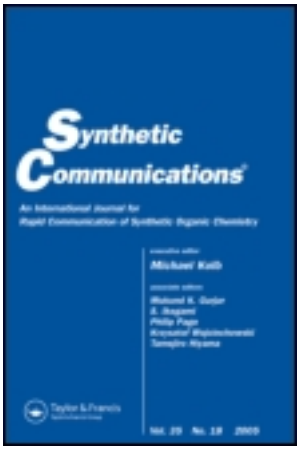

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Synthesis of Novel Tetrahydro-3H-benzothieno[2,3-d]-imidazoles

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SYNTHESIS OF NOVEL TETRAHYDRO-3*H*-BENZOTHIENO[2,3-*d*]-IMIDAZOLES

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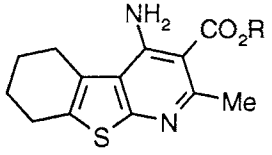
ABSTRACT The synthesis of novel tetrahydro 3*H*-benzothieno[2,3-*d*]imidazole **2b** and the corresponding 2-carboxylate **2a** is described. Intramolecular cyclisation of a key 1,2-diacylaminobenzothiophene **9** was utilised.

For a number of years, we have been involved with the synthesis of fused pyridine derivatives which proved to be of interest[1] as a novel type of $GABA_A$ modulator and, in particular, esters of 4-amino-tetrahydrobenzo[b]thieno[2,3-*b*]pyridine **1** showed potential in the treatment of anxiety disorders.[2] As part of this programme



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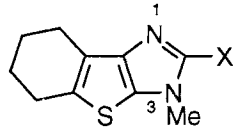

2a X=CO_2Et
2b X=Me

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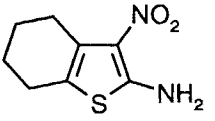
we were interested in the 3-alkyl-3*H*-tetrahydrobenzothieno[2,3-*d*]imidazole ring system **2** as a target for chemical synthesis and biological evaluation. A synthetic method for assembly of the related aromatised isomeric 1-alkyl-1*H*-benzothieno[2,3-*d*]imidazole nucleus has already been reported using 3-amino-2-nitro-benzothiophene.[3,4] We report here the results of our investigations directed towards the unambiguous synthesis of the novel 3-methyl-3*H*-2-substituted compounds **2a** and **2b**.



3

The initial strategy was to modify the published approach to the isomeric compounds. The desired 2-amino-3-nitrotetrahydrobenzothiophene **3** was made in low yield (18%) from α-mercapto-cyclohexanone, which was prepared using a literature procedure[5]. However, in agreement with related attempted cyclizations,[3] our efforts to prepare the 3-desmethyl derivative of **2b** by catalytic hydrogenation of **3** in the presence of triethyl orthoacetate were unsuccessful. A second investigation aimed at synthesis from N-alkyl derivatives of **3,** based on literature approaches *via* an imidazole N-oxide strategy[6] for benzimidazoles, also failed. The successful synthetic approach to **2** was initiated from commercially available ethyl 2-amino-4,5,6,7-tetrahydro-benzothiophene-3-carboxylate **4** as shown in the Scheme. Conversion into the corresponding benzyl ester **5** was achieved in good

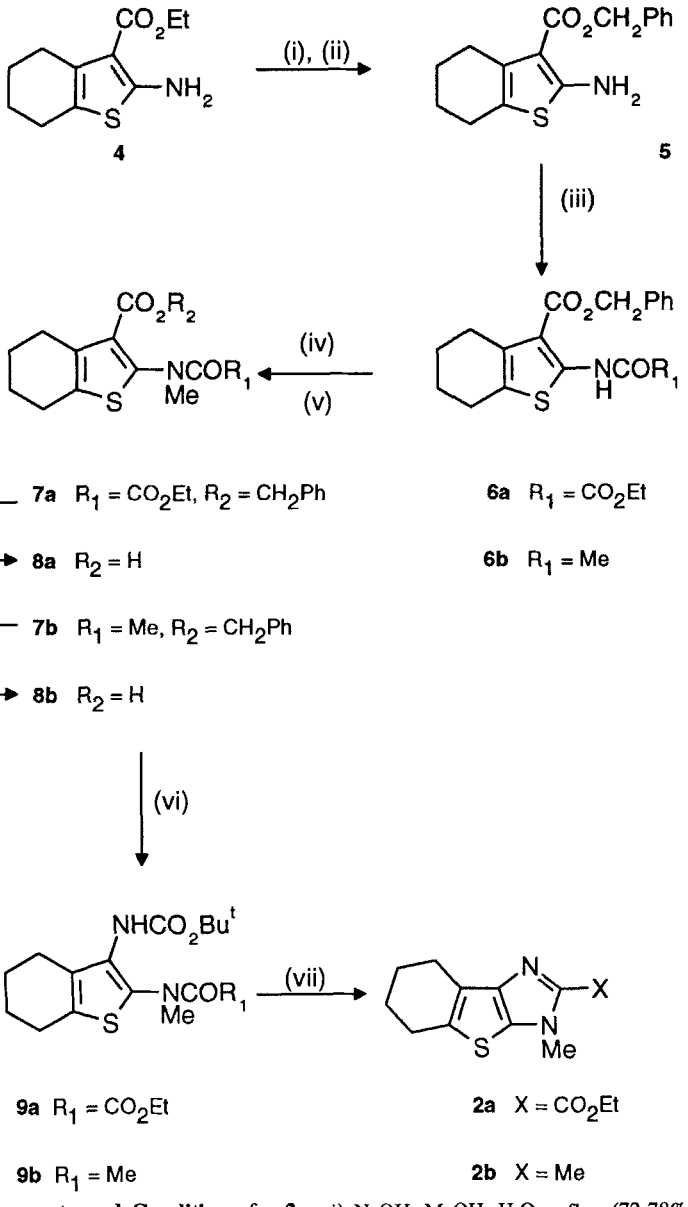
yield using standard methodology. Acylation with ethyl oxalyl chloride followed by N-methylation gave the diester **7a**. Hydrogenolysis (Pd black) gave the acid **8a** which on treatment with diphenyl phosphoryl azide and *t*-butanol afforded the 1,2-diacylamino-benzothiophene **9a** *via* a modified Curtius rearrangement.[7] This sequence allowed direct introduction of a protected amino group thus avoiding the problems found with the nitro reduction step in earlier routes. The synthesis of **2a** was completed by cyclization of **9a** with polyphosphoric acid (PPA) on heating at 100°C for 1.5h.

Repetition of the above sequence to give the 2-N^1-methylacetamide intermediate **9b** followed by cyclisation with PPA (71% yield) gave 2,3-dimethyl imidazole **2b.**

Experimental

For general details see ref. (1b). ^{1}H NMR spectra were obtained using either a Bruker AC 250 or a Jeol GX 270 spectrometer. EI mass spectra were determined on a Jeol JMS DX 303/DA 5000 system operating at 70eV. Unless otherwise stated for work-up, reaction mixtures were partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*.

2-Amino-3-nitro-4,5,6,7-tetrahydrobenzo[b]thiophene 3 - A suspension of sodium hydrosulfide hydrate (2.0g) in ethanol (6cm^3) at -5°C was treated with α-chlorocyclohexanone (1.50g, 11.3mmol) as published.[5] After 0.5h a solution of



Reagents and Conditions for **2a**:- i) NaOH, MeOH, H_2O, reflux (72-78%); ii) K_2CO_3, $BrCH_2Ph$, DMF, R.T. (76%); iii) Et_3N, $ClCOCO_2Et$, CH_2Cl_2, R.T. (100%); iv) K_2CO_3, MeI, DMF, Δ (80-90%); v) H_2, Pd black, EtOAc (80%); vi) $(PhO)_2P(O)(N_3)$, Et_3N, ^tBuOH, reflux (56%); vii) PPA, Δ (47%)

nitroacetonitrile (1.03g, 12.0mmol) in ethanol (9cm^3) was added followed by triethylamine (1.20g, 11.9mmol) in ethanol (7cm^3) over 10mins. The mixture was allowed to warm and then heated to 45°C for 19h. Work up, followed by column chromatography on silica using gradient elution with 0→25% ethyl acetate in pentane, afforded the title compound as a bright yellow solid (0.41g, 18%). δ_H (250MHz, $CDCl_3$) 1.80 (4H, m), 2.49 (2H, m), 2.85 (2H, m) and 6.88 (2H, broad s); m/z (NH_3 CI) 216 (MNH_4^+ 100%), 200 (MH^+, 20%), 183 (20) and 169 (60).

Benzyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate ***5*** - NaOH (7.1g, 0.18moles) in water (25cm^3) was added to a stirred solution of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4.0g, 17.8mmol) in methanol (100cm^3) and heated at reflux. Work-up gave the acid as a pale solid (2.72g, 78%). δ_H [250MHz, $(CD_3)_2SO$] 1.66 (4H, m), 2.40 (2H, m), 2.57 (2H, m), 7.18 (2H, broad s) and 11.75 (1H, broad s). A portion of this acid (1.0g, 5.1mmol) was treated with K_2CO_3 (1.80g, 13.0mmol) and benzyl bromide (0.98g, 5.6mmol) in dry DMF (45cm^3). The mixture was allowed to stir at room temperature for 20h and then poured onto aqueous NH_4Cl and extracted twice with dichloromethane. Evaporation, followed by column chromatography on silica using an ethyl acetate-pentane gradient, gave the title compound as a yellow oil (1.11g, 76%). δ_H (270MHz, $CDCl_3$) 1.73 (4H, m), 2.49 (2H, m), 2.70 (2H, m), 5.26 (2H, s), 5.95 (2H broad s) and 7.34 (5H, m).

Benzyl 2-(ethyloxalylamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate ***6a*** - A solution of ethyl oxalyl chloride (4.78g, 25.0mmol) in dichloromethane

($40cm^3$) was added dropwise to a stirred solution of the amine **5** (6.80g, 23.7mmol) and triethylamine (2.84g, 28.1mmol) in dichloromethane ($120cm^3$) with ice cooling. The mixture was stirred at 0°C for 0.5h and then at room temperature for 20h. Work-up with dichloromethane furnished the title compound as a brown oil (9.2g, 100%.). δ_H (250MHz, $CDCl_3$) 1.43 (3H, t), 1.79 (4H, m), 2.68 (2H, m), 2.79 (2H, m), 4.44 (2H, q), 5.38 (2H, s), 7.40 (5H, m) and 12.50 (1H, broad s).

Benzyl 2-(N-ethyloxalyl-N-methylamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate ***7a*** - K_2CO_3 (6.29g, 45.5mmol) was added to a stirred solution of the amide **6a** (7.05g, 18.2mmol) and iodomethane (6.43g, 45.3mmol) in dry DMF ($190cm^3$). The mixture was then heated in an oil bath at 80°C for 20h. Work-up with dichloromethane afforded the title compound as a brown oil (6.90g, 94%). δ_H (250MHz, $CDCl_3$) 1.11 (3H, t), 1.81 (4H, m), 2.70 (2H, m), 2.78 (2H, m), 3.17 (3H, s), 4.10 (2H, q), 5.26 (2H, s) and 7.39 (5H, m).

2-(Ethyloxalyl-N-methylamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid, ***8a*** - A solution of the benzyl ester **7a** (8.35g, 20.8mmol) in ethyl acetate ($150cm^3$) was hydrogenated at ambient temperature and pressure for 10 days over palladium black (a total of 1.5g added fresh in three batches at intervals). The mixture was filtered through Kieselguhr, washing with ethyl acetate. Evaporation *in vacuo* gave the title compound **8a** as a yellow, waxy solid (5.19g, 80%). δ_H (250MHz, $CDCl_3$) 1.12 (3H, t), 1.81 (4H, m), 2.72 (2H, m), 2.80 (2H, m), 3.34 (3H, s) and 4.14 (2H, q).

2-(N-Methylacetylamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic acid ***8b*** - The ethyl ester **7b** was obtained as a pale solid in 60%yield from **4** using the method described for the preparation of compounds **5**, **6a** and **7a**. δ_H (250MHz, $CDCl_3$) 1.86 (4H, m), 2.01 (3H, s), 2.73 (2H, m), 2.84 (2H, m), 3.23 (3H, s) and 7.35 (1H, broad s).

N-(3-t-Butoxycarbonylamino-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-N-methyl-oxalamic acid, ethyl ester, ***9a*** - A solution of the carboxylic acid **8a** (5.04g, 16.2mmol), diphenylphosphoryl azide (5.46g, 19.4mmol) and triethylamine (1.96g, 19.4mmol) in *t*-butanol ($90cm^3$) was refluxed under an atmosphere of nitrogen for 24h. Evaporation *in vacuo* gave a residue which was dissolved in ethyl acetate and washed with aqueous $NaHCO_3$, aqueous NH_4Cl solution and brine. The organic layer was dried and then evaporated. Chromatography on silica with an ethyl acetate-pentane gradient afforded the title compound as a pale yellow solid (3.48g, 56%). δ_H (250MHz, $CDCl_3$) 1.11 (3H, t), 1.49 (9H, s), 1.70 →1.90 (4H, m), 2.43 (2H, m), 2.67 (2H, m), 3.23 (3H, s), 4.16 (2H, q) and 6.13 (1H, broad s).

[2-(Acetylmethylamino)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl]carbamic acid, t-butyl ester ***9b*** - A solution of the carboxylic acid **8b** (5.46g, 21.6mmol), diphenylphosphoryl azide (8.27g, 29.4mmol) and triethylamine (2.95g, 29.1mmol) in *t*-butanol ($100cm^3$) was refluxed under an atmosphere of nitrogen for 42h. The reaction mixture was evaporated *in vacuo* and work-up similar to that for compound **9a** afforded the title compound **9b** as a lemon-yellow solid (3.14g,

45%). δ_H (250MHz, $CDCl_3$) 1.47 (9H, s), 1.82 (4H, m), 2.00 (3H, s), 2.44 (2H, m), 2.68 (2H, m), 3.18 (3H, s) and 5,74 (1H, broad s).

Ethyl 3-methyl-5,6,7,8-tetrahydrobenzothieno[2,3-d]imidazole-2-carboxylate, ***2a*** - A mixture of the *t*-butyl-carbamate **9a** (0.80g, 2.1mmol) and PPA ($8cm^3$) was heated at 100°C for 1.5h. Ice was added and the mixture neutralized ($NaHCO_3$). Extraction into dichloromethane followed by chromatography on silica with an ethyl acetate-pentane gradient afforded the title compound as a beige-solid (0.26g, 47%), m.p. 118-120°C (from ethyl acetate-pentane) (Found: C, 58.88; H, 6.08; N, 10.50. $C_{13}H_{16}N_2O_2S$ requires C, 59.07; H, 6.10; N, 10.60%); δ_H (400MHz, $CDCl_3$) 1.45 (3H, t), 1.85 (2H, m), 1.92 (2H, m), 2.81 (4H, m), 4.10 (3H, s) and 4.47 (2H, q); m/z (EI) 264 (M^+, 80%), 236 (100), 192 (80) and 164 (70).

1,2-Dimethyl-5,6,7,8-tetrahydrobenzothieno[2,3-d]imidazole ***2b*** - A mixture of the *t*-butyl-carbamate **9b** (3.12g, 9.63mmol) and PPA ($70cm^3$) was heated at 110°C for 1.25h to give a brown oil. Work-up as described for the preparation of **2a** followed by column chromatography on silica, initial elution with 30% ethyl acetate-pet. ether, subsequent gradient elution with 0→10% methanol-ethyl acetate, afforded the title compound **2b** as a beige coloured solid (1.40g, 71%), mpt. 127-130°C (from petroleum ether); (Found: C, 64.35; H, 6.86; N, 13.38. $C_{11}H_{14}N_2S$ requires C, 64.04; H, 6.84; N, 13.58%).δ_H (270MHz, $CDCl_3$) 1.86 (4H, m), 2.51 (3H, s), 2.78 (4H, m) and 3.64 (3H, m); m/z (EI) 206 (M^+, 80%) and 178 (100%).

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