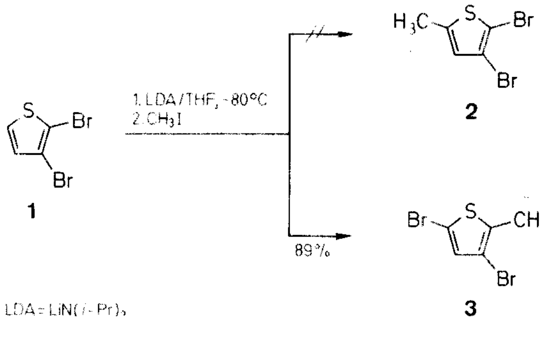
Synthesis of 2-Substituted 3,5-Dibromothiophenes via a Rearrangement Reaction: A New Example of a Base-Catalyzed Halogen Dance Reaction

Fritz Sauter,* Hannes Fröhlich, Wolfram Kalt

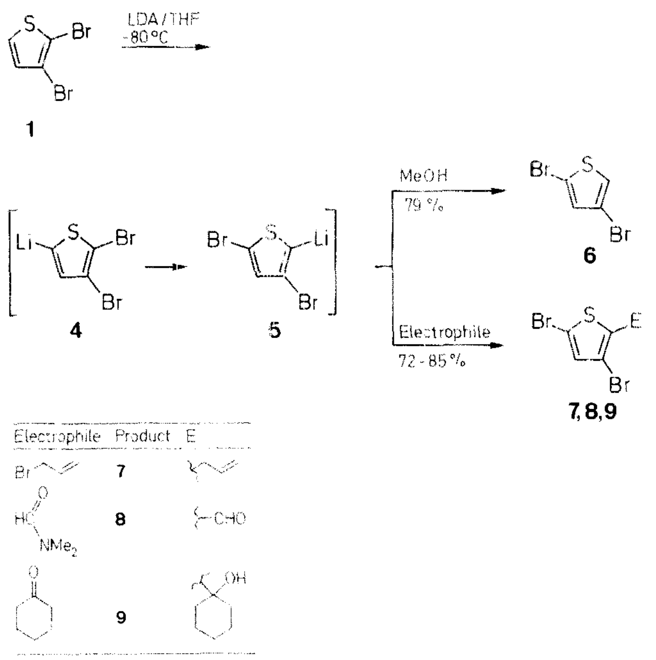
Institute of Organic Chemistry, Technical University, Getreidemarkt 9,
A-1060 Vienna, Austria

The reaction of 2,3-dibromothiophene with 1 equivalent of lithium diisopropylamide at −80 °C, followed by addition of an electrophile (methyl iodide, methanol, allyl bromide, dimethylformamide, cyclohexanone) gives 2-substituted 3,5-dibromothiophenes selectively and in high yields. The substitution pattern of all products was confirmed by unambiguous assignment of all C-atoms via ^{13}C-NMR spectrometry.

For the syntheses of various trisubstituted thiophenes we needed some 5-alkyl-2,3-dibromothiophenes as starting materials. One possible approach, amongst others,[1,2] to such compounds seemed to be the lithiation of 2,3-dibromothiophenes, followed by reaction with various electrophiles. For this purpose, 2,3-dibromothiophene (**1**) was deprotonated with one equivalent of lithium diisopropylamide in tetrahydrofuran at −80 °C and the reaction mixture then quenched with excess methyl iodide. The methylated product thus obtained in 89 % yield gave a ^{1}H-NMR spectrum showing a 2,3,5-substitution pattern, as expected. However, allylic coupling between the methyl group and H-4 as expected for 2,3-dibromo-5-methylthiophene (**2**) on the basis of spectrometric data published for similar thiophene substructures[1,2,3] was not observed. Analysis of the ^{13}C-NMR spectrum of our product as well as comparison of the proton shifts observed with the published data[1,2] of the target compound **2** gave clear evidence that 3,5-dibromo-2-methylthiophene (**3**) had been formed selectively.



These results show that the organolithium intermediate **4** is obviously rearranged to a 2-lithio-3,5-dibromo species **5**. Additional proof for this assumption is provided by the result obtained on quenching the reaction mixture with dry methanol: only 2,4-dibromothiophene (**6**; identified by ^{1}H-NMR spectrometry) was formed and could be isolated in 79% yield (after purification by Kugelrohr distillation).



The formation of compound **6** from **1** may be regarded as a new example of the "Base-Catalyzed Halogen Dance (BCHD) reaction",[2,4,5] which was first observed with aryl halides in the presence of a strong base. In a related investigation on this type of reaction,[6] the lithiation of 2,5-dibromothiophene with LDA under similar conditions was also found to give the rearranged intermediate **5**, in this case, however, via an initial lithiation product different from **4**.

We have utilized our reaction for high yielding syntheses of the 2-substituted 3,5-dibromothiophenes **7–9** by treating the intermediate **5** with electrophiles. According to their physical and ^{1}H-NMR data (Table 1), the compounds thus obtained are identical with those obtained from 2,5-dibromothiophene.[6] In addition, in the ^{13}C-NMR spectra of products **3**, **6–9** the shifts of all C-atoms could be unambiguously assigned to the proposed structures, in part by utilizing thiophene increment tables[7] (Table 2). Further, comparison of the experimental shift values with incremented values for both 2-substituted-3,5-bromo versus 5-substituted-2,3-bromo structures (based on ^{13}C-NMR data of 2,4-dibromothiophene and 2,3-dibromothiophene, respectively) definitely excluded the latter product type.

Mechanistic studies, on the dependence of lithium migration on temperature and on stoichiometry of the base, as well as application of this reaction type to further syntheses in the thiophene field are currently under investigation.

The starting material **1** was prepared according to Lit.[8]. Solvents (THF, Et_2O) were of commercial quality and were dried by distillation from Na. Methyl iodide and DMF were purchased from Merck Chemical Co. and were used without further purification. Allyl bromide and cyclohexanone (both products from Fluka) were distilled before use. The BuLi used was from Aldrich Chemical Co. Diisopropylamine was distilled several times from KOH.

Table 1. Preparation of Compounds **3**, **6–9** via Intermediate **5**

Product	Reaction Conditions Temperature (°C), Time (h)	Yield[a] (%)	bp (°C)/Torr[b] or mp (°C)[c]	Lit. bp (°C)/Torr
3	−80, 0.5 20, 0.5	89	96–98/13	70–75/2[6]
6	−80, 0.5	79	92–95/12	83–85/9[9]
7	−80, 0.5 −25, 0.6	75	50–55/0.05	108–113/3[6]
8	−80, 0.5	72	58–59	117–120/3[6]
9	−80, 0.5	85	163–164	163–167/3[6]

[a] Yield of isolated product based on **1**.
[b] Kugelrohr distillation.
[c] Uncorrected, determined on a Kofler micro hot stage.

Table 2. ^{1}H-NMR and ^{13}C-NMR Data of Compounds **3**, **6–9**

Compound	^{1}H-NMR ($CDCl_3$/TMS)[a] δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[a] δ
3	2.33 (s, 3H, CH_3); 6.85 (s, 1H, H-4)	14.7 (q, CH_3); 108.5[b] (s); 108.6[b] (s); 131.9 (d, C-4); 135.9 (s, C-2)
6	6.97 (d, 1H, J_{AB} = 1.7, H-3); 7.15 (d, 1H, J_{AB} = 1.7, H-5)	109.4 (s, C-4); 112.9 (s, C-2); 124.2 (d, C-5); 131.7 (d, C-3)
7	3.45 (m, 2H, H-1); 5.15 (m, 2H, H-3); 5.89 (m, 1H, H-2); 6.88 (d, 1H, H-$4_{thiophene}$)	33.5 (t, C-1); 107.9 (s, C-$3_{thiophene}$); 109.9 (s, C-$5_{thiophene}$); 117.4 (t, C-3); 131.9 (d, C-$4_{thiophene}$); 133.9 (d, C-2); 139.0 (s, C-$2_{thiophene}$)
8	7.13 (s, 1H, H-4); 9.71 (s, 1H, CHO)	119.3 (s, C-3); 124.6 (s, C-5); 134.3 (d, C-4); 138.6 (s, C-2); 181.4 (s, C=O)
9	1.1–2.34 (m, 10H); 2.33 (s, 1H, OH); 6.88 (s, 1H, H-$4_{thiophene}$)	21.6 (t, C-3, C-5); 24.9 (t, C-4); 36.2 (t, C-2, C-6); 73.9 (s, C-1); 102.6 (s, C-$3_{thiophene}$); 109.9 (s, C-$5_{thiophene}$); 134.0 (d, C-$4_{thiophene}$); 149.5 (s, C-$2_{thiophene}$)

[a] Recorded on a Jeol FX 90-FT-NMR spectrometer at ambient temperature.
[b] Signals which could not be assigned.

2-Substituted 3,5-Dibromothiophenes 3, 6–9, General Procedure:
To a well stirred solution of diisopropylamine (0.9 g, 8.9 mmol) in anhydrous THF (50 mL) under N_2 at −80 °C, a solution of BuLi (2.5 M in hexane; 3.4 mL, 8.5 mmol) in dry Et_2O (10 mL) is added dropwise, stirring is continued for 30 min at −80 °C. Then, a solution of 2,3-dibromothiophene (**1**; 2 g, 8.3 mmol) in anhydrous THF (10 mL) is added rapidly at −80 °C and stirring is continued for 30 min at −80 °C, the intermediate **5** thus formed is trapped by the slow addition of a solution of the electrophile (mol ratio **5**: E = 1:1) in THF (5 mL), and stirring is continued for 30 min at −80 °C. For products **6**, **8**, **9**, the mixture is then poured into aq. 1 N HCl (100 mL). For products **3** and **7**, the solution has to be warmed up before hydrolysis (Table 1). The resultant mixture is extracted with Et_2O (3 × 80 mL) and the organic extract is washed with H_2O (2 × 50 mL) and dried (Na_2SO_4). The solvent is removed at atmospheric pressure and the residue is either distilled under reduced pressure (for **3**, **6**, **7**) or recrystallized from petroleum ether (for **8**, **9**).

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