Monatshefte für Chemie 127, 325–330 (1996)

Monatshefte für Chemie
Chemical Monthly

Synthesis of Trisubstituted Thiophenes *via* a Halogen Dance Reaction at 2-Bromo-5-methylthiophene[§]

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Summary. A new example of a selective halogen dance reaction was observed upon lithiation of 2-bromo-5-methylthiophene with *LDA* under appropriate reaction conditions. A series of 2-substituted 3-bromo-5-methylthiophenes was prepared by reacting the thus selectively generated intermediate 3-bromo-2-lithio-5-methylthiophene with various electrophiles to study scope and limitations of the reaction.

Keywords. Halogen dance; Trisubstituted thiophenes; 2-Bromo-5-methylthiophene; Lithiumdiisopropylamide; Aryl bromide catalyzed dance reaction.

Synthese dreifachsubstituierter Thiophene durch eine Halogenwanderungsreaktion an 2-Brom-5-methylthiophen

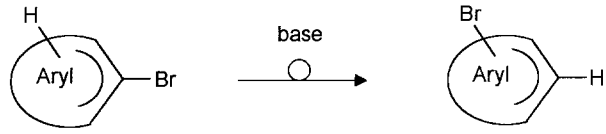
Zusammenfassung. Bei der Lithiierung von 2-Brom-5-methylthiophen mit *LDA* wurde durch Anwendung geeigneter Reaktionsbedingungen eine kontrollierte Halogenwanderungsreaktion erreicht. Durch Umsetzung des auf diese Weise selektiv generierten 3-Brom-2-lithio-5-methylthiophens mit verschiedenen Elektrophilen wurden einige 2-substituierte 3-Brom-5-methylthiophene dargestellt.

Introduction

Treatment of aryl bromides with bases like sodium or potassium amide under appropriate reaction conditions and structural premises of the starting materials leads to a formation of rearranged compounds. Such reaction types have been referred to in literature by different names such as halogen scrambling, halogen migration, halogen isomerization, halogen dance (*HD*), or base-catalyzed halogen dance (*BCHD*) reactions and are depicted in a generalized manner in Scheme 1.

The first observation of a nonselective halogen dance reaction at aromatic systems was made by *Vaitiekunas* who, on treatment of 2-bromothiophene with sodium acetylide, isolated mixtures of polybrominated thiophenes instead of the expected thienylacetylene [1]. *Gronowitz* was the first to present some suggestions

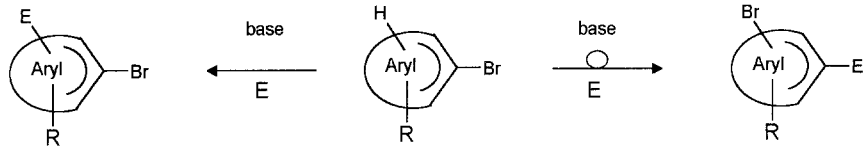
[§] Dedicated to Prof. emeritus *Hans Suschitzky*, University of Salford, UK, on the occasion of his 80th birthday



Scheme 1

about the reactions involved when studying the interaction between dibromothiophenes and *n*-butyllithium [2, 3] (mainly aimed at metal-halogen exchange reactions). A thorough investigation of the mechanism of alkali amide induced halogen migrations at polybromobenzenes was carried out by *Bunnett*; a detailed summary of this work is given in Ref. [4]. The first example of a halogen dance reaction with subsequent introduction of an electrophile was published by *Kano* [5]; this important extension towards broader synthetic utilization was made possible mainly by the use of *LDA* as base. A comprehensive overview of alkaliamide induced migrations covering the classical *BCHD* reactions can be found in Ref. [6].

Our own work in this field started with migrations at 2,3- and 2,5-dibromothiophenes [7, 8], the latter leading to the correction of erroneously published results concerning the prevention of halogen dance at 2,5-dibromothiophene [9]. In continuation of our efforts to approach new trisubstituted heterocycles *via* halogen dance reactions and their controlled prevention at five-membered monoheterocycles and hetero-biaryls prone to migrations (Scheme 2; recent results are also given in Ref. [6]), we now report on the synthesis of 2-substituted 3-bromo-5-methylthiophenes from 2-bromo-5-methylthiophene.



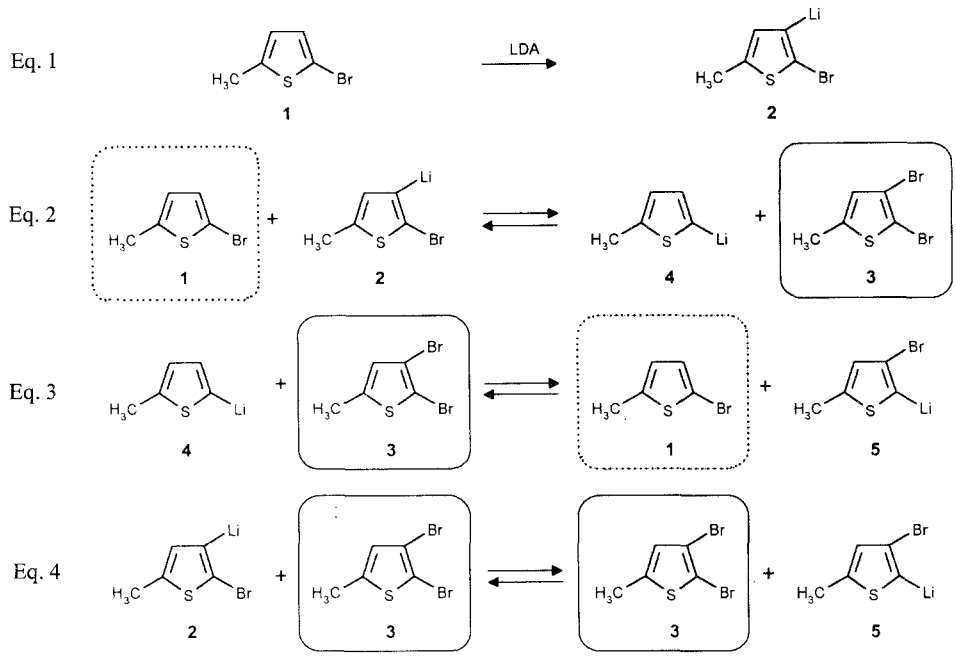
Scheme 2

The extension of the scope of this method at thiophenes is the first example of *LDA* induced bromine migration in the presence of a second nonhalogen substituent.

Results and Discussion

Scheme 3 displays an overview of the mechanism of halogen migration at 2-bromo-5-methylthiophene (**1**) based on findings and suggestions recently published [6].

The sequence starts with lithiation of the starting compound (**1**) at the most acidic site (eqn. 1), followed by a key step common to all halogen migration reactions (eqn. 2): if the initial lithiation product **2** comes into contact with unreacted **1**, a lithium-halogen exchange reaction leading to the dibrominated thiophene **3** takes place. A polybromo compound of this type is a crucial prerequisite in all halogen



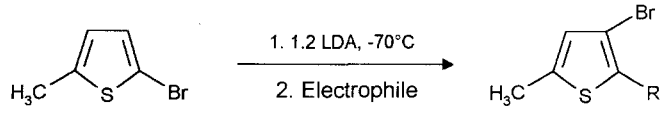
Scheme 3

dance examples known [6, 16], serving as a co-catalyst for the two possible ensuing transmetalation steps (eqns. 3, 4) which complete the migration. In eqn. 3, the transbrominating agent **3** is consumed under formation of scrambling product **5**, but above all also under regeneration of starting compound **1**, which, according to eqn. 2, is responsible for **3** to be formed again. In addition, the initial lithiation product **2** and the dibromide **3** produce the migration target **5** *via* an autocatalytic step as revealed by eqn. 4. Therefore, to the advantage of a total rearrangement at least small amounts of **3** are kept alive during the whole reaction time. Apparently, reactive bromo intermediates (and not bases) play the catalytic role; therefore, we proposed the term **a**ryl **b**romide **c**atalyzed **d**ance (*ABCD*) reaction [6] for such *LDA*-induced halogen migrations and prefer it to the term base-catalyzed halogen dance (*BCHD*) reaction [4], introduced for alkali amide induced rearrangements. As a matter of fact, both processes represented by eqn. 3 and eqn. 4 give rise to the formation of the most stable, 'final' lithium intermediate **5** with the Li atom at the most acidic site. Although the equilibrium positions of eqns. 2, 3, and 4 do have some influence on the overall reaction rate, the main factor for a migration to occur is the simultaneous presence of **1** and **2** and their potential to react. These preconditions are mainly influenced by the sequence of addition and by the ratio of starting compounds: reacting the educt with a slightly less than equimolar amount of base or by adding *LDA* to the starting compound (inverse addition) provides the optimum conditions for a rearrangement, whereas slow addition of **1** to an excess of base (thus enabling immediate and complete metalation and therefore preventing the formation of transbrominating species like **3**) is the method of choice for retaining the halogen dance. Other factors that influence the reaction rate of the initial lithiation (eqn. 1) are the type of solvent (more polar solvents have been found to accelerate the

metalation rate and are therefore helpful in preventing *HD*) and, to some extent, the temperature.

By reacting the final intermediate **5** with different electrophiles it is possible to synthesize a whole series of trisubstituted compounds with the 'rearranged' substitution pattern by a one-pot procedure.

The lithiation of educt **1** occurs solely at position 3; this can be explained by the pronounced acidity of this proton due to the electron withdrawing effect of the neighboring bromine atom. This selectivity is absolutely essential for the synthetic usefulness of the reaction. By contrast, the methyl group increases the electron density *via* its electron donating effect not only at the neighboring position 4, thus lowering the acidity of the attached proton, but also within the entire thiophene system (as compared to *e.g.* dibromothiophenes), therefore also exerting a decreasing effect on the rate of metalation. Lithiation is therefore slow enough that none of the above mentioned additional measures have to be taken to ensure successful rearrangement: fast addition of the starting material to *LDA* provides sufficient contact between **1** and **2** to initiate halogen migration. It has even proved necessary to use 1.2 equivalents of *LDA* and up to two hours reaction time to complete metalation and halogen dance. Subsequently, the target lithium intermediate **5** can be reacted with various electrophiles, yielding 2-substituted 3-bromo-5-methylthiophenes – no traces of retained isomers could be detected by NMR analysis of the crude reaction mixtures (*cf.* Scheme 4).



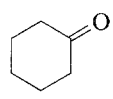
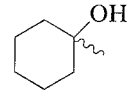
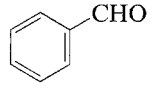
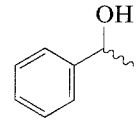
1 **6-12**

Scheme 4

To investigate the scope of this method, various types of electrophiles like carbonyl compounds, non-carbon electrophiles, and alkyl halides have been applied. Table 1 presents an overview of compounds thus obtained. Two more experiments not cited in the table have been undertaken but failed to give pure rearranged products: quenching the reaction with O-deuterated methanol yielded a 85:15 mixture of the desired 2-D product and its protonated analogue **6** due to competing H/D exchange between diisopropylamine, deliberated in the course of the lithiation, and MeOD, induced by excess *LDA* necessarily present in the reaction mixture. A reaction with allyl bromide gave very low yield due to competing deprotonation of the electrophile by the lithium intermediate **5** – which also is a strong base – as a side reaction.

Although 4-bromo-2-methylthiophene (**6**) has already been prepared *via* a classical halogen migration by *Reinecke* [10], the used method (sodium amide as a base) cannot be generalized and extended to directly introduce further substituents. Therefore, the presented new example of an *ABCD* reaction is of synthetic interest as it offers smooth access to trisubstituted thiophenes in a one-pot sequence.

Table 1

Compd.	Electrophile	R	Yield (%)
6	MeOH	$-H$	53
7	CH_3I	$-CH_3$	62
8	$(CH_3S)_2$	$-SCH_3$	82
9	$(CH_3)_3SiCl$	$-Si(CH_3)_3$	53
10			75
11			89
12	$HCON(CH_3)_2$	$-CHO$	84

Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer (*TMS* as internal standard, $CDCl_3$, δ in ppm, J in Hz).

2-Bromo-5-methylthiophene was prepared by reaction of 2-methylthiophene with bromine in dioxane [15]. Diisopropylamine was distilled twice over KOH and once over *Bu*Li. Tetrahydrofuran was pre-dried over potassium hydroxide and distilled from sodium/benzophenone before use. Compounds **6** [10], **7** [11], **8** [12], **9** [13], and **12** [14] have been prepared before by different methods; spectroscopic and physical properties are in agreement with published data.

General procedure

Diisopropylamine (0.77 g, 7.6 mmol) was dissolved in 50 ml of anhydrous *THF* under nitrogen and cooled to $-30\,°C$. *n*-Butyllithium (6.8 mmol) was added and the mixture stirred for 20 min. After cooling to $-70\,°C$, 2-bromo-5-methylthiophene (1 g, 5.6 mmol) was added quickly and stirring was continued at this temperature for 105 min. The electrophile (7 mmol), dissolved in 10 ml of anhydrous *THF*, was added, and stirring was continued for further 30 min. The reaction mixture was then allowed to reach ambient temperature, poured on water, and extracted with ether. The combined organic layers were dried and concentrated and the product purified by bulb-to-bulb distillation.

4-Bromo-2-methylthiophene (**6**; C_5H_5BrS)

Yield: 53%; b.p.: 55–58 °C/15 mm; ^1H NMR: 6.98 (d, 1 H, H-5, $J_{35} = 1.5$ Hz), 6.68 (dq, 1 H, H-3, $J_{3,CH_3} = 1.1$ Hz), 2.47 (d, 3 H, CH_3); ^{13}C NMR: 141.0 (s, C-2), 127.8 (d, C-3), 120.3 (d, C-5), 108.9 (s, C-4), 15.3 (q, CH_3).

3-Bromo-2,5-dimethylthiophene (**7**; C_6H_7BrS)

Yield: 62%; b.p.: 65–68 °C/15 mm ^1H NMR: 6.56 (q, 1 H, H-4, $J_{4,5\text{-}CH_3} = 1.2$ Hz), 2.40 (dq, 3 H, 5-CH_3, $J_{2\text{-}CH_3,\,5\text{-}CH_3} = 0.7$ Hz), 2.33 (q, 3 H, 2-CH_3); ^{13}C NMR: 136.8 (s, C-5), 131.5 (s, C-2), 127.5 (d, C-4), 107.9 (s, C-3), 15.2 (q), 14.4 (q).

3-Bromo-5-methyl-2-(methylthio)-thiophene (**8**; $C_6H_7BrS_2$)

Yield: 82%; b.p.: 81–84 °C/15 mm; ^{1}H NMR: 6.67 (q, 1 H, H-4, J_{4,CH_3} = 1.1 Hz), 2.43 (d, 3 H, CH_3), 2.41 (s, 3 H, SCH_3); ^{13}C NMR: 142.6 (s, C-5), 129.1 (s, C-2), 128.7 (d, C-4), 116.0 (s, C-3), 20.8 (q, SCH_3), 15.7 (q, CH_3).

(3-Bromo-5-methyl-2-thienyl)-trimethylsilane (**9**; $C_8H_{13}BrSSi$)

Yield: 53%; b.p.: 71–74 °C/15 mm; ^{1}H NMR: 6.79 (q, 1 H, H-4, J_{4,CH_3} = 1.1 Hz), 2.48 (d, 3 H, CH_3), 0.39 (s, 9 H, Si-CH_3); ^{13}C NMR: 145.2 (s, C-5), 132.0 (s, C-2), 130.7 (d, C-4), 116.4 (s, C-3), 15.1 (q, CH_3), −0.7 (q, Si-CH_3).

1-(3-Bromo-5-methyl-2-thienyl)-cyclohexanol (**10**; $C_{11}H_{15}BrOS$)

Yield: 75%; m.p.: 84–85 °C; ^{1}H NMR: 6.60 (q, 1 H, H-4′, J_{4',CH_3} = 1.1 Hz), 2.39 (d, 3 H, CH_3), 2.30–1.10 (m, 10 H); ^{13}C NMR: 144.4 (s, C-2′), 136.7 (s, C-5′), 129.9 (d, C-4′), 102.6 (s, C-3′), 73.2 (s, C-1), 36.7 (2t, C-2, C-6), 25.1 (t, C-4), 21.7 (2t, C-3, C-5), 14.9 (q, CH_3).

3-Bromo-5-methyl-α-phenyl-2-thiophenemethanol (**11**; $C_{12}H_{11}BOS$)

Yield: 89%; b.p. 76–79 °C/0.01 mm; ^{1}H NMR: 7.55–7.30 (m, 5 H), 6.60 (q, 1 H, H-4, J_{4,CH_3} = 1.2 Hz), 6.12 (bs, 1 H, CHOH), 2.40 (d, 3 H, CH_3); ^{13}C NMR: 142.1 (s, C-2), 140.1 (s, C-5), 139.8 (s, C-1′), 128.4 (2d, C-3′, C-5′), 128.0 (d, C-4), 127.6 (d, C-4′), 126.1 (2d, C-2′, C-6′), 107.4 (s, C-3), 71.2 (d, C-α), 15.4 (q, CH_3).

3-Bromo-5-methyl-2-thiophenecarbaldehyde (**12**; C_6H_5BrOS)

Yield: 84%; m.p.: 45–47 °C; ^{1}H NMR: 9.86 (s, 1 H, CHO), 6.84 (q, 1 H, H-4, J_{4,CH_3} = 1.0 Hz), 2.54 (d, 3 H, CH_3); ^{13}C NMR: 182.4 (d, CHO), 151.0 (s, C-5), 135.8 (s, C-2), 130.4 (d, C-4), 120.2 (s, C-3), 16.2 (q, CH_3).

Acknowledgements

J. F. is grateful to the *Hochschuljubiläumsstiftung der Stadt Wien* for financial support.

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Received September 18, 1995. Accepted October 4, 1995