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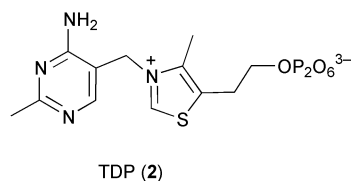
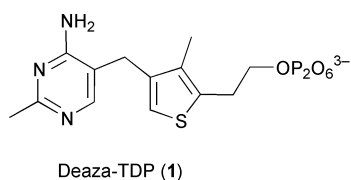
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An efficient ten-step synthesis of deazathiamine is described. The synthesis starts from commercially available α -acetyl- γ -butyrolactone and proceeds *via* deamination of the key aminothiophene **6**. The Gewald synthesis of thiophenes is shown to give a mixture of isomeric products with the unsymmetric ketone used here and so a modified procedure giving a single isomer is developed.

Deazathiamine diphosphate (deaza-TDP) **1** is an analogue of thiamine diphosphate (TDP) **2**, the biologically active form



of thiamin[†] (vitamin B₁), with a neutral thiophene replacing the positively charged thiazolium ring. TDP is the co-enzyme present in a number of enzymes, including pyruvate decarboxylase, transketolase, acetolactate synthase, the pyruvate dehydrogenase complex, pyruvate oxidase, and deoxyxylulose 5-phosphate synthase.

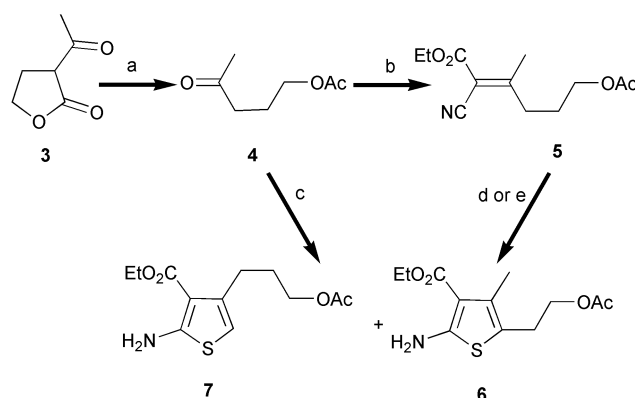
Deaza-TDP is isoelectronic with TDP and so studies of its binding to TDP-dependent enzymes would give accurate information as to the polarity of the active site since the only difference between the two is the difference in charge. Indeed, previous studies have suggested that neutral analogues of TDP may have increased binding affinity.^{1,2} Functionalisation of deaza-TDP at C-2 would give rise to analogues which mimic key reaction intermediates in TDP dependent enzymes. These could then be tested for binding to, and inhibition of, such enzymes. Such inhibitors may also lead to the development of novel herbicides. In this paper we describe the first reported synthesis of deazathiamine.

Results and discussion

The intended route to deazathiamine was *via* the key intermediate aminothiophene **6**. This tetrasubstituted thiophene has been synthesised before³ using a synthesis of thiophenes developed originally by Gewald in the mid 1960's.^{4,5} The published synthesis of **6** involves the conversion of olefin **5** into

aminothiophene **6** by reaction with sulfur in the presence of diethylamine.³

Attempts to repeat this strategy for the synthesis of **6** were only partially successful. Ethyl cyanoacetate and 5-acetoxypentan-2-one **4**, generated from the acetylation of commercially available α -acetyl- γ -butyrolactone **3**, were heated at reflux in benzene in the presence of ammonium acetate and acetic acid using a Dean–Stark apparatus, to give olefin **5** (1 : 1 ratio of *E* and *Z* isomers) in yields of up to 73%. This was subsequently reacted with flowers of sulfur in ethanol, in the presence of diethylamine at 60 °C.³ Work-up however gave a thick black oil which was difficult to purify by column chromatography. Furthermore, ¹H NMR revealed that the product was a mixture of two compounds with identical *R*_f values. A sharp singlet at 5.86 ppm and signals corresponding to three consecutive methylene groups indicated that, along with the desired aminothiophene **6**, there was also present the isomeric thiophene **7** (Scheme 1). No way could be found to separate the two isomers by column chromatography.



Scheme 1 (a) AcOH, HCl, 85%; (b) NCCH₂CO₂Et, AcONH₄, AcOH, C₆H₆, 73%; (c) see Table 1; (d) S, Et₂NH, EtOH, 34%; (e) S, morpholine, *t*-BuOH, 38%.

It was also possible to effect this reaction in a simpler one-pot, three-component condensation.^{4,5} 5-Acetoxypentan-2-one **4** was condensed with ethyl cyanoacetate and flowers of sulfur in either ethanol or *tert*-butyl alcohol in the presence of a disubstituted amine at 50–60 °C. However, these conditions again gave a mixture of aminothiophenes **6** and **7**. Varying the solvent and increasing the steric demands of the base improved the product ratio in favour of the desired aminothiophene, but yields were low and purification remained laborious (Table 1).

[†] The IUPAC name for thiamin is 3-(4-amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium.

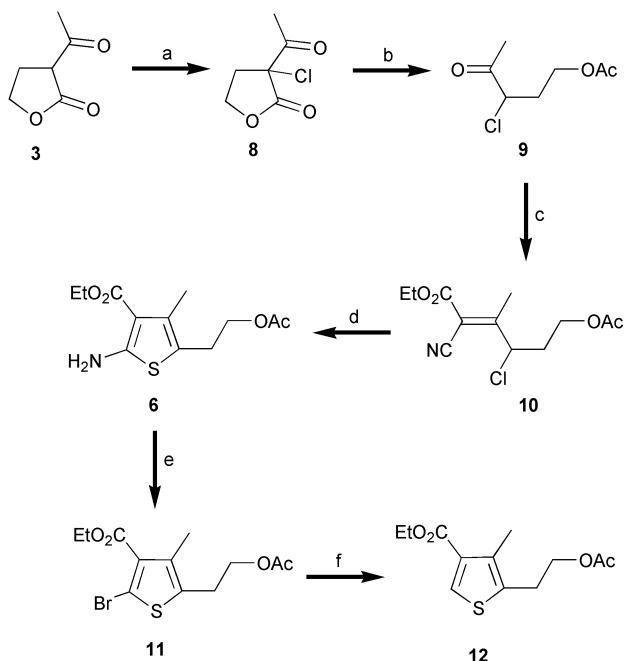
Table 1 Formation of isomeric thiophenes **6** and **7** from ketone **4**

Entry	Solvent	Base	Time ^a /h	Ratio 6:7 ^b	Yield of 6 (%)
1	EtOH	Morpholine	10	2:1	35
2	EtOH	Et ₂ NH	14	3:1	31
3	EtOH	Pr ₂ NH	36	5:1	25
4	Bu ^t OH	Morpholine	6	2:1	33
5	Bu ^t OH	Et ₂ NH	10	3:1	30
6	Bu ^t OH	Pr ₂ NH	16	30:1	18

^a Reaction time at 50–60 °C required for consumption of **4**, as determined by TLC. ^b Determined by ¹H NMR on the crude mixture.

The formation of two alternative products when unsymmetrical ketones are used was not reported by Gewald^{4,5} or other workers who reported the synthesis of aminothiophene **6** by this method.³ Formation of the two possible isomers has, however, been reported in a more recent paper which employed the Gewald method for the synthesis of slightly different thiophenes.⁶

In order to improve the synthesis of **6** it was necessary to modify the precursor to ensure that in the cyclisation reaction, only the desired product was formed. This was achieved by employing a route *via* an α -chloroketone.^{4,7} The chloride would subsequently be displaced by a nucleophilic sulfur atom, thus ensuring only one of the isomeric thiophenes would be produced. α -Acetyl- γ -butyrolactone **3** was chlorinated with sulfonyl chloride to give **8** in 89% yield (Scheme 2). This was



Scheme 2 (a) SO₂Cl₂, 89%; (b) i) AcOH, HCl, ii) Ac₂O, 85%; (c) NCCH₂CO₂Et, AcONH₄, AcOH, PhMe, 43%; (d) NaSH, EtOH, 82%; (e) CuBr₂, *t*-BuONO, CH₃CN; (f) Zn, AcOH, 87% (over 2 steps).

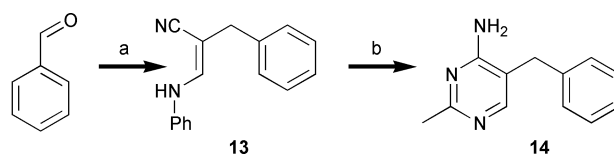
then decarboxylated and acetylated by heating with acetic and hydrochloric acids followed by the addition of acetic anhydride to give 5-acetoxy-3-chloropentan-2-one **9** in 85% yield.⁸ Condensation of **9** with ethyl cyanoacetate, using the conditions previously outlined for the analogous condensation of **4** with ethyl cyanoacetate, gave the desired product (as a 1:1 mixture of *E* and *Z* isomers) in a rather low 43% yield. However, the starting materials were recovered, during the purification by vacuum distillation, and could be recycled. The final step in the sequence involved the addition of olefin **10** to a solution of anhydrous sodium hydrogen sulfide⁷ in ethanol at –40 °C. After one hour at –10 °C, addition of water precipitated out

aminothiophene **6**, in a yield of 82% (Scheme 2), with none of the isomer **7** being formed.

The next step, deamination of aminothiophene **6**, proved more problematic than anticipated. This reaction had been reported before; it was effected by diazotisation followed by loss of nitrogen with the hydrogen coming from the solvent ethanol.⁹ However, the yield obtained was only 24%. When we attempted this, we found that the diazonium salt could be formed by slow addition of aqueous sodium nitrite to a vigorously stirred solution of aminothiophene **6** in hydrochloric acid, at –10 °C (it was important that the temperature did not rise above –5 °C as this caused the solution to turn deep purple and become very viscous, presumably due to polymerisation and diazo-coupling reactions). A variety of reducing agents were tried, including hypophosphorous acid,¹⁰ thiophenol,¹¹ ethanol,¹² and sodium azide.¹³ Deaminations using alkyl nitrites in either DMF or acetonitrile¹⁴ (where the solvent acts as the hydrogen donor) were also tried. Some of the desired product **12** was obtained using hypophosphorous acid or ethanol but yields were poor and it was difficult to obtain pure product from the thick purple oil. The reactions using thiophenol and sodium azide failed to give the desired reduction product **12** but instead gave the corresponding substitution products in good yield.

Eventually it was decided to first replace the amino group by a halogen, and then replace that, in turn, with hydrogen. The conditions which gave the best results with least side-reactions was a modification of the conventional Sandmeyer procedure,¹⁵ using *tert*-butyl nitrite and anhydrous cupric bromide in acetonitrile.¹⁶ The resulting bromide **11** was treated, without purification, with zinc and acetic acid¹⁷ to give the desired α -free thiophene **12**, which required no further purification, in 87% yield over the two steps (Scheme 2). This is far superior to the reported direct deamination of **6**.⁹

The methodology to be used for the formation of the aminopyrimidine ring was based upon a synthesis of trimethoprim analogues,¹⁸ which involved condensation of an aromatic aldehyde with β -anilinopropionitrile followed by reaction with guanidine. In our case it would be necessary to use acetamidine in place of guanidine. This chemistry was first tested using benzaldehyde as a model. Reaction of benzaldehyde with anilinopropionitrile gave the desired adduct **13** in 74% yield (Scheme 3). The second step, using acetamidine instead of

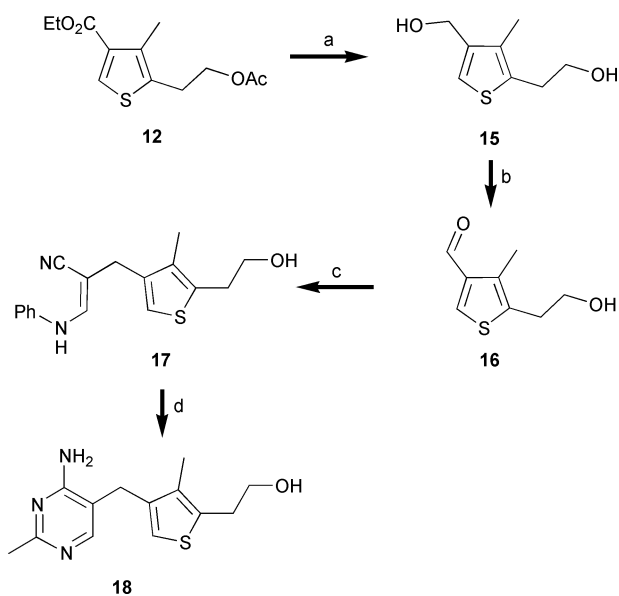


Scheme 3 (a) PhNHCH₂CH₂CN, *t*-BuOK, *t*-BuOH, DMSO, 74%; (b) CH₃C(=NH)NH₂·HCl, NaOEt, EtOH, 84%.

guanidine, was also successful, giving 2-methyl-4-amino-5-benzylpyrimidine **14** in 84% yield. The aminopyrimidine ring of **14** is identical to that required for deazathiamine.

Returning to the synthesis of deazathiamine, conversion of ester **12** into the corresponding aldehyde was accomplished in two steps. Firstly, reduction of the ester with LiAlH₄ gave the diol **15** (Scheme 4). Oxidation using freshly prepared activated MnO₂¹⁹ then gave the aldehyde **16**, with no apparent oxidation of the non-benzylic alcohol. Treatment of a solution of aldehyde **16** and β -anilinopropionitrile in DMSO at 50 °C with a solution of sodium methoxide in methanol gave the condensation product **17** in 94% yield. (Sodium methoxide in methanol was found to give better results than potassium *tert*-butoxide in *tert*-butyl alcohol.¹⁷) The major double-bond isomer of **17** (presumably the *Z*-isomer) precipitated upon addition of ice-water, whereas the minor isomer could be obtained by extraction of the filtrate with ethyl acetate. In the final step the major

isomer of **17** was heated at reflux in dry ethanol with acetamidine overnight, in the presence of excess base, to give deazathiamine **18** in 81% yield (Scheme 4).



Scheme 4 (a) LiAlH_4 , Et_2O , 81%; (b) MnO_2 , CHCl_3 , 74%; (c) $\text{PhNH-CH}_2\text{CH}_2\text{CN}$, NaOMe , DMSO , MeOH , 94%; (d) $\text{CH}_3\text{C(=NH)NH}_2 \cdot \text{HCl}$, NaOEt , EtOH , 81%.

A crystal structure of the final product, deazathiamine **18**, was obtained.† This showed two molecules of **18** in the unit cell along with one molecule of water (which is confirmed by elemental analysis). Fig. 1 shows the structure of one of the two molecules of **18**.

Conclusion

The synthesis of deazathiamine **18** was effected in ten chemical steps, though it was not necessary to isolate in pure form either the bromide **11** or nitrile **17**. Furthermore, the first six steps can be carried out on a large scale without the need for chromatography. Deamination of aminothiophene **6** via the bromide **11** was very efficient, displaying none of the side reactions and complications observed with more direct methods. The readily available and inexpensive starting materials and reagents, and the lack of protection–deprotection steps makes this a particularly efficient synthesis. Conversion of deazathiamine to its pyrophosphate ester **1** and enzymic experiments with the deaza-TDP will be described in a future publication.

Experimental

General procedures

Mps were determined on a Reichert melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 FTIR spectrophotometer, using sodium chloride plates for thin film spectra and spectra recorded in Nujol mulls. Proton NMR spectra were recorded on either a Bruker AM/DPX 250 (250 MHz), a Bruker AM/DPX 400 (400 MHz) or a Bruker DPX 500 (500 MHz) spectrometer. All coupling constants (J) are given in Hz. ^{13}C NMR spectra were recorded with proton decoupling on either a Bruker AC/DPX 250 (62 MHz), a Bruker AC/DPX 400 (100 MHz) or a Bruker DPX 500 (125

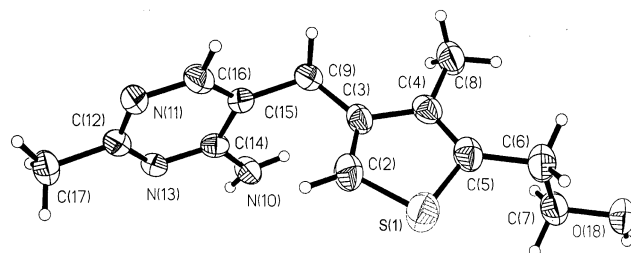


Fig. 1 Crystal structure of deazathiamine **18** (one of the two molecules in the unit cell).

MHz) spectrometer. APT spectra (J -resolved spin echo) were also run to assist in the assignment. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Mass spectra were run on either a Micromass Q-ToF or a Micromass Concept spectrometer using electron impact (EI) or electrospray ionisation (ESI) in positive ion mode. Analytical TLC was performed on commercial Merck glass plates, coated to a thickness of 0.25 mm with Kieselgel 60 F_{254} silica. Column chromatography was performed using Merck Kieselgel 60 (230–400 mesh) silica using a small positive pressure of air. All solvents were redistilled before use. Solvents and reagents for anhydrous reactions were dried by conventional methods²⁰ and such reactions were performed under a small positive pressure of argon.

5-Acetoxy-pentan-2-one **4**

α -Acetylbutyrolactone **3** (5 g, 39 mmol) was stirred with AcOH (4 ml), water (0.7 ml) and concentrated HCl (0.3 ml) for 16 h at 90 °C, then cooled, and concentrated under reduced pressure to give a brown oil. Bulb-to-bulb distillation gave ketone **4** (4.8 g, 85%) as a liquid, bp 40 °C (0.1 mmHg) [lit.²¹ bp 91 °C (11 mmHg)]; $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1740 (CO–O) and 1717 (C=O); $\delta_{\text{H}}(250 \text{ MHz}, \text{CDCl}_3)$ 1.86 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.00 (3 H, s, OAc), 2.12 (3 H, s, CH_3), 2.48 (2 H, t, J 7.2, $\text{CH}_2\text{CH}_2\text{CH}_2$) and 4.02 (2 H, t, J 6.4, CH_2O).

Ethyl 6-acetoxy-2-cyano-3-methylhex-2-enoate **5**

A solution of 5-acetoxy-pentan-2-one **4** (2.26 g, 15.6 mmol) and ethyl cyanoacetate (1.77 g, 15.6 mmol) in benzene (10 ml) was heated at reflux in a Dean–Stark apparatus with AcOH (0.37 g, 6.2 mmol) and AcONH_4 (0.19 g, 2.5 mmol) for 4 h, and then cooled, diluted with ethyl acetate and washed with successive portions of water and brine. The organic layer was dried (MgSO_4) and concentrated under reduced pressure to give a brown oil. Bulb-to-bulb distillation gave alkene **5** (130 °C, 0.1 mmHg) as an oil (2.73 g, 73%) containing a 1:1 mixture of *E*- and *Z*-isomers [Found: M^+ (EI), 239.1147. $\text{C}_{12}\text{H}_{17}\text{NO}_4$ requires M , 239.1157]; $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 2254 (CN) and 1743 (CO–O); $\delta_{\text{H}}(250 \text{ MHz}, \text{CDCl}_3)$ 1.32 (3 H, t, J 7.1, CH_3CH_2), 1.86 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.04 and 2.05 (3 H, 2 \times s, OAc), 2.28 and 2.37 (3 H, 2 \times s, CH_3), 2.64 and 2.84 (2 H, 2 \times dd, J 7.4 and 8.0, and J 7.7 and 8.0, $\text{CH}_2\text{CH}_2\text{CH}_2$), 4.08 and 4.09 (2 H, 2 \times t, J 6.2, and J 6.4, $\text{CH}_2\text{CH}_2\text{CH}_2$), and 4.24 and 4.25 (2 H, 2 \times q, J 7.1 and J 7.1, CH_3CH_2); $\delta_{\text{C}}(100 \text{ MHz}, \text{CDCl}_3)$ 13.9 (CH_3CH_2), 20.7 (CH_3CO), 20.8 and 25.0 (CH_3C), 25.5 and 26.3 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 31.9 and 36.9 (CCH_2), 61.6, 62.8 and 63.5 (2 \times CH_2O), 105.3, 105.4, 115.1 and 115.4 (C=C and CN), and 161.2, 161.6, 170.7, 170.7, 175.5 and 175.9 (C=C and 2 \times CO).

Ethyl 6-acetoxy-2-cyano-3-methyl-4-chlorohex-2-enoate **10**

To a solution of ethyl cyanoacetate (34.2 g, 0.30 mol), AcOH (6.7 g, 0.11 mol) and AcONH_4 (3.4 g, 43.8 mmol) in toluene (500 ml) containing 3 Å molecular sieves (25 g) was added 5-acetoxy-3-chloropentan-2-one **9** (45 g, 0.25 mol) with stirring. The reaction mixture was heated at reflux for 6 h, cooled, diluted with ethyl acetate and washed with a mixture of

† CCDC reference number 207/498. See <http://www.rsc.org/suppdata/p1/b0/b006962k/> for crystallographic files in .cif format. Crystal data: $\text{C}_{13}\text{H}_{18}\text{N}_3\text{O}_{1.5}\text{S}$, $M = 272.36$, monoclinic, $C2/c$, $a = 47.033(2)$, $b = 11.2180(7)$, $c = 10.5570(5)$ Å, $V = 5564.7(5)$ Å³, $Z = 16$, $\mu = 0.230 \text{ mm}^{-1}$, 5846 measured reflections, 3532 unique reflections, $R = 0.1063$, $wR = 0.2368$. Data collected at 220(2) K.

water and saturated aqueous sodium hydrogen carbonate (4:1), which was subsequently re-extracted with ethyl acetate. The combined organic layers were washed with brine, dried (MgSO₄) and concentrated under reduced pressure. Distillation gave firstly a mixture of the two unreacted starting materials (76–79 °C, 0.15 mmHg) and then *alkene 10* (130 °C, 0.15 mmHg), as an oil (29.3 g, 43%) containing a 1:1 mixture of *E*- and *Z*-isomers [Found: *M* + Na⁺ (ESI), 296.0673. C₁₂H₁₆³⁵ClNO₄ requires *M* + Na, 296.0666; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2250 (CN), and 1740 (CO–O); $\delta_{\text{H}}(250 \text{ MHz, CDCl}_3)$ 1.35 (3 H, t, *J* 7.1, CH₃CH₂), 2.07 and 2.09 (3 H, 2 × s, OAc), 2.17 (2 H, m, CHCH₂CH₂), 2.36 and 2.40 (3 H, 2 × s, CH₃), 4.16 and 4.24 (2 H, t, *J* 6.3 and *J* 6.6, CHCH₂CH₂), 4.28 and 4.31 (2 H, 2 × q, *J* 7.1 and *J* 7.1, CH₃CH₂), and 5.27 and 6.23 (2 H, 2 × dd, *J* 6.2 and 8.2, and *J* 6.2 and 8.2, CHCH₂CH₂); $\delta_{\text{C}}(100 \text{ MHz, CDCl}_3)$ 13.8 and 13.9 (CH₃CH₂), 15.5 and 15.5 (CH₃CO), 19.4 and 20.7 (CH₃C), 34.9 and 35.0 (CH₂CHCl), 53.9 and 59.2 (CHCl), 60.0, 60.3, 62.4 and 62.5 (2 × CH₂O), 106.2, 107.1, 113.7 and 114.6 (C=C and CN), and 160.5, 160.9, 169.3, 170.3, 170.6 and 170.7 (C=C and 2 × CO).

Ethyl 5-(2-acetoxyethyl)-2-amino-4-methylthiophene-3-carboxylate 6

Method a. To a stirred mixture of 5-acetoxypentan-2-one 4 (3 g, 20.8 mmol), ethyl cyanoacetate (2.22 ml, 20.8 mmol), and flowers of sulfur (0.67 g, 20.8 mmol) in *tert*-butyl alcohol (10 ml) was added morpholine (1.82 ml, 20.8 mmol) dropwise. The mixture was heated to 60 °C for 6 h, cooled and concentrated under reduced pressure. The resultant oil was dissolved in ethyl acetate and washed successively with 0.2 M aqueous sulfuric acid, water and brine. The organic layer was dried (MgSO₄) and concentrated under reduced pressure. Silica gel chromatography (dichloromethane–ethyl acetate, 9:1, *R_f* 0.4) and then crystallisation from hexane–diethyl ether afforded crystals (3.05 g) composed of thiophenes 6 (38% effective yield) and 7 (16% effective yield).

Method b. To a stirred mixture of *alkene 5* (1.45 g, 6.1 mmol) and flowers of sulfur (0.19 g, 6.1 mmol) in ethanol (5 ml) was added diethylamine (0.47 g, 6.1 mmol). The mixture was heated to 50–60 °C for 14 h, cooled, and concentrated under reduced pressure. Work-up and purification as in **method a** gave pale yellow crystals (0.74 g) composed of 6 (34% effective yield) and 7 (11% effective yield).

Method c. Acetic acid (9.9 g, 0.17 mol) was added dropwise to a stirred solution of Na₂S (13.3 g, 0.17 mol) in dry ethanol (200 ml) at –40 °C. A solution of chloroalkene 10 (18 g, 66 mmol) in EtOH (30 ml) was added dropwise, over 15 min. The mixture was stirred at –40 °C for 1 h, then allowed to warm slowly to –10 °C, stirred for a further hour and then quenched by the addition of ice–water. The precipitated solid was separated, washed with ice–water and dried to give *thiophene 6* as a solid (14.6 g, 82%), mp 64–65 °C (from EtOH) [Found: C, 53.1; H, 6.3; N, 5.1%; M⁺ (EI), 271.0879. C₁₂H₁₇NO₄ requires: C, 53.1; H, 6.3; N, 5.2%; *M*, 271.0878]; $\nu_{\max}(\text{Nujol})/\text{cm}^{-1}$ 3425 and 3315 (NH₂), 1734 and 1718 (2 × CO–O) and 1589 (NH₂); $\delta_{\text{H}}(250 \text{ MHz, CDCl}_3)$ 1.34 (3 H, t, *J* 7.1, CH₃CH₂), 2.05 (3 H, s, OAc), 2.20 (3 H, s, CH₃), 2.87 (2 H, t, *J* 6.9, ArCH₂CH₂), 4.13 (2 H, t, *J* 6.9, ArCH₂CH₂), 4.27 (2 H, q, *J* 7.1, CH₂CH₂), and 5.97 (2 H, br s, NH₂); $\delta_{\text{C}}(62 \text{ MHz, CDCl}_3)$ 14.4, 14.9 and 21.0 (3 × CH₃), 26.6 (CH₃CH₂), 59.3 and 64.2 (2 × CH₂O), 107.0, 114.3 and 132.2 (3 × ArC), and 161.7, 166.0 and 170.9 (2 × CO and CNH₂).

For thiophene 7 $\delta_{\text{H}}(250 \text{ MHz, CDCl}_3)$ 1.35 (3 H, t, *J* 7.1, CH₃CH₂), 1.89 (2 H, m, ArCH₂CH₂CH₂), 2.05 (3 H, s, OAc), 2.75 (2 H, t, *J* 7.5, ArCH₂CH₂CH₂), 4.09 (2 H, t, *J* 6.6, ArCH₂CH₂CH₂), 4.27 (2 H, q, *J* 7.1, CH₃CH₂), 5.86 (1 H, s, ArH) and 6.07 (2 H, br s, NH₂).

Ethyl 5-(2-acetoxyethyl)-2-bromo-4-methylthiophene-3-carboxylate 11

To a stirred solution of aminothiophene 6 (13.9 g, 51.3 mmol) and *tert*-butyl nitrite (10.1 ml, 77 mmol) in acetonitrile (200 ml) at 0 °C was added dropwise, a solution of copper(II) bromide (13.7 g, 61.6 mmol) in acetonitrile (20 ml) over 15 min. The mixture was stirred for a further 30 min at 0 °C, until gas evolution was complete, then allowed to warm to room temperature, and poured into 2 M hydrochloric acid (400 ml) and extracted with ethyl acetate (3 × 100 ml). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated under reduced pressure to give the bromide 11 as a dark brown oil (16.1 g, 93%), which was used without further purification in the next step; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1744 and 1715 (2 × CO–O); $\delta_{\text{H}}(250 \text{ MHz, CDCl}_3)$ 1.38 (3 H, t, *J* 7.1, CH₃CH₂), 2.06 (3 H, s, OAc), 2.26 (3 H, s, CH₃), 2.99 (2 H, t, *J* 6.6, ArCH₂CH₂), 4.18 (2 H, t, *J* 6.6, ArCH₂CH₂), and 4.36 (2 H, q, *J* 7.1, CH₃CH₂); $\delta_{\text{C}}(62 \text{ MHz, CDCl}_3)$ 13.8, 14.2 and 20.9 (3 × CH₃), 27.2 (CH₃CH₂), 61.0 and 63.6 (2 × CH₂O), 114.8, 132.7, 134.8 and 135.0 (4 × arylC), and 163.3 and 170.7 (2 × CO); MS (ESI) *m/z* 358.97 [MNa⁺ (⁸¹Br)], 356.97 [MNa⁺ (⁷⁹Br)].

Ethyl 5-(2-acetoxyethyl)-4-methylthiophene-3-carboxylate 12

A mixture of crude bromothiophene 11 (16.1 g, 48 mmol) and zinc dust (15.7 g, 240 mmol) were heated at reflux in acetic acid (100 ml) for 16 h. After cooling, the mixture was poured onto ice and neutralised by the cautious addition of sodium hydrogen carbonate. The resulting aqueous suspension was extracted with ethyl acetate (3 × 100 ml). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated under reduced pressure to give *thiophene 12* as a mobile oil (11.5 g, 94%) [Found: *M* + Na⁺ (ESI), 279.0670. C₁₂H₁₆SO₄ requires *M* + Na, 279.0667; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1739 and 1715 (2 × CO–O); $\delta_{\text{H}}(250 \text{ MHz, CDCl}_3)$ 1.34 (3 H, t, *J* 7.1, CH₃CH₂), 2.06 (3 H, s, OAc), 2.37 (3 H, s, CH₃), 3.07 (2 H, t, *J* 6.8, ArCH₂CH₂), 4.22 (2 H, t, *J* 6.8, ArCH₂CH₂), 4.29 (2 H, q, *J* 7.1, CH₃CH₂), and 7.94 (1 H, s, ArH); $\delta_{\text{C}}(125 \text{ MHz, CDCl}_3)$ 13.1, 13.9 and 20.6 (3 × CH₃), 27.1 (ArCH₂), 60.0 and 63.7 (2 × CH₂O), 130.9 (arylCH), 132.4, 134.3 and 134.8 (3 × arylC), and 163.0 and 170.5 (2 × CO).

5-(2-Hydroxyethyl)-4-methylthiophene-3-methanol 15

A suspension of LiAlH₄ (0.63 g, 16.7 mmol) in dry diethyl ether (100 ml) was heated to reflux until most of the LiAlH₄ had dissolved. A solution of ester 12 (7.12 g, 27.8 mmol) in dry diethyl ether (50 ml) was added dropwise at such a rate that the ether refluxed gently. The mixture was heated at reflux for a further 3 h, then cooled, diluted with ethyl acetate (200 ml) and washed successively with 1 M hydrochloric acid, water and brine. The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. Chromatography over silica gel (ethyl acetate–hexane, 2:1, *R_f* 0.2) gave the *diol 15* as an oil (3.87 g, 81%) [Found: *M* + Na⁺ (+ESI), 195.0464. C₈H₁₂O₂S requires *M* + Na, 195.0456]; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3324 (OH); $\delta_{\text{H}}(250 \text{ MHz, CDCl}_3)$ 2.15 (3 H, s, CH₃), 2.98 (2 H, t, *J* 6.5, ArCH₂CH₂), 3.81 (2 H, t, *J* 6.5, ArCH₂CH₂), 4.57 (2 H, s, ArCH₂OH), and 7.04 (1 H, s, ArH); $\delta_{\text{C}}(62 \text{ MHz, CDCl}_3)$ 11.9 (CH₃), 31.5 (ArCH₂CH₂), 60.3 and 63.1 (2 × CH₂OH), 120.1 (arylCH), and 132.8, 135.3 and 141.7 (3 × arylC).

5-(2-Hydroxyethyl)-4-methylthiophene-3-carbaldehyde 16

To a stirred solution of diol 15 (2.12 g, 12.2 mmol) in chloroform (60 ml) was added activated manganese dioxide¹⁹ (10.6 g, 122 mmol). The mixture was stirred at room temperature for 5 h, filtered and concentrated. Chromatography over silica gel (ethyl acetate–hexane, 1:1, *R_f* 0.2) gave the *aldehyde 16* as an oil (1.55 g, 74%) [*M* + Na⁺ (+ESI), 193.0299. C₈H₁₀SO₂ requires *M* + Na 193.0299]; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3402 (OH), 2802 and 2720

(CHO), and 1681 (C=O); δ_{H} (250 MHz, CDCl_3) 2.41 (3 H, s, CH_3), 3.02 (2 H, t, J 6.4, ArCH_2CH_2), 3.86 (2 H, t, J 6.4, ArCH_2CH_2), 7.93 (1 H, s, ArH), and 9.91 (1 H, s, CHO); δ_{C} (62 MHz, CDCl_3) 12.4 (CH_3), 30.5 (ArCH_2), 62.4 (CH_2OH), 133.2 (arylC), 136.9 (arylCH), 137.0 and 141.1 ($2 \times$ arylC), and 185.9 (CHO).

2-Benzyl-3-(phenylamino)acrylonitrile 13

A mixture of benzaldehyde (5.30 g, 50 mmol) and β -anilino-propionitrile (8.04 g, 55 mmol) was heated in dry Me_2SO (25 ml) to 40 °C under N_2 and a solution of potassium *tert*-butoxide (6.5 g, 55 mmol) in *tert*-butyl alcohol (40 ml) was added dropwise. The mixture was stirred for 1.5 h at 55 °C, then cooled and slurried with ice-water (100 ml). The precipitated solid was separated and dried to give crude **13** (8.6 g, 74%) which was used directly in the next step. A small portion was recrystallised to give pure *acrylonitrile* **13**, mp 157–158 °C (from toluene) [Found: C, 81.9; H, 6.1; N, 12.0%; $M + \text{Na}^+$ (+ES), 257.1051. $\text{C}_{16}\text{H}_{14}\text{N}_2$ requires C, 82.0; H, 6.0; N, 12.0%; $M + \text{Na}$, 257.1055]; ν_{max} (film)/ cm^{-1} 3310 (NH), 2196 (CN), and 1603, 1585 and 1498 (Ph); δ_{H} (250 MHz, CDCl_3) 3.51 (2 H, s, CH_2), 6.73 (1 H, d, J 12.8, NH), 6.85 (2 H, d, J 7.7, anilino *o*-H), 7.00 (1 H, t, J 7.4, anilino *p*-H), 7.13 (1 H, d, J 12.8, CH), and 7.30 (7H, m, ArH); δ_{C} (125 MHz, CDCl_3) 32.7 (CH_2), 82.4 (CCN), 115.0 (anilino *o*-CH), 122.3 (CN), 122.6 and 127.0 ($2 \times$ *p*-CH), 127.9, 128.8 and 129.5 (benzyl *o*-CH and $2 \times$ *m*-CH), 136.6 and 139.8 ($2 \times$ phenylC), and 140.3 (CHNH).

4-Amino-5-benzyl-2-methylpyrimidine 14

To a stirred solution of **13** (0.50 g, 2.14 mmol) in dry ethanol (5 ml) was added dropwise a suspension containing acetamidine hydrochloride (0.61 g, 6.41 mmol) and sodium ethoxide (0.48 g, 7.06 mmol) in dry ethanol (2 ml). The mixture was heated under reflux for 40 h and cooled. Ice-water (30 ml) was added and the precipitated solid was separated and dried to give *pyrimidine* **14** (0.36 g, 84%), mp 140–141 °C (from toluene) [Found: C, 72.2; H, 6.65; N, 21.1%; MH^+ (+ES), 200.1178. $\text{C}_{12}\text{H}_{13}\text{N}_3$ requires C, 72.3; H, 6.6; N, 21.1%; $M\text{H}$, 200.1188]; ν_{max} (Nujol)/ cm^{-1} 3290 (NH_2), 1655 (NH_2), and 1593 and 1587 (Ph); δ_{H} (400 MHz, DMSO) 2.28 (3 H, s, CH_3), 3.72 (2 H, s, CH_2), 6.58 (2 H, br s, NH_2), 7.20 (5H, m, phenyl-H), and 7.78 (1 H, s, ArH); δ_{C} (125 MHz, CDCl_3) 25.9 (CH_3), 35.0 (CH_2), 113.0 (CCNH₂), 127.5 (*p*-C), 128.6 and 129.4 (*o*-C and *m*-C), 137.5 (CCH₂), 156.3 (CHN), and 162.0 and 166.8 (CNCNH₂).

3-(2-Cyano-3-phenylaminoprop-2-en-1-yl)-5-(2-hydroxyethyl)-4-methylthiophene 17

A mixture of aldehyde **16** (0.75 g, 4.4 mmol) and β -anilino-propionitrile (0.77 g, 5.3 mmol) was heated in dry Me_2SO (15 ml) to 40 °C under N_2 and a solution of sodium methoxide (0.29 g, 5.3 mmol) in methanol (2 ml) was added dropwise. The mixture was stirred for 2 h at 40 °C, then cooled and slurried with ice-water (50 ml) and left in the refrigerator overnight. The resultant precipitate was separated and dried to give one isomer of crude **17** (1.10 g, 84%) which was used directly in the next step. A small portion was recrystallised to give pure *acrylonitrile* **17** as white crystals, mp 134–135 °C (from toluene) [Found: C, 68.4; H, 6.1; N, 9.4%; $M + \text{Na}^+$ (+ES), 321.1022. $\text{C}_{17}\text{H}_{18}\text{N}_2\text{OS}$ requires C, 68.4; H, 6.1; N, 9.4%; $M + \text{Na}$, 321.1038]; ν_{max} (Nujol)/ cm^{-1} 3406 (OH), 2178 (CN), and 1601, 1584 and 1508 (Ph); δ_{H} (400 MHz, CDCl_3) 2.14 (3 H, s, CH_3), 3.01 (2 H, t, J 6.4, ArCH_2CH_2), 3.45 (2 H, s, $\text{C}=\text{CCH}_2\text{Ar}$), 3.83 (2 H, t, J 6.4, ArCH_2CH_2), 6.29 (1 H, br d, J 12.9, NH), 6.75 (2 H, d, J 7.9, phenyl *o*-H), 6.97 (1 H, s, thiopheneH), 6.99 (1 H, t, J 7.4, phenyl *p*-H), 7.27 (2 H, dd, J 7.4 and J 7.9, phenyl *m*-H), and 7.34 (1 H, d, J 12.9, CH); δ_{C} (100 MHz, CDCl_3) 12.1 (CH_3), 27.9 and 31.5 ($2 \times$ ArCH_2), 62.8 (CH_2OH), 81.0 (CCN), 114.9 ($2 \times$ *o*-CH), 118.8 (ArCH),

122.3 (CN), 122.6 (ArCH), 129.5 ($2 \times$ *m*-CH), 133.0, 136.0, 136.6 and 139.8 ($4 \times$ ArC), and 140.6 (CHNH).

The filtrate was extracted with ethyl acetate, washed with brine, dried (MgSO_4) and concentrated under reduced pressure to give the other isomer of **17** as an oil (56 mg, 4%); δ_{H} (250 MHz, CDCl_3) 2.10 (3 H, s, CH_3), 3.01 (2 H, t, J 6.4, ArCH_2CH_2), 3.38 (2 H, s, $\text{C}=\text{CCH}_2\text{Ar}$), 3.83 (2 H, t, J 6.4, ArCH_2CH_2), 6.71 (1 H, br d, J 13.0, NH), 6.82 (2 H, d, J 7.8, phenyl *o*-H), 6.93 (1 H, s, thiopheneH), 6.99 (1 H, t, J 7.4, phenyl *p*-H), 7.06 (2 H, d, J 13.0, CH), and 7.30 (2 H, dd, J 7.4 and J 7.8, phenyl *m*-H).

3-Deazathiamin 18

To a stirred solution of **17** (0.78 g, 2.6 mmol) in dry ethanol (7 ml) was added dropwise a suspension containing acetamidine hydrochloride (0.50 g, 5.3 mmol) and sodium ethoxide (0.72 g, 10.6 mmol) in ethanol. The mixture was heated at reflux for 48 h and cooled. Ice-water (30 ml) was added and the precipitated solid was separated and dried to give *3-deazathiamine* **18** (0.56 g, 81%), mp 204–205 °C (from CHCl_3 – MeOH – H_2O) [Found: C, 57.05; H, 6.6; N, 15.1%; M^+ , 263.1100. $\text{C}_{13}\text{H}_{17}\text{N}_3\text{OS} \cdot 0.5\text{H}_2\text{O}$ requires C, 57.3; H, 6.7; N, 15.4%; M , 263.1092]; ν_{max} (Nujol)/ cm^{-1} 3385 and 3323 (NH_2), 3142 (OH), and 1653 (NH_2); δ_{H} (400 MHz, DMSO) 1.96 and 2.27 ($2 \times$ 3 H, s, CH_3), 2.83 (2 H, t, J 7.0, ArCH_2CH_2), 3.58 (2 H, s, ArCH_2Ar), 3.58 (2 H, dt, J 5.3 and 7.0, CH_2OH), 4.76 (1 H, t, J 5.3, OH), 6.58 (2 H, br s, NH_2), 6.76 (1 H, s, thiopheneH), and 7.57 (1 H, s, pyrimidineH); δ_{C} (100 MHz, DMSO) 12.3 and 25.4 ($2 \times$ CH_3), 27.8 and 32.1 ($2 \times$ ArCH_2), 62.1 (CH_2OH), 112.0 (CCNH₂), 118.6 (thiopheneCH), 132.8, 135.5 and 138.5 ($3 \times$ ArC), 154.5 (pyrimidineCH), and 162.1 and 164.9 (CNCNH₂).

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