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Expeditious and Efficient Syntheses of Pure 4-Methyl and 4,6-Disubstituted Dibenzothiophenes

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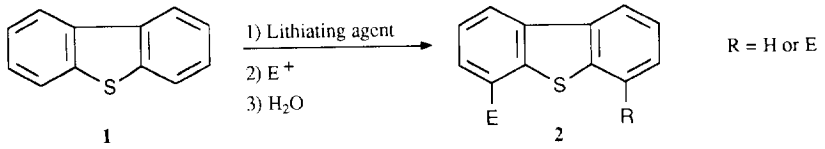
Abstract : 4-Lithio and 4,6-dilithiodibenzothiophenes were efficiently obtained by lithiation of dibenzothiophene with BuLi and BuLi-TMEDA, respectively. Very pure 4-methyl- and 4,6-dimethyldibenzothiophenes, substrates of great request in hydrosulfurization studies were easily prepared, on large scale and in excellent yields.

As part of a program dealing with sulfur containing heterocycles,[1] we were confronted with large scale preparations of 4-methyl and 4,6-disubstituted dibenzothiophenes. From the literature devoted to such derivatives, it appeared that 4-methyl- and 4,6-dimethyldibenzothiophenes (4-MDBT and 4,6-DMDBT respectively) attracted much attention.[2-4] Indeed, these products, present in mineral oils, must be removed in order to obtain non-polluting fuels. On that account, their desulfurizations were and still are actively investigated.[1a,5] However, due to the difficulties encountered during their syntheses,[2,3] such studies are slowed down. On this basis, we undertook the synthesis of the derivatives described below and needed for our further investigations. A very recent publication on this topic in this journal[4] prompts us to presently publish our own results in this area.

Examination of earlier work[2,3] had led us to conclude that the simplest and less expensive pathway leading to such substrates should pass through mono- and bis-lithiation of dibenzothiophene (DBT). Where the preparation of 4,6-DMDBT by such a process was reported as leading to a low 15% yield,[2b] the synthesis of 4-MDBT was described in 93% yield using *n*-BuLi and Me_2SO_4 as metallating and methylating agents,

respectively.[3c] However, in our hands, we were unable to obtain more than 50% yield of 4-MDBT, disclosing that the described experiments were difficult to reproduce by organic chemists unfamiliar with this chemistry. So we decided to explore the synthesis of 4-MDBT, as well as the syntheses of 4,6-disubstituted dibenzothiophenes. The reactions performed are symbolized in Scheme 1 and our best results are collected in Table 1, where the monomethylation performed according to Katritzky[2e] is also given for comparison (Run 1).



1 2

Scheme 1

Interestingly, the replacement of methyl sulfate by methyl iodide considerably increased the yields of 4-MDBT (compare runs 2 and 3 with run 1). This observation completely agrees with the results of Lemaire and coll.[4] who have used the same reagents. However, their isolated yield (63 %) is lower than ours. This difference is due to the fact these authors used only 1.5 eq. of *n*-BuLi at 0°C in THF instead of the 2 or 3 eq. and -78°C in the present work. Under their conditions, THF is easily attacked by lithium reagent as described by Gilman[6a,b] and Bates.[6c] The destruction of part of *n*-BuLi, and may be of 4-Li-DBT, must result and consequently an appreciable amount of unchanged DBT remains which is difficult to remove from 4-MDBT. Finally, we have shown that the presence of TMEDA (Run 4) does not improve the reaction yield.

We then turned to the preparation of 4,6-DMDBT. Note that Lemaire and coll. designed an elegant and univocal three steps synthesis of this compound.[4] However, this way is more expensive and time consuming, and the global yield only reaches 20 %. Under the usual conditions (run 5),[2b] we obtained no more than 15 to 17% of 4,6-DMDBT in complete agreement with preceding publications. On the contrary the use of appropriate metallating agent under optimal conditions (see Table 1, runs 6 to 8) allowed us to obtain 4,6-DMDBT in better yields with a GC purity up to 97%. After an exploratory study, we found that activation of *n*-BuLi with TMEDA allowed a high yield metallation of DBT in hexane at only 60°C. The key point of the synthesis is the addition of MeI which must be performed all at once under vigorous stirring and very efficient cooling (see Experimental Part). Under these conditions a simple crystallization after the workup led to a pure product. Note that we were able to prepare 20 g batches of 4-MDBT or 4,6-DMDBT. For such large amounts the more economical conditions of run 2 or run 6 were used, respectively. In fact, large scale experiments were only limited by the capacity of very efficiently cooling the reaction medium during the reaction with the electrophile.

A recent publication of Haenel and coll.[7] showed that bis-lithiation of DBT could lead to a mixture of 4,6- and 1,9-dilithiated DBT questioning the structure of the product obtained by the lithiation pathway. However, an X-ray analysis of a single crystal of the 4,6-DMDBT presently obtained confirmed the structure.[8]

Table 1. Syntheses of 4-MDBT and 4,6-disubstituted DBT.

Run	Lithiating Agent		Solvent	Metallation		Electrophilic condensation			2		
	BuLi (eq.)	TMEDA (eq.)		T(°C)	t (h)	E+	Eq.	T(°C)	E	R	Isolated Yield (%)
1	2	-	THF-hexane	-78	5	Me_2SO_4	2	-78	Me	H	50
2	2	-	THF-hexane	-78	5	MeI	2	-78	Me	H	81
3	3	-	THF-hexane	-78	5	MeI	3	-78	Me	H	94
4	3	3	THF-hexane	-78	5	MeI	3	-78	Me	H	83
5	4	-	Bu_2O	60	21	Me_2SO_4	10	-78	Me	Me	15-17
6	3	3	Hexane	60	2	MeI	3	-78	Me	Me	48
7	4	4	Hexane	60	2	MeI	3	-78	Me	Me	57
8	4	2	Hexane	60	4.5	MeI	3	-78	Me	Me	60
9	3	3	Hexane	60	2	EtI	10	0	Et	Et	40
10	3	3	Hexane	60	2	DMF	3	-40	CHO	CHO	49
11	3	3	Hexane	60	2	DMF	10	-40	CHO	CHO	63
12	4	4	Hexane	60	2	DMF	10	-40	CHO	CHO	62
13	4	2	Hexane	60	2	DMF	10	-40	CHO	CHO	58
14	4	4	Hexane	60	2	$(HCHO)_n$	10	-40	CH_2OH	CH_2OH	48

We then prepared other 4,6-disubstituted DBT derivatives. When EtI was used instead of MeI a larger amount of electrophile must be used to obtain acceptable yield (Run 9). With only 3 equivalents of EtI (not reported experiment) the yield dropped to 10 %. Such a result must be due to a destruction of the electrophile in the reaction medium.With an formylation reagent (Runs 10 to 13) better results were obtained also when a large excess of electrophile was used, the metallation being carried out with *n*-BuLi (3 eq.) - TMEDA (3 eq.). The use of a larger amount of *n*-BuLi did not improve these results. Finally, we also succeeded in the condensation of paraformaldehyde showing the generality of our procedure. This electrophile must also be used in excess and *n* -BuLi (4 eq.) - TMEDA (4 eq.) were necessary in order to obtain acceptable yields.

In conclusion, the present work brings a simple solution to the difficult problem of the synthesis of 4,6-disubstituted dibenzothiophenes. Of particular interest is the easy and inexpensive preparation on a large scale of 4-methyl and above all 4,6-dimethyl DBT.

Experimental Part

Dry tetrahydrofuran (THF) and hexane were obtained by the standard method. Melting points were determined on a system Koffler (± 1°C). The ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker AM 400 using tetramethylsilane as an internal standard. Chemical shifts were reported in ppm. IR spectra were obtained an a 580 B Perkin Elmer spectrophotometer. Elementary analyses were performed by the Service Central d'Analyses, CNRS, Solaize, France. X-Ray analysis were performed by the Service Commun de RX, Université Henri Poincaré, Nancy 1.

4-Methyldibenzothiophene (4-MDBT)

Dibenzothiophene (19.6 g, 106 mmoles) was dissolved in dry THF (400 ml) under argon atmosphere. The solution was cooled at -78 °C and 200 ml of a 1.6 M solution of *n*-butyllithium in hexane (320 mmoles) were dropwise added. The reaction mixture was then warmed up and stirred at room temperature during 5 h. After cooling at -78 °C, 45.5 g of methyl iodide (320 mmoles) were dropwise added over a period of 3-5 min. The exothermic reaction must be controlled by a vigourous agitation and cooling. The mixture was kept for 12 h. at room temperature. It was then poured into 1 l. of ice-water. The product was extracted with methylene chloride (3 x 250 ml). The organic phase was acidified with HCl 1N (300 ml), dried over magnesium sulfate and solvents were removed under vacuum. 19.7 g of 4-MDBT (94 % yield, > 98 % GC purity) were obtained as white plates from the crude product after recrystallization from hexane (400 ml), mp 66°C. Spectroscopic data are identical to that reported in Ref. 2e.

4,6-Dimethyldibenzothiophene (4,6-DMDBT)

200 ml of a 1.6 M solution of n-butyllithium in hexane (320 mmoles) were dropwise added at 0 °C to a solution of TMEDA (320 mmoles) in 100 ml ofdry hexane. After stiring during 30 min at 0 °C and 30 min at room temperature, the mixture was diluted with 200 ml of hexane. Then, 19.6 g of dibenzothiophene (106 mmoles) were added through a solid addition funnel. After 2 h. heating at 60 °C, the reaction mixture was cooled at -78 °C and 45.5 g of methyl iodide (320 mmoles) were added all at once. The exothermic reaction must be controlled by a vigourous agitation and cooling. After completion, the mixture was let 12 h. at room temperature. It was then poured into a flask containing 1 l. of ice-water. The product was extracted with methylene chloride (3 x 250 ml). The organic phase was acidified with HCl 1N (300 ml) and washed with water (3 x 300 ml), dried over magnesium sulfate and solvents were removed under vacuum. 10.8 g of 4,6-DMDBT (48 % yield, > 97 % GC purity) were obtained as white needles from the crude product after recrystallizations from tetrahydrofuran (2 x 120 ml), mp 154 °C. Spectroscopic data and X-ray structure are identical to that reported in Ref. 4.

4,6-Diethyldibenzothiophene (4,6-DEDBT)

4,6-DEDBT was prepared on a 10 mmole scale of DBT by the same procedure given above for 4,6-DMDBT using ethyl iodide (15.6 g, 100 mmoles) as electrophile added all at once at 0 °C. The exothermic reaction must be controlled by vigourous stirring and cooling. After classical workup, 1 g of 4,6-DEDBT (40% yield) were obtained as white crystal after recrystallization from hexane (20 ml), mp 58 °C. Spectroscopic data are identical to that reported in Ref. 2e.

Dibenzothiothene-4,6-dicarboxaldehyde

The preparation was performed on a 10 mmole scale of DBT by the same procedure given above for 4,6-DMDBT using dimethylformamide (7.6 g, 100 mmoles) as electrophile added all at once at -40°C. The exothermic reaction must be controlled by vigourous stirring and cooling. After classical workup, 1.36 g of dibenzothiothene-4,6-dicarboxaldehyde (63 %) were obtained after recrystallization from tetrahydrofuran (30 ml), mp 249 °C. ^{1}H NMR (400 MHz) (D6 dimethylsulfoxyde) : δ 7.55 (t, 2 H, H-2, J_{2-3} = 8 Hz), 8.09 (d, 2 H, H-1, J_{1-2} = 8 Hz) , 8.52 (d, 2 H, H-3, J_{3-2} = 8 Hz), 10.36 (s, 2 H, C-H). ^{13}C NMR (400 MHz) (D6 dimethylsulfoxyde) : δ 123.52 (C_1, C_9), 125.83 (C_2, C_8), 129.16 (C_3, C_7), 132.35 (C_4, C_6), 133.44 (C_{10}, C_{11}), 137.37 (C_{12}, C_{13}), 190.15 (2 x CHO). Anal. Calcd.: $C_{14}H_8O_2S$: C 69.98; H 3.35; S 13.34; O 13.32; Found: C 69.83; H 3.13; S 13.56; O 13.61. Authentification of 4,6-DCDBT was achieved by derivatization in 4,6-DMDBT using a known procedure.[9]

4,6-Dihydroxymethyldibenzothiophene (4,6-DHMDBT)

The preparation was performed on a 10 mmole scale of DBT by the same procedure given above for 4,6-DMDBT using paraformaldehyde (100 mmoles) as electrophile added all at once at -40 °C. The exothermic reaction must be controlled by vigourous stirring and cooling. After classical workup, 1.1 g of 4,6-DHMDBT (45 %) were obtained after recrystallization of crude product from isopropanol (30 ml), mp 222 °C. ^{1}H NMR (400 MHz) (D6 dimethylsulfoxyde) : δ 4.83 (d, 2 H, 2 x CH_2), 5.42 (t, 2 H, O-H), 7.45 (t, 2 H, H-3, J_{3-2} = 8 Hz), 7.50 (t, 2 H, H-2, J_{2-3} = 8 Hz) , 8.12 (d, 2 H, H-1, J_{1-2} = 8 Hz). ^{13}C NMR (400 MHz) (D6 dimethylsulfoxyde) : δ 60.95 (C_4-CH_2OH, C_6-CH_2OH), 118.62 (C_1, C_9), 122.73 (C_2, C_8), 122.83 (C_3, C_7), 133.79 (C_{10}, C_{11}), 134.81 (C_4, C_6), 135.06 (C_{12}, C_{13}). 4,6-DHMDBT was identified by comparison of its spectroscopic data and mp with an authentic sample obtained by reduction of 4,6-DCDBT with $NaBH_4$ using classical procedure.[10]

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