.

Deprotection of **7a** with 5 M aq HCl led to complete conversion to the HCl salt of **3a**. Basification gave a 95% conversion to the amine **3a** with only traces of the disulfide **6a** observed. The amine was isolated in an 88% yield (Table 2, entry i). In contrast, deprotection of **7b** with 5 M aq HCl gave the HCl salt of **3b** in 86% yield but basification led to rearrangement, with **4b**, **5b** and **6b** present in the



Scheme 3. Proposed mechanism of the Smiles rearrangement for 2-(5′-nitropyridin-2′-ylsulfanyl)ethanamine **3b**.

Table 2
Ratio of products (determined by ^{1}H NMR. spectroscopy) observed from *tert*-BOC deprotection of compound **7** with HCl or TFA

Entry	7	Time	Products ratio[a] %			
			3	4	5	6
i[b]	Ar=a	19 h	>95 (88)	—	—	<5 (0)
ii[b]	Ar=b	5 h	—	25	50	25
iii[c]	Ar=b	5 min	—	55	20	25
iv[c]	Ar=c	5 min	8	—	88	4

[a] Purified yield in brackets; a; b; c; as in Table 1.
[b] *tert*-BOC deprotection of compound **7** with HCl.
[c] *tert*-BOC deprotection of compound **7** with TFA.

ratio 25:50:25, respectively (Table 2, entry ii). Deprotection of **7b** with TFA for 5 min gave a 93% isolated yield of the TFA salt of **3b**. Basification again led to rearrangement of **3b** to **4b**, **5b** and **6b** in the ratio of 55:20:25, respectively (Table 2, entry iii).

The results of the reactions of **1a** and **1b**, and **7a** and **7b**, suggest that NO_2-substitution of the pyridine core in the 5-position contributed significantly to the propensity for Smiles rearrangement to occur. Interestingly, both Morak-Mlodawska and Pluta[20] and Ma et al.[21] have reported that with 2-substituted nitro- or halo-pyridines, the rearrangement is followed by cyclisation with loss of the *ortho*-nitro or *ortho*-halogen substituent, respectively, whereas we observed no evidence for any loss of the nitro-group or pyrido[1,4]thiazinone cyclisation product formation in the reaction of **1a**.

The TFA salt of the triazine ethylamine **3c** was prepared in 89% yield from the *tert*-BOC protected compound **7c**. Basification gave small amounts of **3c** and **6c** with conversion mainly to the thiol **5c** (Table 2, entry iv). This result is consistent with the attempted preparation of **3c** from **1c**, which also gave mainly the thiol **5c** (Table 1, entry iv).

In the presence of base, Smiles rearrangement of some heteroaryl thioethylamines led to the corresponding thiols, which can further react or oxidise. These results are consistent with the S→N rearrangement of similar cysteamine and related derivatives described previously.[5–7] While the *tert*-BOC protected heteroaryl thioethylamines **7** can be readily prepared in excellent yield and deprotected to give the amine salts of **3**, treatment of these salts with base gives variable results, with rearrangement again usually occurring. As such, it is essential that the free base of **3** is liberated in situ if required for further reaction. Inert conditions are more likely to favour the formation of compound **5** with the exclusion of air during work-up and purification limiting the potential for disulfide formation by oxidation of **5** to **6**. Furthermore, the presence of base and heat is likely to cause compound **5** to either react with compound **3** or self react to give **4**.

3. Experimental

3.1. General

Nuclear magnetic resonance spectra were recorded at 300 MHz (^{1}H) or 75 MHz (^{13}C) with a Bruker DPX-300 spectrometer or at 400 MHz (^{1}H) or 100 MHz (^{13}C) with a Bruker DRX-400 spectrometer. The NMR. spectra refer to solutions in deuterated base-washed (Na_2CO_3) $CDCl_3$ where tetramethylsilane (TMS) was used as the internal standard (δ 0.00 ppm) for ^{1}H spectra and the residual solvent peak used as an internal reference in ^{13}C NMR. spectra. Chemical shift values (δ) are given in parts per million (ppm) relative to the residual solvent peak (or TMS) and coupling constants are given in hertz (*J* Hz). Infrared spectra were recorded on a Perkin Elmer 1600 series Fourier Transform infrared spectrometer. High-resolution electrospray mass spectra (HRMS) were recorded on a Bruker BioApex 47e Fourier Transform mass spectrometer. Melting points were determined using a Gallenkamp melting point apparatus with a digital thermometer and are uncorrected. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride, stored over sodium wire and distilled from sodium and benzophenone prior to use. Reagents and compounds were purchased from Sigma–Aldrich, Castle Hill, NSW, Australia.

3.2. General procedure (A) for the preparation of heteroaryl sulfanylethanamines. Exemplified by the preparation of 2-(3′-nitropyridin-2′-ylsulfanyl)ethanamine (3a)

2-Aminoethanethiol hydrochloride (80 mg, 0.69 mmol) was suspended in dry THF (3 mL). NaH (dry, 95%) (35 mg, 1.46 mmol) (or anhydrous K_2CO_3, 200 mg, 1.46 mmol) was added portion-wise and the mixture stirred under a nitrogen atmosphere with ice bath cooling. 2-Chloro-3-nitropyridine (0.10 g, 0.63 mmol) was added to the mixture, which was stirred for 2 h before the ice bath was removed and the mixture stirred at ambient temperature for 1 h. Water (10 mL) was added slowly and the THF removed in vacuo. The aqueous solution was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was dried ($MgSO_4$), filtered and solvent removed in vacuo to give a brown oil (0.11 g). Preparative TLC. (SiO_2, CH_2Cl_2/MeOH/NH_4OH, 9:1:0.1) gave traces of *N*,*N*′-(disulfanediyldiethane-2′,1′-diyl)-bis-(3-nitropyridine-2-amine) **6a** and the desired product **3a** as yellow oils. The IR of **3a** exhibited the following ν_{max} (neat): 3374m, 3076m, 2930m, 2863m, 1585s, 1556s, 1509s, 1396s, 1333s, 1257s, 1226m, 1152m, 1128m, 1071s, 1013w, 858s, 817m, 743s cm^{-1}. The IR spectra of the various other PSEA derivatives exhibited very similar spectra to **3a**, with absorbances for the aromatic, –CH_3, OCH_3 or N–CH_2 vibrational frequencies in region of ν_{max} ~2900–2800 cm^{-1}, aromatic NO_2 or NH_2 in region of ν_{max} ~1580–1530 cm^{-1}, NO_2 in region of ν_{max} 1350–1320 cm^{-1}, C–NO_2 in the region of ν_{max} 1560 cm^{-1} and 1350 cm^{-1}, lowered by ~30 cm^{-1} when conjugated, and the aromatic ν_{max} at 1600 cm^{-1}, 1580 cm^{-1} and 1500 cm^{-1}, respectively.

*3.2.1. 2-(3′-Nitropyridin-2′-ylsulfanyl)ethanamine (**3a**).* IR (neat): 3374, 3076, 2930, 2863, 1585, 1556, 1509, 1396, 1333, 1257, 1226, 1152, 1128, 1071, 1013, 858, 817, 743 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (br s, 2H, NH_2), 3.04 (t, *J*=6.5 Hz, 2H, H1), 3.35 (t, *J*=6.5 Hz, 2H, H2), 7.21 (dd, *J*=8.2, 4.6 Hz, 1H, H5′), 8.48 (dd, *J*=8.2, 1.7 Hz, 1H, H4′), 8.69 (dd, *J*=4.6, 1.7 Hz, 1H, H6′). ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.3, 41.2, 118.8, 133.8, 142.2, 153.1, 157.6. MS (ESI): *m*/*z* 200.1 $(M+H)^+$ (48%), 165.1 (100). HRMS (ESI^+, MeOH): $(M+H)^+$, found *m*/*z* 200.0488. $C_7H_{10}N_3O_2S$ requires 200.0494.

*3.2.2. N,N′-(Disulfanediyldiethane-2′,1′-diyl)-bis-(3-nitropyridine-2-amine) (**6a**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.03 (t, *J*=6.6 Hz, 4H, H2′), 4.01 (apparent q, *J*=6.6 Hz, 4H, H1′), 6.68 (dd, *J*=8.2, 4.6 Hz, 2H, H5), 8.41 (dd, *J*=4.6, 1.8 Hz, 2H, H6), 8.43 (dd, *J*=8.2, 1.8 Hz, 2H, H4), NH not observed. ^{13}C NMR (50 MHz, $CDCl_3$): δ 37.9, 40.4, 112.4, 128.6, 135.5, 152.6, 155.8. MS (ESI): *m*/*z* 397.2 $(M+H)^+$ (60%), 322.1 (34), 197.9 (100). HRMS (ESI^+, CH_2Cl_2/MeOH, 1:4): $(M+Na)^+$, found *m*/*z* 419.0566. $C_{14}H_{16}N_6NaO_4S_2$ requires 419.0572.

*3.2.3. 5-Nitro-N-{2′-[(5″-nitropyridin-2″-yl)sulfanyl] ethyl}pyridin-2-amine (**4b**).* Orange solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.56 (t, *J*=6.4 Hz, 2H, H2′), 3.84 (apparent q, *J*=6.4 Hz, 2H, H1′), 5.93 (br s, 1H, NH), 6.42 (d, *J*=9.2 Hz, 1H, H3), 7.36 (dd, *J*=8.9, 0.7 Hz, 1H, H3″), 8.19 (dd, *J*=9.2, 2.6 Hz, 1H, H4), 8.27 (dd, *J*=8.9, 2.7 Hz, 1H, H4″), 9.02 (d, *J*=2.6 Hz, 1H, H6), 9.26 (dd, *J*=2.7, 0.7 Hz, 1H, H6″). ^{13}C NMR (75 MHz, DMSO): δ 29.1, 30.6, 108.6, 121.7, 131.4, 131.9, 134.7, 141.3, 144.7, 146.7, 161.2, 166.5. HRMS (ESI^+, CH_2Cl_2/MeOH, 1:4): $(M+Na)^+$, found *m*/*z* 344.0428. $C_{12}H_{11}N_5NaO_4S$ requires 344.0429.

*3.2.4. 2-[(5-Nitropyridin-2-yl)amino]ethanethiol (**5b**).* Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.82 (t, *J*=6.4 Hz, 2H, H2), 3.68 (apparent

q, J=6.4 Hz, 2H, H1), 5.97 (br s, 1H, NH), 6.45 (d, J=9.2 Hz, 1H, H3′), 8.16 (dd, J=9.2, 2.6 Hz, 1H, H4′), 8.99 (d, J=2.6 Hz, 1H, H6′), SH not observed.

*3.2.5. N,N′-(Disulfanediyldiethane-2′,1′-diyl)-bis-(5-nitropyridin-2-amine) (**6b**).* Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.97 (t, J=6.4 Hz, 4H, H2′), 3.84 (apparent q, J=6.4 Hz, 4H, H1′), 5.68 (br s, 2H, NH), 6.42 (d, J=9.2 Hz, 2H, H3), 8.18 (dd, J=9.2, 2.7 Hz, 2H, H4), 9.03 (d, J=2.7 Hz, 2H, H6). MS (ESI): m/z 419.2 $(M+Na)^+$ (100%). HRMS (ESI^+, CH_2Cl_2/MeOH, 1:4): $(M+Na)^+$, found m/z 419.0575. $C_{14}H_{16}N_6NaO_4S_2$ requires 419.0572.

*3.2.6. N-{2′-[(4″,6″-Dimethoxy-1″,3″,5″-triazin-2″-yl)sulfanyl]ethyl}-4,6-dimethoxy-1,3,5-triazin-2-amine (**4c**).* Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40 (t, J=6.4 Hz, 2H, H2′), 3.82 (apparent q, J=6.4 Hz, 2H, H1′), 3.91 (s, 3H, OMe), 3.97 (s, 3H, OMe), 4.02 (s, 6H, OMe), 6.15 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.1, 40.8, 54.8, 54.9, 55.5, 168.4, 171.3, 172.3, 172.8, 184.6. MS (ESI): m/z 378.1 $(M+Na)^+$ (100%). HRMS (ESI^+): $(M+Na)^+$, found m/z 378.0954. $C_{12}H_{17}N_7NaO_4S$ requires 378.0960.

*3.2.7. 2-(4′,6′-Dimethoxy-1′,3′,5′-triazin-2′-ylamino) ethanethiol (**5c**).* White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (t, J=8.4 Hz, 1H, SH), 2.77 (dt, J=8.4, 6.6 Hz, 2H, H1), 3.64 (apparent q, J=6.6 Hz, 2H, H2), 3.94 (s, 3H, OMe), 3.97 (s, 3H, OMe), 6.67 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 44.1, 54.7, 54.8, 168.4, 172.3, 172.8. MS (ESI): m/z 239.0 $(M+Na)^+$ (100%). HRMS (ESI^+): $(M+Na)^+$, found m/z 239.0571. $C_7H_{12}N_4NaO_2S$ requires 239.0579.

*3.2.8. N,N′-(Disulfanediyldiethane-2′,1′-diyl)bis(4,6-dimethoxy-1,3,5-triazin-2-amine) (**6c**).* Cream solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (t, J=6.4 Hz, 4H, H2′), 3.78 (apparent q, J=6.4 Hz, 4H, H1′), 3.93 (s, 6H, OMe), 3.97 (s, 6H, OMe), 5.88 (br s, 2H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.1, 40.0, 54.8, 54.9, 168.4, 172.4, 172.8. MS (ESI): m/z 453.1 $(M+Na)^+$, (100%). HRMS (ESI^+): $(M+Na)^+$, found m/z 453.1101. $C_{14}H_{22}N_8NaO_4S_2$ requires 453.1103.

3.3. General procedure (B) for the preparation of heteroaryl sulfanylethanamines via the *tert*-BOC protected derivatives 7. Exemplified by the preparation of *tert*-butyl{2-[(3′-nitropyridin-2′-yl)sulfanyl]ethyl}carbamate (7a)

tert-Butyl (2-sulfanylethyl)carbamate **8** (1.84 g, 10.4 mmol) was dissolved in dry THF (20 mL) and cooled in an ice bath under a nitrogen atmosphere. NaH (dry, 95%) (0.28 g, 11.4 mmol) was added portion-wise over 20 min and the mixture allowed to stir for 10 min before portion-wise addition of 2-chloro-3-nitropyridine (1.50 g, 9.46 mmol). The mixture was stirred for 20 min then allowed to warm to ambient temperature and stirred for 1.5 h. Water (30 mL) was added slowly and the THF removed under reduced pressure. The aqueous solution was extracted with CH_2Cl_2 (4×15 mL). The combined organic layer was dried ($MgSO_4$), filtered and solvent removed in vacuo to give a brown oil (3.30 g). Column chromatography (SiO_2, CH_2Cl_2/hexane, 7:1) afforded the title compound **7a** as a yellow oil (2.82 g, 99%). *tert*-Butyl{2-[(3′-nitropyridin-2′-yl)sulfanyl]ethyl}carbamate **7a** (1.50 g, 5.01 mmol) was dissolved in EtOAc (10 mL) and 5 M aq HCl (10 mL). The mixture was stirred at ambient temperature for 19 h. The volatile components were removed in vacuo and the HCl salt of the compound **3a** was obtained as a yellow solid (1.36 g, 100%). The yellow solid (0.54 g) was dissolved in water (30 mL), cooled in an ice bath and CH_2Cl_2 (15 mL) was added. The mixture was carefully basified to pH 8.5 with 1 M aq NaOH solution. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (5×15 mL). The combined organic layer was dried ($MgSO_4$), filtered and solvent removed in vacuo to give 2-(3′-nitropyridin-2′-ylsulfanyl)ethanamine (**3a**) as a brown oil (0.35 g, 88%).

*3.3.1. tert-Butyl{2-[(3′-nitropyridin-2′-yl)sulfanyl]ethyl}carbamate (**7a**).* Yellow oil. IR (neat): 3358, 2979, 2933, 1700, 1586, 1557, 1518, 1455, 1398, 1367, 1336, 1254, 1166, 1129, 1071, 1054, 950, 911, 859, 815, 744, 648 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H, CH_3), 3.38 (m, 2H, H2), 3.47 (m, 2H, H1), 5.21 (br s, 1H, NH), 7.25 (dd, J=8.3, 4.6 Hz, 1H, H5′), 8.48 (dd, J=8.3, 1.7 Hz, 1H, H4′), 8.70 (dd, J=4.6, 1.7 Hz, 1H, H6′). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.4, 30.7, 39.7, 79.3, 119.0, 133.8, 142.2, 153.1, 155.9, 157.2. MS (ESI): m/z 322.3 $(M+Na)^+$ (100%). HRMS (ESI^+, MeOH): $(M+H)^+$, found m/z 300.1010. $C_{12}H_{18}N_3O_4S$ requires 300.1018.

*3.3.2. 2-(3′-Nitropyridin-2′-ylsulfanyl)ethanamine hydrochloride (**3a**·HCl salt).* Yellow solid. Mp 198–200 °C. ^{1}H NMR (300 MHz, MeOD): δ 3.32 (m, 2H) and 3.36 (t, J=6.6 Hz, 2H) (H1, H2), 7.44 (dd, J=8.3, 4.6 Hz, 1H, H5′), 8.61 (dd, J=8.3, 1.6 Hz, 1H, H4′), 8.81 (dd, J=4.6, 1.6 Hz, 1H, H6′).

*3.3.3. tert-Butyl{2-[(5′-nitropyridin-2′-yl)sulfanyl]ethyl}-carbamate (**7b**).* General procedure B was followed employing 2-chloro-5-nitropyridine (0.20 g, 1.26 mmol) to give the title compound **7b** as a yellow solid (0.38 g, 100%).

Mp 142–144 °C. IR (KBr): 3374, 2983, 1678, 1586, 1569, 1513, 1445, 1398, 1367, 1339, 1278, 1250, 1163, 1137, 1101, 1059, 1005, 949, 655, 638, 790, 750, 627, 522 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H, CH_3), 3.37–3.48 (m, 4H, H1, H2), 4.94 (br s, 1H, NH), 7.32 (dd, J=8.9, 0.7 Hz, 1H, H3′), 8.23 (dd, J=8.9, 2.7 Hz, 1H, H4′), 9.23 (dd, J=2.7, 0.7 Hz, 1H, H6′). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.6, 30.8, 40.3, 79.8, 121.9, 130.7, 141.6, 145.2, 156.0, 167.3. MS (ESI): m/z 322.2 $(M+Na)^+$ (100%). HRMS (ESI^+, MeOH): $(M+H)^+$, found m/z 300.1011. $C_{12}H_{18}N_3O_4S$ requires 300.1018.

*3.3.4. 2-(5′-Nitropyridin-2′-ylsulfanyl)ethanamine hydrochloride (**3b**·HCl salt).* *tert*-Butyl{2-[(5′-nitropyridin-2′-yl)sulfanyl]ethyl} carbamate **7b** (150 mg, 0.50 mmol) was deprotected as described in general procedure B. The title compound was obtained as a yellow solid (117 mg, 86%). ^{1}H NMR (400 MHz, D_2O): δ 3.48 (t, J=6.4 Hz, 2H) and 3.66 (t, J=6.4 Hz, 2H) (H1, H2), 7.65 (d, J=8.9 Hz, 1H, H3′), 8.49 (dd, J=8.9, 1.8 Hz, 1H, H4′), 9.32 (d, J=1.8 Hz, 1H, H6′).

The attempted conversion of the HCl salt to the free base **3b** using the method described in the general procedure B, Section 3.3 resulted in rearrangement to **4b**, **5b** and **6b** in the ratio 25:50:25, respectively (Table 2, entry ii).

*3.3.5. 2-(5′-Nitropyridin-2′-ylsulfanyl)ethanamine trifluoroacetate (**3b**·TFA salt).* *tert*-Butyl{2-[(5′-nitropyridin-2′-yl)sulfanyl]ethyl} carbamate **7b** (150 mg, 0.50 mmol) was dissolved in trifluoroacetic acid (1.0 mL) and strirred for 5 min. The solvent was removed to give the title compound as a colourless oil (200 mg, 93%). ^{1}H NMR (400 MHz, D_2O): δ 3.46 (t, J=6.4 Hz, 2H) and 3.63 (t, J=6.4 Hz, 2H) (H1, H2), 7.62 (d, J=8.9 Hz, 1H, H3′), 8.46 (dd, J=8.9, 2.3 Hz, 1H, H4′), 9.29 (d, J=2.3 Hz, 1H, H6′).

The attempted conversion of the TFA salt to the free base **3b** using the method described in the general procedure B, Section 3.3 resulted in rearrangement to **4b**, **5b** and **6b** in the ratio 55:20:25, respectively (Table 2, entry iii).

*3.3.6. tert-Butyl 2-(4′,6′-dimethoxy-1′,3′,5′-triazin-2′-ylthio)ethylcarbamate (**7c**).* General procedure B was followed employing 2-chloro-4,6-methoxy-1,3,5-triazine (1.26 g, 7.18 mmol) to give the title compound **7c** as a white solid (1.80 g, 79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H, CH_3), 3.28 (t, J=6.3 Hz, 2H, H2), 3.48 (apparent q, J=6.3 Hz, 2H, H1), 4.02 (s, 6H, OMe). ^{13}C

NMR (100 MHz, $CDCl_3$): δ 28.4, 30.7, 40.1, 55.3, 79.5, 155.8, 171.2, 184.6. HRMS (ESI^+): $(M+Na)^+$, found m/z 339.1090. $C_{12}H_{20}N_4NaO_4S$ requires 339.1103.

*3.3.7. 2-[(4′,6′-Dimethoxy-1′,3′,5′-triazin-2′-yl)sulfanyl] ethanamine trifluoroacetate (**3c**·TFA salt).* *tert*-Butyl 2-(4′,6′-dimethoxy-1′,3′,5′-triazin-2′-ylthio)ethyl carbamate **7c** (0.30 g, 0.95 mmol) was dissolved in trifluoroacetic acid (2 mL) and stirred for 5 min. The solvent was removed to give the title compound as a colourless oil (0.57 g, 89%). ^1H NMR (400 MHz, D_2O): δ 3.39–3.54 (m, 4H, H1, H2), 4.07 (s, 6H, OMe).

The conversion of the TFA salt to the free base **3c** using the method described in the general procedure B, Section 3.3 gave **3c** (8%) and resulted in rearrangement to **5b** and **6b** in the ratio 88:4, respectively (Table 2, entry iv).

Acknowledgements

The support of the Australian Research Council for funding this research is gratefully acknowledged.

References and notes

1. Rodig, O. R.; Collier, R. E.; Schlatzer, R. K. *J. Org. Chem.* **1964**, *29*, 2652–2658.
2. Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273–412.
3. Nagai, T.; Fukushima, Y.; Kuroda, T.; Shimizu, H.; Sekiguchi, S.; Matsui, K. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2600–2602.
4. Takahashi, T.; Maki, Y. *Chem. Pharm. Bull.* **1958**, *6*, 369–373.
5. Knyazev, V. N.; Drozd, V. N.; Minov, V. M. *Tetrahedron Lett.* **1976**, 4825–4828.
6. Kondo, H.; Moriuchi, F.; Sunamoto, J. *J. Org. Chem.* **1981**, *46*, 1333–1336.
7. Sako, M.; Totani, R.; Hirota, K.; Maki, Y. *Chem. Pharm. Bull.* **1994**, *42*, 806–810.
8. Maki, Y.; Hiramitsu, T.; Suzuki, M. *Tetrahedron* **1980**, *36*, 2097–2100.
9. Sako, M.; Ichioka, T.; Totani, R.; Hirota, K. *J. Org. Chem.* **1995**, *60*, 8115–8116.
10. Kachhee, T. L.; Gupta, V.; Gautam, D. C.; Gupta, R. R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 2671–2678.
11. Warren, L. A.; Smiles, S. *J. Chem. Soc.* **1931**, 914–922.
12. Smith, K.; Matthews, I.; Martin, G. E. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2839–2843.
13. Harayama, T.; Okada, K.; Sekiguchi, S.; Matsui, K. *J. Heterocycl. Chem.* **1970**, *7*, 981–986.
14. Bates, I.; Maudru, E.; Phillips, D. A. S.; Renfrew, A. H. M.; Rosenau, T. *Dyes Pigments* **2004**, *63*, 291–299.
15. Mital, R. L.; Jain, S. K. *J. Chem. Soc. C* **1969**, *16*, 2148–2150.
16. Volkova, N. N.; Tarasov, E. V.; Van Meervelt, L.; Toppet, S.; Dehaen, W.; Bakulev, V. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1574–1580.
17. Zahra, J. A.; El-Abadelah, M. M.; Abu Thaher, B. A.; El-Abadla, N. S.; Boese, R. *Heterocycles* **2006**, *68*, 1595–1605.
18. Matsui, K.; Maeno, N.; Suzuki, S.; Shizuka, H.; Morita, T. *Tetrahedron Lett.* **1970**, 1467–1469.
19. Maki, Y.; Suzuki, M. *Chem. Pharm. Bull.* **1972**, *20*, 607–609.
20. Morak-Mlodawska, B.; Pluta, K. *Heterocycles* **2007**, *71*, 1347–1361.
21. Ma, C.; Zhang, Q.; Ding, K.; Xin, L.; Zhang, D. *Tetrahedron Lett.* **2007**, *48*, 7476–7479.
22. Zuo, H.; Li, Z.-B.; Ren, F.-K.; Falck, J. R.; Lijuan, M.; Ahn, C.; Shin, D.-S. *Tetrahedron* **2008**, *64*, 9669–9674.
23. Barthelon, A.; El Kaïm, L.; Gizolme, M.; Grimaud, L. *Eur. J. Org. Chem.* **2008**, 5974–5987.
24. Gandon, L. A.; Russell, A. G.; Güveli, T.; Brodwolf, A. E.; Kariuki, B. M.; Spencer, N.; Snaith, J. S. *J. Org. Chem.* **2006**, *71*, 5198–5207.
25. Li, J.; Wang, L. *Aust. J. Chem.* **2009**, *62*, 176–180.
26. Shin, D.-S.; Park, J. K. *Bull. Korean Chem. Soc.* **2007**, *28*, 2219–2225.