

Thienothiophenes. Part 2.¹ Synthesis, metallation and bromine→lithium exchange reactions of thieno[3,2-*b*]thiophene and its polybromo derivatives

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Methods for the large-scale synthesis of thieno[3,2-*b*]thiophene [including a catalytic vapour-phase reaction (at 550 °C) between 2-(2-thienyl)ethanol and carbon disulfide], its 2-carboxylic acid and its 3,6-dibromo and 2,3,5,6-tetrabromo derivatives are reported. With 2 mol equiv. of butyllithium thieno[3,2-*b*]thiophene gives its 2,5-dilithiated derivative and its 3,6-dibromo derivative gives the 3,6-dilithiated compound. By quenching with suitable electrophilic reagents these dilithiated compounds have been converted into various 2,5- or 3,6-disubstituted thieno[3,2-*b*]thiophenes, respectively. Likewise 2,3,5,6-tetrabromothieno[3,2-*b*]thiophene has been converted into 2,5-disubstituted 3,6-dibromothieno[3,2-*b*]thiophenes.

Polythiophene, poly(alkylthiophenes) and other oligomers and polymers containing thiophene rings are attracting considerable attention currently as molecules with potential electro-optical properties for use as molecular devices.^{2–11} These polymers are more stable in the environment and often possess better electrical conducting properties than some others, *e.g.* polyacetylene or polypyrrole. Indeed, the most stable molecular switching devices discovered to date are thiophene derivatives.^{12–15} This interest in thiophenes has been extended recently to thieno[3,2-*b*]thiophenes.^{11,16–34} However, research in this area has been impeded by the lack of good synthetic routes to thieno[3,2-*b*]thiophene and its derivatives.^{24,25,27,29,35–38} In this paper we report convenient reproducible methods for the large-scale syntheses of thieno[3,2-*b*]thiophene, its 2-carboxylic acid and its 3,6-dibromo and 2,3,5,6-tetrabromo derivatives and the synthesis of 2,5- and 3,6-disubstituted derivatives through dilithiation of the parent system or *via* Br→Li exchange reactions involving 3,6-dibromo- or 2,3,5,6-tetrabromo-thieno[3,2-*b*]thiophene.

The preferred route for construction of the thieno[3,2-*b*]thiophene ring system, which is based on some of our earlier work,^{1,39,40} is summarised in Scheme 1. The starting material, 3-bromothiophene **1**,⁴¹ is available commercially.⁴²

Gronowitz *et al.*⁴³ have synthesized 3-bromothiophene-2-carbaldehyde **2** previously in 70% yield from 2,3-dibromothiophene through its successive treatment with butyllithium (see also ref. 44) and *N,N*-dimethylformamide (DMF). We found that better yields (80% after distillation; 95% crude, which was pure enough to carry forward) of the aldehyde **2** could be obtained more conveniently and on a larger scale by deprotonation of 3-bromothiophene **1** with lithium diisopropylamide (LDA–THF, 0 °C) followed by a *N*-formylpiperidine quench. With DMF as the quenching reagent the yield fell to 60% whilst use of methyl formate gave only the bithienylmethanol derivative **9** (84%). At –78 °C we found that deprotonation of 3-bromothiophene occurred in both α -positions of the thiophene ring but, as the temperature increased to 0 °C, the reaction showed greater selectivity for deprotonation at position-2. When *o*-bromoaldehyde **2** was treated with ethyl 2-sulfanylacetate (DMF–K₂CO₃, ambient temp.)^{1,24,40} it gave ethyl thieno[3,2-*b*]thiophene-2-carboxylate **3** (81%; 95% for smaller scale reactions). Its hydrolysis with

aqueous lithium hydroxide in THF²⁴ gave the corresponding acid **4** (90%).

Thermal decarboxylation of thiophene and thienothiophenecarboxylic acids is possible in quinoline in the presence of copper.^{11,24,35,36,45,46} Thieno[3,2-*b*]thiophene-2-carboxylic acid **4** was decarboxylated in this way, to give the parent ring system **5** (88% yield).^{24,35} Use of a Woods-metal bath allowed us to control the temperature at a constant 260 °C (*cf.* ref. 24; decarboxylation at 160 °C) whilst, following removal of the bulk of quinoline with hydrochloric acid, flash chromatography of the crude product on silica²⁴ allowed efficient removal of the final amounts of quinoline and gave the thieno[3,2-*b*]thiophene in higher yields and better quality than previous work-up procedures allowed.³⁵

Thiophene⁴² is prepared commercially by a vapour-phase catalytic reaction between various C₄ starting materials (*e.g.* butanol) and carbon disulfide.^{47,48} Derivatives of thiophene (*e.g.* 3-methylthiophene from Me₂CHCH₂CH₂OH)^{47,48} and benzo[*b*]thiophene (from C₂ substituted benzene derivatives and H₂S in the order of reactivity: PhC≡CH > PhCH=CH₂ PhCH₂CH₂SH > PhCHMeSH > PhCOMe⁴⁹)^{47–51} may be prepared similarly. For thiophene synthesis an alkali-promoted chrome–alumina catalyst is used.^{47,48} We now report that thieno[3,2-*b*]thiophene **5** can be prepared similarly from C₂ substituted thiophenes and carbon disulfide.

2-(2-Thienyl)ethanol was prepared in 68% yield from 2-thienyllithium and ethylene oxide (oxirane) and treated with carbon disulfide (ratio 1 : 2). We varied the catalyst contact time and reaction temperature (see Experimental section for details) and analyzed the liquid condensate by gas liquid chromatography (GLC). With a contact time of 7.5 s the yield of thieno[3,2-*b*]thiophene **5** obtained increased from 5% at 480 °C to 7% at 500 °C to 12% at 525 °C to 16% at 550 °C. With an increased contact time of 10 s three runs were completed at 500, 525 and 550 °C; the yields of product were 8, 10 and 6%, respectively. Using 2-(2-thienyl)ethanol as the feedstock it was possible to prepare multigram quantities of thieno[3,2-*b*]thiophene **5** at 550 °C with a 7.5 s contact time. We have made no attempts to optimize conditions further, *e.g.* by varying the feedstock: CS₂ ratio.

We found it more convenient to prepare 1-(2-thienyl)ethanol (82%) from 2-thienyllithium and acetaldehyde. However, with a

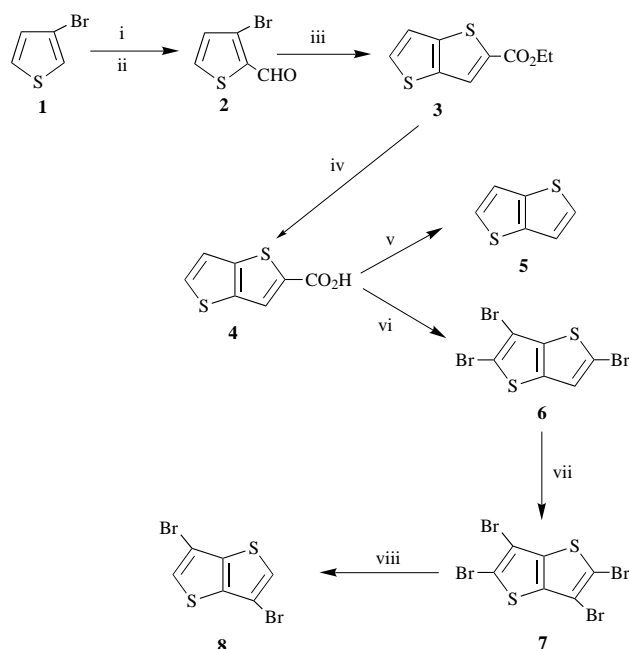
contact time of 7.5 s and by varying the reactor temperature from 425 to 550 °C at 25 °C intervals the best yield of thieno[3,2-*b*]thiophene **5** produced from this feedstock was only 5% (at 475–500 °C). Commercially available 2-acetylthiophene was converted also into thieno[3,2-*b*]thiophene **5** (best yield 9% with a contact time of 7.5 s at 550 °C) but considerable carbonisation of the catalyst occurred with this feedstock and continuous flow of the reactor was not possible for more than 3 h before regeneration of the catalyst became necessary. Increased contact times exacerbated the carbonisation problem and resulted in lower yields of product.

With all these reactions varying amounts of α -terthienyl (identified using GLC analysis by comparison with an authentic sample) were formed also. In the synthesis of benzo[*b*]thiophene from various C₂ substituted benzene derivatives Venuto *et al.*⁴⁹ detected varying yields of 2,5-diphenylthiophene in their products. This became the major product at 400 °C. It is possible, therefore, that α -terthienyl can be produced in greater quantities by our vapour-phase process but we have not investigated this possibility. The best yield (4%) obtained by us was using 2-(2-thienyl)ethanol as the feedstock with a contact time of 7.5 s at 480 °C. At 550 °C (our preferred operating temperature for thieno[3,2-*b*]thiophene **5** production) α -terthienyl was present in the product in only trace (<5%) amounts and was removed by flash chromatography of the crude product on silica.

By contrast with thiophenecarboxylic acids,^{52–54} bromodecarboxylation of thieno[3,2-*b*]thiophenecarboxylic acids has not been investigated to date. We have investigated bromodecarboxylation of the acid **4** under a range of reaction conditions; both bromine–acetic acid⁵² and bromine–aqueous sodium hydroxide⁵³ have been used. In glacial acetic acid only bromination of the ring system was observed with no accompanying bromodecarboxylation. Addition of water to the acetic acid caused decarboxylation; as more water was added more di- and tri-bromo derivatives were obtained until even 2,3,5,6-tetrabromothieno[3,2-*b*]thiophene **7** began to form. For the synthesis of the tetrabromo compound **7**^{31,55} the preferred procedure involved initial monobromination of the carboxylic acid **4** in acetic acid. After addition of the first mol equiv. of bromine at ambient temperature water was added until all the monobrominated thieno[3,2-*b*]thiophene-2-carboxylic acid was precipitated. Then the mixture was heated under reflux when a further 1.5 mol equiv. of bromine was added to it. The initial precipitate redissolved and the mixture was heated further until thin-layer chromatographic (TLC) analysis indicated absence of the intermediate monobrominated acid (~3 h, depending on scale) when more bromine (4 mol equiv.) was added to the refluxing mixture. After a further 12 h the sole product was the tetrabromo compound **7** (70%). Bromodecarboxylation of thieno[3,2-*b*]thiophene-2-carboxylic acid **4** in 10% aqueous sodium hydroxide gave the 2,3,5,6-tetrabromo derivative **7** but in only 18% yield; again, insolubility of initial products was a problem but the known³⁶ instability of 2-bromothieno[3,2-*b*]thiophene, even at ambient temperature, probably contributed greatly to the low yield of this reaction. 2,3,5,6-Tetrabromothieno[3,2-*b*]thiophene **7** can be prepared also by elemental bromination of the parent system **5** [*e.g.* in carbon disulfide (87%)³¹].

With zinc and acetic acid^{36,56,57} we converted 2,3,5,6-tetrabromothieno[3,2-*b*]thiophene **7** (Scheme 1) into 3,6-dibromothieno[3,2-*b*]thiophene **8** (76%).

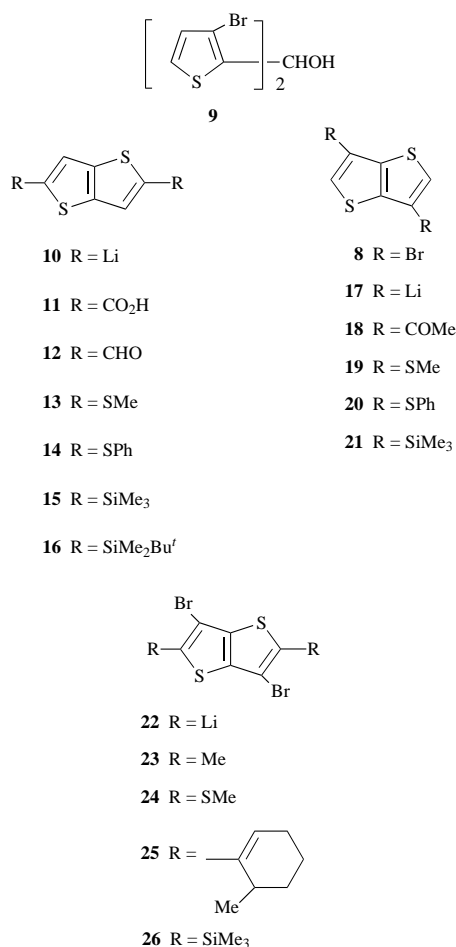
Thieno[3,2-*b*]thiophene **5**^{26–28,33,35,36,45,58} and its 2-ethyl⁵⁹ and 3,6-dimethyl^{18,28,33} derivatives have been monometallated with butyllithium in an α -position and the resulting lithiated derivative used to introduce various α -substituents [Br,³⁶ I,²⁶ MgBr,¹⁸ ZnCl,²⁷ SnBu₃,²⁷ B(OH)₂,²⁷ SeLi→SMe,²⁸ TeLi→TeMe (both with MeI),²⁸ SLi→SR (with MeBr or C₁₈H₃₇Br),³³ SMe,⁵⁸ SLi→SEt (with EtI),⁵⁹ SO₂Me,³³ SO₂Li→SO₂NH₂ (with *N*-chlorosuccinimide followed by ammonia),³³ CHO,⁴⁵ CO₂H,³⁵



Scheme 1 Reagents and conditions: i, LDA, THF, 0 °C; ii, *N*-formylpiperidine; iii, HSCH₂CO₂Et, K₂CO₃, DMF; iv, LiOH, THF; v, Cu, quinoline, 260 °C; vi, Br₂, aq. AcOH; vii, LDA, THF, –80 °C, then Br₂; viii, Zn, AcOH.

or CO₂Me³³]. The only dilithiations carried out to date are dilithiation of the parent system **5** followed by carbonation (CO₂) or formylation (DMF) of the resulting dilithium derivative **10**, which gave the dicarboxylic acid **11**³⁵ or dialdehyde **12**,⁶⁰ respectively. We now report similar syntheses of the 2,5-disubstituted thieno[3,2-*b*]thiophenes **13–16** (73, 62, 66 and 41% yields, respectively). We also prepared the dialdehyde **12** [86% crude yield, mp 269–270 °C (lit.,⁶⁰ mp of crude product, 272–275 °C); this compound decarboxylates on attempted recrystallisation, *e.g.* from acetic acid] but using *N*-formylpiperidine instead of DMF as the quenching reagent. Bugge³⁵ used butyllithium in refluxing diethyl ether to synthesize the dilithium compound **10** but we used butyllithium in ether at much lower temperatures (*cf.* ref. 60).

The 2,5-dilithiated compound **10** has been prepared also from 2,5-dibromothieno[3,2-*b*]thiophene *via* a Br→Li exchange reaction and reacted with 2 mol equiv. of fluorenone.⁶¹ 2-Bromothieno[3,2-*b*]thiophene and its 3-, 5- and 6-methyl-, 3-phenyl- and 3,5- and 3,6-dimethyl derivatives undergo Br→Li exchange and the resulting lithiated derivatives have been treated with butyl borate, to give the corresponding boronic acids [TB(OH)₂].⁶² Their oxidation with hydrogen peroxide leads to the formation of tautomeric hydroxythieno[3,2-*b*]thiophenes. Thieno[3,2-*b*]thiophene-3-carbaldehyde has been prepared (57% yield) *via* a Br→Li exchange reaction of 3-bromothieno[3,2-*b*]thiophene followed by a DMF quench⁴⁵ of the resulting thieno[3,2-*b*]thien-3-yl lithium compound; this lithium derivative has also been treated with *N,N*-dimethylacetamide to give 3-acetylthieno[3,2-*b*]thiophene,⁶² and with bis(3-thienyl) disulfide and bis(phenylsulfonyl) sulfide to give sulfides (82 and 23% yields, respectively),^{11,29,30} whilst 2,3,5-tribromothieno[3,2-*b*]thiophene **6** has been converted into the 3,5-dibromo compound *via* Br→Li exchange followed by an aqueous quench.³⁶ Successive treatment of 2,3,5-tribromo-6-methylthieno[3,2-*b*]thiophene with butyllithium (Et₂O, –70 °C), magnesium bromide and *tert*-butyl perbenzoate gave a mixture of 3,5-dibromo-6-methylthieno[3,2-*b*]thiophene and 3,5-dibromo-2-*tert*-butoxy-6-methylthieno[3,2-*b*]thiophene (major product).⁶² The latter product was converted into its 3,5-dilithiated derivative by treatment with butyllithium and, following hydrolysis with water, this gave 2-*tert*-butoxy-6-methylthieno[3,2-*b*]thiophene.⁶²



We treated 3,6-dibromothieno[3,2-*b*]thiophene **8** with 2 mol equiv. of butyllithium (THF, $-100\text{ }^{\circ}\text{C}$) and quenched the resulting lithium compound **17** with dimethyl disulfide, diphenyl disulfide and trimethylsilyl chloride, which gave compounds **19** (71% yield in ether), **20** (64% in hexane-THF), and **21** (42% in ether; 62% in hexane-THF), respectively. It is important that the temperature is kept low during these reactions; we shall report on the stability of 3,6-dilithiated thieno[3,2-*b*]thiophenes elsewhere. Attempts to synthesize the 3,6-diacetyl compound **18** through quenching the dilithiated derivative **17** with acetonitrile or *N,N*-dimethylacetamide were not very successful. Only the latter reagent allowed compound **18** to be isolated, albeit in very low (16%) yield [the major product was 3-acetylthieno[3,2-*b*]thiophene (28% yield)].

We treated the tetrabromo compound **7** with 2 mol equiv. of butyllithium (THF, ambient temp.) and quenched the resulting dilithiated derivative **22** with dimethyl sulfate, dimethyl disulfide, 2-methylcyclohexanone and trimethylsilyl chloride, which gave compounds **23** (55%), **24** (54%), **25** (55%); after dehydration of the initially produced carbinol) and **26** (75%), respectively.

Experimental

IR spectra were recorded with a Perkin-Elmer 1710 FT IR spectrometer (liquids as films and solids as Nujol mulls between sodium chloride plates); ¹H NMR spectra were recorded in deuteriochloroform (CDCl₃) with a Bruker AC300 FT (300.13 MHz) instrument with tetramethylsilane as internal standard unless stated otherwise; *J* values in Hz. Low-resolution mass spectra were recorded using a Finnegan 4500 machine and high-resolution mass spectra were obtained with a Kratos Concept 1S mass spectrometer, all operating at 70 eV (CI unless stated otherwise). Reported molecular weights are given for the ⁷⁹Br isotope unless stated otherwise. The isotopic

abundance ratios were as expected for the compounds containing bromine.

Catalytic vapour-phase conversions were carried out by continuous pumping of a 2:1 (by volume) mixture of carbon disulfide and the thiophene feedstock through a stainless-steel tube (*ca.* 20 cm long and 1 cm i.d.) packed for 5 cm with carborundum through which a thermocouple passed (the pre-heater) followed by 5 cm³ of the alkali-promoted chrome-alumina catalyst.^{47,48} Product condensates were collected below the reactor in a glass separating funnel and analyzed both by TLC and GLC. Both the pre-heater and reactor zones were heated by an insulated salt bath. Regeneration of the catalyst was achieved by heating it *in situ* with an air flow at 500 °C.

Camlab Polygram silica G/UV₂₅₄ plates were used for TLC and flash chromatography was performed using gradient elution techniques on Merck Kieselgel type 60H silica.

Quantitative GLC was carried out on a Polar BPX 70 column (25 cm long; 0.22 mm i.d.) using a Pye Unicam GCD machine fitted with a flame ionisation detector (H₂ pressure 11 psi; air pressure 13 psi). Helium was the carrier gas (inlet pressure 12 psi; linear velocity 32.2 cm s⁻¹). The injector and detector temperatures were maintained at 200 and 300 °C, respectively, whilst the oven temperature was raised for each run from 50 to 250 °C at a rate of 8 °C min⁻¹, after which the temperature was held at 250 °C for 5 min. Commercially available 5-chlorobenzob[*b*]thiophene was used as an internal standard and products were identified by comparing their retention times with those of authentic samples.

All reactions involving organolithium reagents were carried out under dry, oxygen-free nitrogen or argon and reagents and solvents were dried by standard procedures. Reagents were transferred with syringes through a rubber septum cap fitted to the reaction flask.

Light petroleum refers to the fraction of bp range 40–60 °C unless stated otherwise. Ether refers to diethyl ether. In all cases organic extracts were combined, dried (MgSO₄), filtered and evaporated under reduced pressure on a rotary evaporator.

Small-scale distillations were carried out with a Kugelrohr bulb-to-bulb distillation apparatus and the 'bp' temperatures recorded are those of the oven at the time of distillation. Mps were recorded with a Gallenkamp mp apparatus and are uncorrected.

α -Terthienyl was supplied by Aldrich and thiophene,⁴² 2-acetylthiophene, 3-bromothiophene,⁴² and 5-chlorobenzob[*b*]thiophene by Synthetic Chemicals Ltd.

2-(2-Thienyl)ethanol

Ethylene oxide was bubbled through a stirred solution of 2-thienyllithium in tetrahydrofuran [prepared by addition of butyllithium (1.5 mol dm⁻³ in hexane; 172 cm³, 260.0 mmol) to thiophene (21.7 g, 260.0 mmol) in tetrahydrofuran (500 cm³)] at 0 °C. When TLC analysis of the reaction mixture indicated absence of thiophene the reaction was quenched by addition of an excess of hydrochloric acid (1.0 mol dm⁻³) and then extracted with ether. The combined organic extracts were dried (MgSO₄) and distillation of the solvents gave the product (22.5 g, 68%), bp 65 °C at 0.1 mmHg (lit.,⁶³ 44% yield and bp 122–126 °C at 17 mmHg; prepared by reaction of 2-thienylmagnesium bromide with ethylene oxide); δ_{H} 3.05 (2 H, t, *J* 6.3, CH₂), 3.81 (2 H, t, *J* 6.3, CH₂OH), 6.85 (1 H, d, *J*_{3,4} 3.5, H-3), 6.93 (1 H, dd, *J*_{4,3} 3.5, *J*_{4,5} 5.0, H-4) and 7.14 (1 H, d, *J*_{5,4} 5.0, H-5).

1-(2-Thienyl)ethanol

Butyllithium (1.4 mol dm⁻³ in hexane; 59.5 cm³, 83.0 mmol) was added to a stirred solution of thiophene (7.0 g, 83.0 mmol) in tetrahydrofuran (250 cm³) at 0 °C and the resulting mixture was stirred at 0 °C for a further 1 h prior to addition of acetaldehyde (4.7 cm³, 3.70 g, 84.0 mmol). After a further 1 h the reaction mixture was quenched by addition of an excess of

hydrochloric acid (1.0 mol dm⁻³) and extracted with ethyl acetate to give 1-(2-thienyl)ethanol (8.73 g, 82%), bp (Kugelrohr distillation) 65 °C at 0.2 mmHg (lit.,⁶⁴ 86.5% yield and bp 90–92 °C at 6.0 mmHg; prepared by reaction of 2-thienylmagnesium bromide with acetaldehyde); δ_{H} 1.52 (3 H, d, *J* 6.5, Me), 3.30 (1 H, br s, OH), 5.02 (1 H, q, *J* 6.5, CH), 6.91 (2 H, m, H-3/4) and 7.18 (1 H, m, H-5).^{cf. 65}

3-Bromothiophene-2-carbaldehyde 2

3-Bromothiophene **1** (44.7 g, 274.0 mmol) was added dropwise to a stirred solution of lithium diisopropylamide (LDA) [prepared by addition of butyllithium (1.37 mol dm⁻³ in hexane; 200 cm³, 274.0 mmol) to diisopropylamine (38.40 cm³, 27.73 g, 274.0 mmol)] in tetrahydrofuran (500 cm³) at 0 °C and the resulting mixture was stirred for a further 30 min at this temperature prior to addition of *N*-formylpiperidine (30.38 cm³, 30.96 g, 274.0 mmol). The mixture was stirred further until TLC analysis indicated that all the starting material had been consumed (~ 3 h) when an excess of 20% aqueous ammonium chloride was added to it. Extraction of the mixture with ether gave 3-bromothiophene-2-carbaldehyde **2** (41.9 g, 80%), bp (Kugelrohr distillation) 75 °C at 0.2 mmHg (lit.,⁴³ 70% crude yield and bp 113–115 °C at 10.0 mmHg; prepared from 2,3-dibromothiophene); $\nu_{\text{max}}/\text{cm}^{-1}$ 1734 (CO); δ_{H} 7.11 (1 H, d, *J*_{4,5} 5.0, H-4), 7.69 (1 H, dd, *J* 1.4, *J*_{5,4} 5.0, H-5) and 9.92 (1 H, d, *J* 1.4, CHO); *m/z* (CI) 227 (M⁺ + 35, 100%), 225 (M⁺ + 35, 99%), 210 (M⁺ + 18, 52%), 208 (M⁺ + 18, 50%), 192 (M⁺, 6%) and 190 (M⁺, 4%). The crude product (49.6 g, 95%) from an identical experiment was found to be pure enough to use in the following reaction.

Ethyl thieno[3,2-*b*]thiophene-2-carboxylate 3

3-Bromothiophene-2-carbaldehyde **2** (25.71 g, 134.0 mmol) was added to a stirred mixture of ethyl 2-sulfanylacetate (14.8 cm³, 16.22 g, 135.0 mmol), potassium carbonate (25.0 g) and *N,N*-dimethylformamide (250 cm³) at ambient temperature and the resulting mixture was stirred for a further 72 h. Then it was poured into water (500 cm³) and extracted with dichloromethane. The combined extracts were dried (MgSO₄), filtered and distillation of the solvents under reduced pressure gave the ester **3** (23.0 g, 81%), bp (Kugelrohr distillation) 120–125 °C at 0.1 mmHg; $\nu_{\text{max}}/\text{cm}^{-1}$ 1707 (CO); δ_{H} 1.37 (3 H, t, *J* 7.0, Me), 4.34 (2 H, q, *J* 7.0, CH₂), 7.24 (1 H, d, *J*_{6,5} 5.0, H-6), 7.55 (1 H, d, *J*_{5,6} 5.0, H-5) and 7.97 (1 H, s, H-3); *m/z* 247 (M⁺ + 35, 18%), 230 (M⁺ + 18, 100%) and 213 (M⁺ + 1, 35%) (Found: C, 51.1; H, 3.9; S, 30.6. C₉H₆S₂O₂ requires C, 50.9; H, 3.8; S, 30.2%).

Thieno[3,2-*b*]thiophene-2-carboxylic acid 4

A stirred mixture of the ester **3** (15.0 g, 71.0 mmol), aqueous lithium hydroxide (1.0 mol dm⁻³; 150 cm³) and tetrahydrofuran (150 cm³) was heated under reflux for 3 h (until TLC analysis indicated absence of starting material) when the solvent was distilled off under reduced pressure and conc. hydrochloric acid (300 cm³) was added to the residue. The precipitate was filtered off, washed with water and dried in a vacuum desiccator, to give the acid **4** (11.76 g, 90%), mp 221–222 °C (lit.,^{24,35,66} mp 218–220 and 219–220 °C); $\nu_{\text{max}}/\text{cm}^{-1}$ 1672 (CO); δ_{H} ([²H₆]-DMSO; 300 MHz) 7.50 (1 H, d, *J*_{6,5} 5.0, H-6), 7.91 (1 H, d, *J*_{5,6} 5.0, H-5) and 8.09 (1 H, s, H-3); *m/z* 202 (M⁺ + 18, 100%), 184 (M⁺, 75%) and 140 (M⁺ - 44, 10%).

Thieno[3,2-*b*]thiophene 5

(a) A stirred solution of the acid **4** (10.0 g, 54.3 mmol), copper powder (2.0 g) and quinoline (80 cm³) was heated at 260 °C in a Woods-metal bath. When no further bubbles of carbon dioxide gas could be seen escaping from the mixture (~ 30 min) the reaction mixture was cooled to ambient temperature. TLC analysis confirmed the absence of starting material. Ether (100 cm³) was added to the mixture and most of the quinoline was removed by repeated washing of the resulting solution with hydrochloric acid (1.0 mol dm⁻³), after which the residue was

chromatographed on silica. Light petroleum eluted compound **5** (6.70 g, 88%), mp 55–56 °C (lit.,^{24,35,66} mp 55–57, 55–56 and 56–56.5 °C); δ_{H} 7.25 (2 H, d, *J* 5.0, H-3/6) and 7.37 (2 H, d, *J* 5.0, H-2/5); *m/z* 140 (M⁺, 100%).

(b) A 2:1 mixture (v/v) of carbon disulfide and 2-(2-thienyl)ethanol was pumped at a rate of 2.76 cm³ h⁻¹ into the reactor maintained at 550 °C. The condensate was washed with 20% aqueous sodium hydroxide and then flash chromatographed on silica. Light petroleum (bp 60–80 °C) eluted compound **5** (16%), mp 55–56 °C, identical in all other respects with the sample prepared as described in (a).

Bis(3-bromo-2-thienyl)methanol 9

3-Bromothiophene **1** (20.0 g, 123.0 mmol) was added dropwise to a solution of lithium diisopropylamide (LDA) [prepared by addition of butyllithium (1.5 mol dm⁻³ in hexane; 82.0 cm³, 123.0 mmol) to diisopropylamine (17.3 cm³, 12.49 g, 123.0 mmol)] in tetrahydrofuran (200 cm³) at 0 °C and the resulting mixture was stirred at this temperature for a further 30 min. Methyl formate (8.0 cm³, 7.79 g, 130.0 mmol) was then added to the mixture after which it was stirred until no further starting material could be detected by TLC analysis (3 h). An excess of 20% aqueous ammonium chloride was added to the mixture which was then extracted with ether to give, on work-up, the crude product which was chromatographed on silica. Light petroleum–ethyl acetate (ratio 6:1) eluted compound **9** (18.5 g, 84%) as an oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 3349 (OH); δ_{H} 3.02 (1 H, d, *J* 3.0, OH), 6.40 (1 H, d, *J* 3.0, ArCH), 6.93 (2 H, d, *J*_{4,5} 5.0, H-4) and 7.26 (2 H, d, *J*_{5,4} 5.0, H-5); *m/z* 354 (M⁺, 2%), 339 (M⁺ - 17, 39%), 337 (M⁺ - 17, 70%) and 335 (M⁺ - 17, 35%) (Found: M⁺ + 1, 352.8289. C₉H₆Br₂OS₂ requires M + 1, 352.8306).

2,3,5-Tribromothieno[3,2-*b*]thiophene 6

Bromine (0.62 cm³, 1.93 g, 12.0 mmol) was added dropwise to a stirred solution of the acid **4** (2.0 g, 11.0 mmol) in acetic acid (500 cm³) at ambient temperature and the resulting mixture was stirred for a further 1 h. After this water (100 cm³) was added to the mixture which was then heated under reflux. More bromine (2.47 cm³, 7.68 g, 48.0 mmol) was added to this hot, stirred solution which was then heated under reflux until no starting material could be detected by TLC analysis. The white precipitate of compound **6** (3.84 g, 93%) was filtered off, washed with 10% aqueous sodium thiosulfate and recrystallised from trichloromethane, mp 140–142 °C (lit.,³⁶ mp 140–143.5 °C); δ_{H} 7.21 (1 H, s, H-6).

2,3,5,6-Tetrabromothieno[3,2-*b*]thiophene 7

(a) Bromine (2.06 cm³, 6.41 g, 40.1 mmol) was added dropwise to a stirred solution of the acid **4** (7.41 g, 40.1 mmol) in acetic acid (1 l) at ambient temperature and the resulting mixture was stirred for a further 1 h before it was diluted with water (100 cm³) to give a precipitate. The mixture was then heated under reflux when more bromine (2.06 cm³, 6.41 g, 40.1 mmol) was added to it. When TLC analysis showed that the intermediate monobrominated acid had all reacted (~ 3 h) more bromine (8.20 cm³, 160.0 mmol) was added dropwise to the mixture during 15 min. The resulting solution was then heated at 60–70 °C and stirred for a further 12 h. After this the white precipitate was filtered off, washed with water and recrystallised from tetrahydrofuran, to give compound **7** (12.65 g, 70%), mp 229–230 °C [lit.,^{31,55} mp 237–238.5 (sealed tube) and 229–230 °C]; *m/z* 460 (M⁺, 13%), 458 (M⁺, 68%), 456 (M⁺, 100%), 454 (M⁺, 68%) and 452 (M⁺, 12%) (Found: M⁺, 452.6254. C₆Br₄S₂ requires M, 452.6255).

(b) 2,3,5-Tribromothieno[3,2-*b*]thiophene **6** (0.3 g, 0.79 mmol) in tetrahydrofuran (5.0 cm³) was added to a stirred solution of LDA [prepared by addition of butyllithium (1.5 mol dm⁻³ in hexane; 0.53 cm³, 80.0 mmol) to diisopropylamine (0.12 cm³, 0.86 g, 0.85 mmol)] in tetrahydrofuran (50 cm³) at -80 °C and the resulting mixture was stirred for a further 5 min

prior to addition of bromine (0.5 cm³, 1.56 g, 9.7 mmol). The resulting mixture was allowed to warm slowly to ambient temperature, after which it was poured into water (50 cm³). The resulting precipitate was filtered off, washed with 10% aqueous sodium thiosulfate (10 cm³) and dried in an oven, to give compound **7** (0.283 g, 78%), mp 229–230 °C, identical in all respects with the sample prepared as described in (a).

3,6-Dibromothieno[3,2-*b*]thiophene **8**

Compound **7** (1.0 g, 2.20 mmol) was dissolved in acetic acid (100 cm³) heated under reflux, after which zinc dust (0.15 g, 2.30 × 10⁻³ mol) was added to the solution; the resulting mixture was heated under reflux for 30 min. A further quantity of zinc dust (0.15 g, 2.30 × 10⁻³ mol) was added to the mixture after cooling after which refluxing was continued for a further 30 min. The mixture was then cooled to ambient temperature and diluted with water. The precipitate was filtered off, washed with water, dried and chromatographed on silica. Light petroleum eluted compound **8** (0.50 g, 76%), mp 120–122 °C (from light petroleum); $\nu_{\max}/\text{cm}^{-1}$ 727 (C-Br); δ_{H} 7.32 (2 H, s, H-2/5) (Found: C, 24.6; H, 0.8%; $M^+ + 1$, 296.8050. C₆H₂Br₂S₂ requires C, 24.2; H, 0.7%; $M + 1$, 296.8044). The product decomposed slowly with release of bromine.

2,5-Disubstituted thieno[3,2-*b*]thiophenes **13–16**

Butyllithium (1.5 mol dm⁻³ in hexane; 1.3 cm³, 1.95 mmol) was added dropwise to a stirred solution of compound **5** (0.12 g, 0.86 mmol) in ether (50 cm³) at 0 °C and the resulting mixture was stirred for a further 10 min; it was then quenched with dimethyl disulfide (0.50 cm³, 0.52 g, 5.55 mmol). After a further 15 min the mixture was allowed to warm to ambient temperature when it was diluted with water (50 cm³). Extraction of the product with ether gave 2,5-bis(methylsulfanyl)thieno[3,2-*b*]thiophene **13** (0.14 g, 73%), mp 73–75 °C (from light petroleum–ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ 1632 (C=C); δ_{H} 2.50 (6 H, s, SMe) and 7.18 (2 H, s, H-3/6) (Found: C, 41.4; H, 3.45%; $M^+ + 1$, 232.9582. C₈H₈S₄ requires C, 41.4; H, 3.45%; $M + 1$, 232.9587).

The following compounds were prepared similarly: 2,5-bis(phenylsulfanyl)thieno[3,2-*b*]thiophene **14** (62%), mp 137–139 °C (from light petroleum–ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ 1671 (C=C); δ_{H} 7.15–7.30 (10 H, m, 2 × SPh) and 7.40 (2 H, s, H-3/6) (Found: C, 60.65; H, 3.3%; $M^+ + 1$, 356.9895. C₁₈H₁₂S₄ requires C, 60.7; H, 3.4%; $M + 1$, 356.9900); 2,5-bis(trimethylsilyl)thieno[3,2-*b*]thiophene **15** (66%), mp 108–109 °C (from light petroleum–ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ 1644 (C=C); δ_{H} 0.33 (18 H, s, SiMe₃) and 7.31 (2 H, s, H-3/6) (Found: C, 50.5; H, 7.1%; $M^+ + 1$, 285.0618. C₁₂H₂₀Si₂S₂ requires C, 50.6; H, 7.1%; $M + 1$, 285.0623); and 2,5-bis(tert-butyltrimethylsilyl)thieno[3,2-*b*]thiophene **16** (41%), mp 117–118 °C (from aqueous ethanol); $\nu_{\max}/\text{cm}^{-1}$ 1644 (C=C); δ_{H} 0.29 (12 H, s, SiMe₃), 0.93 (18 H, s, SiCMe₃) and 7.31 (2 H, s, H-3/6) (Found: $M^+ + 1$, 369.1544. C₁₈H₃₂Si₂S₂ requires $M + 1$, 369.1562).

3,6-Disubstituted thieno[3,2-*b*]thiophenes **19–21**

Butyllithium (1.5 mol dm⁻³ in hexane; 0.5 cm³, 0.75 mmol) was added dropwise to a stirred solution of compound **8** (0.095 g, 0.32 mmol) in ether (50 cm³) at –100 °C and the resulting mixture was stirred for a further 5 min; it was then quenched at –80 °C by addition of dimethyl disulfide (0.1 cm³, 0.10 g, 1.1 mmol). The reaction mixture was then allowed to warm up slowly to ambient temperature when it was diluted with water (50 cm³) and extracted with ether; work-up gave the crude product which was chromatographed on silica to give with light petroleum as eluent 3,6-bis(methylsulfanyl)thieno[3,2-*b*]thiophene **19** (0.03 g, 71%), mp 82–84 °C (from light petroleum); δ_{H} 2.52 (6 H, s, SMe) and 7.14 (2 H, s, H-2/5) (Found: C, 41.3; H, 3.4%; $M^+ + 1$, 232.9584. C₈H₈S₄ requires C, 41.4; H, 3.45%; $M + 1$, 232.9587).

A mixture of 3,6-diacetylthieno[3,2-*b*]thiophene **18** (16% with *N,N*-dimethylacetamide as the quenching reagent), mp 264–

265 °C (from light petroleum–ethyl acetate); $\nu_{\max}/\text{cm}^{-1}$ 1625 (CO); δ_{H} 2.60 (6 H, s, COMe) and 8.19 (2 H, s, H-2/5) (Found: MH⁺, 225.0052. C₁₀H₈O₂S₂ requires MH, 225.0044) and 3-acetylthieno[3,2-*b*]thiophene (28%), mp 80–81 °C (from light petroleum) (lit.,⁶² mp 80–81 °C); $\nu_{\max}/\text{cm}^{-1}$ 1661 (CO); δ_{H} 2.60 (3 H, s, COMe), 7.24 (1 H, d, $J_{5,6}$ 5.0, H-5), 7.50 (1 H, dd, $J_{6,5}$ 5.0, $J_{6,2}$ 1.5, H-6) and 8.10 (1 H, d, $J_{2,6}$ 1.5, H-2) (Found: MH⁺, 182.9944. C₈H₆OS₂ requires MH, 182.9938) (ether as the solvent); 3,6-bis(phenylsulfanyl)thieno[3,2-*b*]thiophene **20** (64%; reaction carried out in hexane–tetrahydrofuran), mp 134–136 °C (after chromatography on a silica column; light petroleum as eluent); δ_{H} 7.29 (2 H, s, H-2/5) and 7.20–7.50 (10 H, m, 2 × SPh) (Found: C, 60.5; H, 3.3%; $M^+ + 1$, 356.9891. C₁₈H₁₂S₄ requires C, 60.7; H, 3.4%; $M + 1$, 356.9895); and 3,6-bis(trimethylsilyl)thieno[3,2-*b*]thiophene **21** (42% in ether or 62% in hexane–tetrahydrofuran), mp 84–86 °C (after chromatography on neutral alumina; light petroleum as eluent); δ_{H} 0.35 (18 H, s, SiMe₃) and 7.44 (2 H, s, H-2/5) (Found: C, 50.7; H, 7.0%; $M^+ + 1$, 285.0627. C₁₂H₂₀Si₂S₂ requires C, 50.6; H, 7.1%; $M + 1$, 285.0623) were prepared similarly.

3,6-Dibromo-2,5-dimethylthieno[3,2-*b*]thiophene **23**

Butyllithium (1.37 mol dm⁻³ in hexane; 2.10 cm³, 2.90 mmol) was added to a stirred solution of compound **7** (0.64 g, 1.40 mmol) in tetrahydrofuran (50 cm³) at ambient temperature and the resulting mixture was stirred for 30 min prior to addition of freshly distilled dimethyl sulfate (0.3 cm³, 0.34 g, 2.70 mmol). The reaction mixture was stirred overnight at ambient temperature, after which it was quenched with an excess of 20% aqueous ammonium chloride. Extraction with ether gave the product which was flash chromatographed on silica. Light petroleum eluted 3,6-dibromo-2,5-dimethylthieno[3,2-*b*]thiophene **23** (0.25 g, 55%), mp 171–173 °C (from ether); $\nu_{\max}/\text{cm}^{-1}$ 1600 (C=C); δ_{H} 2.47 (6 H, s, Me) (Found: M^+ , 323.8278. C₈H₆Br₂S₂ requires M , 323.8278).

3,6-Dibromo-2,5-bis(methylsulfanyl)thieno[3,2-*b*]thiophene **24** (54%), mp 126–128 °C (from light petroleum); $\nu_{\max}/\text{cm}^{-1}$ 1600 (C=C); δ_{H} 2.50 (6 H, s, SMe) (Found: C, 24.9; H, 1.3%; $M^+ + 1$, 388.7784. C₈H₆Br₂S₄ requires C, 24.6; H, 1.55%; $M + 1$, 388.7798); and 3,6-dibromo-2,5-bis(trimethylsilyl)thieno[3,2-*b*]thiophene **26** (75%), mp 145–147 °C (from light petroleum); $\nu_{\max}/\text{cm}^{-1}$ 1644 (C=C); δ_{H} 0.34 (18 H, s, 2 × SiMe₃); δ_{C} –0.96, 29.7, 108.7 and 138.9 (Found: MH⁺, 442.8800. C₁₂H₁₈⁷⁹Br⁸¹BrSi₂ requires MH, 442.8814) were prepared similarly.

3,6-Dibromo-2,5-bis(6-methylcyclohex-1-enyl)thieno[3,2-*b*]thiophene **25**

Butyllithium (1.37 mol dm⁻³ in hexane; 1.6 cm³, 2.20 mmol) was added to a stirred solution of compound **7** (0.39 g, 0.86 mmol) in tetrahydrofuran (50 cm³) at ambient temperature and the resulting mixture was stirred for a further 30 min. 2-Methylcyclohexanone (0.25 g, 2.20 mmol) was added to the mixture which was then stirred overnight. After this it was washed with hydrochloric acid (2.0 mol dm⁻³; 50 cm³) and extracted with ether to give the crude carbinol. This was dissolved in toluene (100 cm³) to which toluene-4-sulfonic acid (0.1 g) was added; the resulting mixture was heated under reflux for 8 h whilst water was azeotroped off in a Dean–Stark apparatus. After this the toluene was distilled off and the residue was flash chromatographed on silica. Light petroleum eluted the product **25** (0.25 g, 55%) as a colourless oil; $\nu_{\max}/\text{cm}^{-1}$ 1577 (C=C); δ_{H} 0.98 (6 H, d, J 7.0, 2 × Me), 1.24–2.31 (12 H, m, 6 × CH₂), 2.77–2.79 (2 H, m, 2 × CHMe) and 6.06 (2 H, dd, J 3.0, 2 × =CH) [Found: M^+ (EI), 483.9532. C₂₀H₂₂Br₂S₂ requires M , 483.9531].

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