

Synthesis of Some 4-Substituted and 4,6-Disubstituted Dibenzothiophenes

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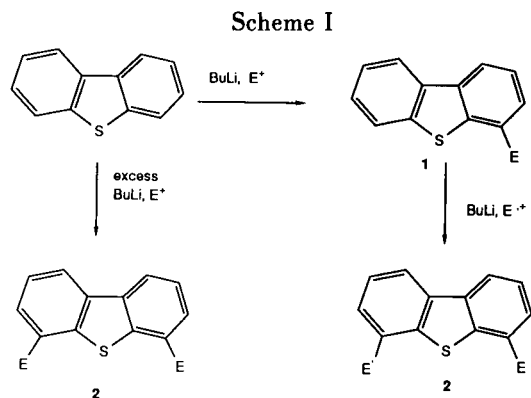
The synthesis is described of various 4-substituted (**1**) and 4,6-disubstituted (**2**) dibenzothiophenes by lithiation reactions. The factors controlling the formation of 4,6-disubstituted dibenzothiophenes by the lithiation of 4-methyl- and 4-ethyl-dibenzothiophene at the 6-position versus lithiation at the α -carbon of the 4-substituent are examined.

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Introduction.

It has been known for over fifty years that the treatment of dibenzothiophene with *n*-butyllithium affords 4-lithiodibenzothiophene which reacts with electrophiles leading to the formation of 4-substituted dibenzothiophenes **1** [1]. The synthetic utility of this reaction has been exploited extensively [1-3].

On the basis of the similarity of the 4- and 6-positions of the dibenzothiophene, 4,6-disubstituted dibenzothiophenes **2** should readily be obtainable either by treating dibenzothiophene with an excess both of *n*-butyllithium and of an electrophile, or by a successive two step introduction of the groups.



Surprisingly, few studies on the synthesis of 4,6-disubstituted dibenzothiophenes **2** have been reported. One pot syntheses of 4,6-disubstituted dibenzothiophenes (**2**) from dibenzothiophene using an excess of *n*-butyllithium (4 equivalents and above) in refluxing ether for a long time (16 hours or above) followed by treatment with dimethyl sulfate or deuterium oxide resulted in low yields of the products: only 15% for 4,6-dimethyldibenzothiophene (**2a**) [4] and only 22% for 4,6-dideuteriodibenzothiophene (**2b**) [5]. Previously, the best overall yield of **2a** (19%) was obtained by a four step synthesis starting from 3-methylcyclohexanone and 2-methylbenzenethiol [6].

In the present work, we have examined the factors that influence the formation of 4,6-disubstituted dibenzothiophenes **2** and report considerably improved methods for their synthesis. During the characterisation of these compounds employing ^1H and ^{13}C nmr spectroscopy, we have prepared several 4-substituted dibenzothiophenes **1** by the reaction of 4-lithiodibenzothiophene with different electrophiles; yields of the 4-substituted dibenzothiophenes **1** varied with the electrophile used. These preparative results are now discussed.

Results and Discussion.

Synthesis of 4-substituted dibenzothiophenes **1**.

Synthesis of 4-substituted dibenzothiophenes **1**.

In the present study, 4-ethyl- (**1a**) and 4-propyldibenzothiophene (**1b**) were prepared by the reaction of 4-lithiodibenzothiophene with ethyl and propyl iodides in 90% and 85% yields, respectively, while 4-chlorodibenzothiophene (**1c**) was obtained in 63% yield by the reaction of 4-lithiodibenzothiophene with *p*-toluenesulfonyl chloride. Previously, **1c** had been prepared in low yields *via* the Sandmeyer reaction of 4-aminodibenzothiophene [7], and also by a three step process starting from 2-chlorocyclohexanone and thiophenol [8].

Similarly, the reaction of 4-lithiodibenzothiophene with paraformaldehyde gave 4-hydroxymethyldibenzothiophene (**1d**) in 80% yield. Alternative literature methods for the preparation of **1d** from dibenzothiophene each consist of two steps: (i) by the LAH reduction of the dibenzothiophene-4-carboxylic acid [9], and (ii) by the sodium borohydride reduction of dibenzothiophene-4-carboxaldehyde [10]. We prepared 4-bromodibenzothiophene (**1e**) by the reaction of 4-lithiodibenzothiophene with cyanogen bromide in 60% yield.

Synthesis of 4,6-Disubstituted Dibenzothiophenes **2**.

The reaction of dibenzothiophene with *n*-butyllithium and dimethyl sulfate (two moles of each) carried out with a view to synthesising 4,6-dimethyldibenzothiophene (**2a**) in THF afforded 4-methyldibenzothiophene (**1f**) in 93% yield as the only product isolated. The non-formation of 4,6-dimethyldibenzothiophene (**2a**), in spite of the use of the excess of *n*-butyllithium and electrophile, as well as similar literature observations [4,5], indicated that the formation

of 4,6-dilithiodibenzothiophene (**2**) is difficult compared to the formation of 4-lithiodibenzothiophene. Consequently, it was felt that the introduction of the substituents in the 4- and 6-positions in two monolithiation-followed-by-substitution steps might be a better approach than the dilithiation-followed-by-disubstitution sequence.

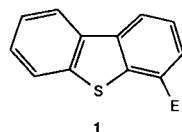
However, 4-methyldibenzothiophene (**1f**) on treatment with *n*-butyllithium and dimethyl sulfate (2 moles of each) afforded 4-ethylidibenzothiophene (**1a**) as the major product in 74% yield *via* lithiation of the methyl group in preference to the 6-position of dibenzothiophene. The residue consisted of starting material **1f** (7.3%) and three isomeric dimethyldibenzothiophenes (11%, 3.0% and 1.4% each). This observation is in consonance with the reaction of 4-methyldibenzothiophene (**1f**) with *n*-butyllithium (2 moles) followed by treatment with deuterium oxide wherein the methyl group was deuterated to a larger extent (70%) than of the 6-position (30%). The ratio of these deuterations was conveniently estimated from the ¹H nmr spectrum of the deuterated product by comparing the intensities of the H-6 (7.88 ppm) and methyl (2.59 ppm) signals with the intensities of the signals of the protons at

undeuterated positions. Interestingly, much higher regioselectivity was found when one equivalent of *n*-butyllithium was employed in this reaction which resulted in 60% deuteration at the methyl group while the deuteration at the 6-position was not significant. The synthetic usefulness of the regioselective lithiation at the methyl group of **1f** has been demonstrated by the preparation of 4-(2-hydroxy-2,2-diphenylethyl)dibenzothiophene (**1g**) from benzophenone and 4-(2-hydroxy-2-methylpropyl)dibenzothiophene (**1h**) from acetone (Table I).

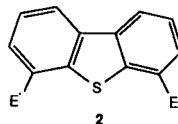
Contrary to the predominant lithiation observed at the methyl group of 4-methyldibenzothiophene (**1f**), lithiation of 4-ethylidibenzothiophene (**1a**) followed by quenching with deuterium oxide revealed 70% lithiation at the 6-position while the lithiation at the ethyl group was negligible. The different regioselectivities observed in the lithiations of **1a** and **1f** may be ascribed to polar and/or steric differences of these alkyl groups.

The regioselective lithiation at the 6-position of **1a** was used in the preparation of some 6-substituted 4-ethylidibenzothiophenes **2c-2g**. A gc/ms analysis of the product obtained in the reaction of 4-ethylidibenzothiophene with

Table I
Preparation of 4-Substituted (**1**) and 4,6-disubstituted (**2**) dibenzothiophenes



- 1
- E
- a Et
b Pr
c Cl
d CH₂OH
e Br
f CH₃
g CH₂C(OH)Ph₂
h CH₂C(OH)Me₂



- 2
- E E
- a Me Me
b D D
c Me Et
d Et Et
e Et CH₂OH
f Et CMe₂OH
g Et Cl

No	Yield (%)	mp (°C)	Recrystallization Solvent	Formula	Analysis (%)			
					Calcd		Found	
				C	H	C	H	
1a	90	35-37 [a]	hexane	C ₁₄ H ₁₂ S	79.20	5.70	79.06	5.64
1b	85	oil	[high resolution mass spectrum:	C ₁₅ H ₁₄ S	Calcd: 226.08162; Found: 226.08237]			
1c	63	80-82	hexane	[lit [8] mp 81-82°]				
1d	80	128-130	ethanol	[lit [11] mp 129-130°]				
1e	60	82-83	ethanol	[lit [12] mp 83-84°]				
1f	93	64-65	dilute ethanol	[lit [1] mp 65°]				
1g	52	136-138	hexane-dichloromethane	C ₂₆ H ₂₀ OS	82.07	5.30	81.90	5.30
1h	62	61-63	hexane-dichloromethane	C ₁₆ H ₁₆ OS	74.96	6.29	74.86	6.38
2c	42	58-60	hexane	C ₁₅ H ₁₄ S	79.20	6.23	79.35	6.26
2d	47	54-55	hexane	C ₁₆ H ₁₆ S	79.95	6.71	79.44	6.69
2e	43	105-107	chloroform	C ₁₅ H ₁₄ OS	74.35	5.82	74.40	5.75
2f	60	126-128	hexane-dichloromethane	C ₁₇ H ₁₈ OS	75.52	6.71	75.28	6.66
2g	43	47-49	hexane	C ₁₄ H ₁₁ ClS	68.16	4.49	68.54	4.60

[a] Lit [6] reports an oil.

n-butyllithium and dimethyl sulfate (two moles each) revealed the predominance of 4-ethyl-6-methyldibenzothiophene (**2c**, 63%), the by-products being other monomethylated (4%), dimethylated (16%) and trimethylated (7%) 4-ethyl-dibenzothiophenes together with unchanged starting material (3.5%). Similarly, the reaction of 4-ethyl-dibenzothiophene with *n*-butyllithium and ethyl iodide afforded predominantly 4,6-diethyl-dibenzothiophene (**2d**, 68%), unchanged starting material (4%), the by-products consisting of other diethyl-dibenzothiophene isomers (14%), and tri- (8%) and tetra- (2%) ethyldibenzothiophenes. In an analogous manner, 4-ethyl-6-hydroxymethyldibenzothiophene (**2e**), 4-ethyl-6-(2-hydroxy-2-propyl)dibenzothiophene (**2f**), and 4-chloro-6-ethyldibenzothiophene (**2g**) were obtained as the major products from the reaction of 4-ethyl-6-lithiodibenzothiophene with the appropriate electrophiles (Table I).

Conclusion.

The results of the present study show that the preparation of 4,6-disubstituted dibenzothiophenes **2** in two monolithiation-followed-by-substitution steps is preferable to dilithiation-followed-by-substitution in a single step. Another advantage associated with this method is that unsymmetrical 4,6-disubstituted dibenzothiophenes can also be prepared. The limitation of this two step approach, however, is that the initially introduced group should not itself be significantly reactive towards lithiation as this will diminish the yield of the 4,6-disubstituted dibenzothiophenes **2**.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The ¹H nmr spectra were taken in deuteriochloroform at 300 MHz on a Varian XL 300 spectrometer with tetramethylsilane as internal reference. The gc analyses of the products were carried out in Hewlett Packard 5890A gas chromatograph and gc/ms were obtained from Varian 3400 gas chromatograph and Finnigan Mat Model 700 Ion Trap Detector. High resolution ms was obtained on a Kratos/AE1-MS 30 mass spectrometer. Elemental analyses were carried out on a Calo Erba-1106 instrument under the supervision of Dr. D. Powell. THF was purified and distilled from sodium/benzophenone prior to use.

4-Substituted **1** and 4,6-Disubstituted dibenzothiophenes **2**. A General Procedure.

To a stirred solution of dibenzothiophene or 4-substituted dibenzothiophene (10 mmoles) in THF (30 ml) under nitrogen at -78° was added dropwise a solution of *n*-butyllithium (20 mmoles) in hexane. The orange colored solution was allowed to warm to room temperature and further stirred for 5 hours. The resulting lithiodibenzothiophene solution was cooled to -78° and the appropriate electrophile (12-20 mmoles) in THF was added dropwise. The reaction mixture was allowed to warm gradually to room temperature and was stirred for 10-15 hours, whereupon it

was quenched with aqueous ammonium chloride solution and extracted with ether. The ether extracts were washed with water, dried (magnesium sulfate) and the solvent removed. The products were purified either by recrystallization or column chromatography. The following compounds were prepared:

4-Ethyldibenzothiophene (**1a**).

Reaction of 4-lithiodibenzothiophene with ethyl iodide in THF afforded **1a**; ¹H nmr: δ 8.15 (m, 1 H), 8.02 (dd, J = 7.95 and 1.12 Hz, 1 H), 7.87 (m, 1 H), 7.45 (m, 3 H), 7.31 (m, 1 H), 2.94 (q, J = 7.57 Hz, 2 H), 1.41 (t, J = 7.57 Hz, 3 H).

4-Propyldibenzothiophene (**1b**).

Compound **1b** was obtained by the reaction of 4-lithiodibenzothiophene with 1-propyl iodide in THF. The product was purified by flash column chromatography using silica gel and pentane; ¹H nmr: δ 8.14 (m, 1 H), 8.02 (d, J = 7.81 Hz, 1 H), 7.87 (m, 1 H), 7.48-7.39 (m, 3 H), 7.28 (d, J = 7.32 Hz, 1 H), 2.88 (t, J = 7.57 Hz, 2 H), 1.85 (m, 2 H), 1.03 (t, J = 7.32 Hz, 3 H).

4-Chlorodibenzothiophene (**1c**).

Reaction of 4-lithiodibenzothiophene with *p*-toluenesulphonyl chloride afforded **1c**; ¹H nmr: δ 8.14 (m, 1 H), 8.06 (m, 1 H), 7.89 (m, 1 H), 7.53-7.39 (m, 3 H), 7.42 (m, 1 H).

4-Hydroxymethyldibenzothiophene (**1d**).

The reaction of 4-lithiodibenzothiophene with paraformaldehyde afforded this compound; ¹H nmr: δ 8.17 (m, 1 H), 8.12 (m, 1 H), 7.89 (m, 1 H), 7.52-7.44 (m, 4 H), 5.00 (d, J = 5.97 Hz, 2H), 1.54 (t, J = 5.97 Hz, 1H).

4-Bromodibenzothiophene (**1e**).

Reaction of 4-lithiodibenzothiophene with cyanogen bromide provided this compound; ¹H nmr: δ 8.13 (m, 1 H), 8.12 (m, 1H), 7.89 (m, 1 H), 7.62 (dd, J = 7.63 and 0.87 Hz, 1 H), 7.53-7.47 (m, 2 H), 7.36 (m, 1H).

4-Methyldibenzothiophene (**1f**).

This compound was obtained by the reaction of 4-lithiodibenzothiophene with dimethyl sulfate [1]; ¹H nmr: δ 8.15 (m, 1 H), 8.02 (d, J = 7.82 Hz, 1 H), 7.88 (m, 1 H), 7.46 (m, 2 H), 7.40 (m, 1 H), 7.28 (d, J = 7.19 Hz, 1H), 2.59 (s, 3 H).

4-(2,2-Diphenyl-2-hydroxyethyl)dibenzothiophene (**1g**).

This compound was obtained by the reaction of 4-methyldibenzothiophene (**1f**) (10.1 mmoles) with *n*-butyllithium (20 mmoles) followed by reaction with benzophenone (10.2 mmoles) in THF. The product was purified by flash column chromatography followed by recrystallisation; ¹H nmr: δ 8.10 (m, 1 H), 7.99 (d, J = 7.95 Hz, 1 H), 7.82 (m, 1H), 7.47 (m, 4 H), 7.43 (m, 2 H), 7.36-7.22 (m, 6H), 7.18 (t, J = 7.73 Hz, 1 H), 6.72 (d, J = 7.51 Hz, 1 H), 3.95 (s, 2 H), 2.44 (s, 1 H).

4-(2-Hydroxy-2-methylpropyl)dibenzothiophene (**1h**).

This compound was obtained by the reaction of 4-methyldibenzothiophene (**1f**) (10.1 mmoles) with *n*-butyllithium (20 mmoles) followed by treatment with acetone (10.2 mmoles) in THF. The product was purified by flash column chromatography employing silica gel and hexane-dichloromethane and recrystallisation; ¹H nmr: δ 8.15 (m, 1 H), 8.07 (dd, J = 7.84 and 1.32 Hz, 1 H), 7.85 (m, 1 H), 7.49-7.42 (m, 3 H), 7.36 (dd, J = 7.29 and 1.19 Hz, 1H), 3.10 (s, 2 H), 1.55 (s, 1 H), 1.35 (s, 6 H).

4-Ethyl-6-methyldibenzothiophene (2c).

This compound was obtained by the reaction of 4-ethyl-6-lithiodibenzothiophene with dimethyl sulfate; ^1H nmr: δ 8.00 (d, J = 7.86 Hz, 2 H), 7.43 (m, 1 H), 7.39 (m, 1 H), 7.33-7.26 (m, 2 H), 2.96 (q, J = 7.57 Hz, 2 H), 2.61 (s, 3 H), 1.43 (t, J = 7.57 Hz, 3 H).

4,6-Diethyldibenzothiophene (2d).

4-Ethyl-6-lithiodibenzothiophene on reaction with ethyl iodide afforded this compound; ^1H nmr: δ 8.00 (d, J = 7.81 Hz, 2 H), 7.42 (m, 2 H), 7.30 (d, J = 7.36 Hz, 2 H), 2.96 (q, J = 7.52 Hz, 4 H), 1.42 (t, J = 7.52 Hz, 6 H).

4-Ethyl-6-hydroxymethyldibenzothiophene (2e).

This compound was obtained by the reaction of 4-ethyl-6-lithiodibenzothiophene with paraformaldehyde. The product was purified by flash column chromatography using silica gel and dichloromethane followed by recrystallization; ^1H nmr: δ 8.10 (m, 1 H), 8.02 (d, J = 8.06 Hz, 1 H), 7.51-7.41 (m, 3 H), 7.32 (d, J = 7.38 Hz, 1 H), 5.02 (d, J = 6.10 Hz, 2 H), 2.96 (q, J = 7.57 Hz, 2 H), 1.88 (t, J = 6.10 Hz, 1 H), 1.42 (t, J = 7.57 Hz, 3 H).

4-Ethyl-6-(1-hydroxy-1-methylethyl)dibenzothiophene (2f).

The reaction of 4-ethyl-6-lithiodibenzothiophene with acetone afforded this compound; ^1H nmr: δ 8.08 (m, 1 H), 8.01 (d, J = 8.01 Hz, 1 H), 7.47-7.38 (m, 3 H), 7.30 (d, J = 7.21 Hz, 1 H), 2.98 (q, J = 7.57 Hz, 2 H), 2.05 (s, 1 H), 1.80 (s, 6 H), 1.42 (t, J = 7.57 Hz, 3 H).

4-Chloro-6-ethyldibenzothiophene (2g).

This compound was obtained by the reaction of 4-ethyl-6-lithiodibenzothiophene with *p*-toluenesulfonyl chloride; ^1H nmr: δ 8.04 (dd, J = 7.52 and 1.47 Hz, 1 H), 7.99 (d, J = 8.30 Hz, 1 H), 7.49-7.38 (m, 3 H), 7.34 (d, J = 6.84 Hz, 1 H), 2.96 (q, J = 7.57 Hz, 2 H), 1.43 (t, J = 7.57 Hz, 3 H).

Deuteration Studies.

The compound **1a** or **1f** (10 mmoles) in THF was treated with *n*-butyllithium in hexane (20 mmoles in the case of **1a** and 10 or 20 mmoles in the case of **1f**) at -78° and allowed to warm to room temperature followed by stirring for a further 5 hours. The dark coloured solution was then quenched by the addition of 2 ml of deuterium oxide and vigorously stirred for 4 hours. The mixture was treated with aqueous ammonium chloride, poured into water and worked up in the usual way. The products were purified by passing through columns of silica gel with pentane as eluent and recrystallised.

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