

First example of base-promoted tandem alkylation–bromination of 2-bromothiophene via halogen dance process: a remarkable temperature effect

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Abstract—Metalation–alkylation of 2-bromothiophene **1** when conducted at low temperature led to the 5-alkylated 2-bromo products **2**. While, at room temperature, the same sequential reactions afforded the original dibromo-alkylated thiophenes **3** following an unprecedented halogen transfer-based halogen dance process in highly regiocontrolled and ordered way.
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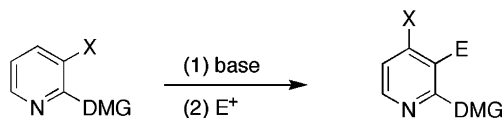
The halogen dance reaction (HDR) is a process that induces halogen shift on aromatic systems (Scheme 1). This interesting reaction, was extensively studied for pyridines and benzannulated series and was successfully applied in natural product synthesis.¹ However, only few examples were reported in the case of other heterocycles with a few notable exceptions.¹ Moreover, polyfunctionalized thiophenes are of interest in research fields such as natural product synthesis,² drug design,³ and material science.⁴ Therefore, new synthetic methods, which allow access to suitable precursors are of great importance.

In connection with our ongoing project aimed at using 2-bromothiophene **1** as a starting point to prepare various probe-like C-nucleosides following their incorpor-

ation into oligonucleotides,⁵ we have envisioned the possibility of preparing new functionalized thiophene C-nucleosides following post-synthetic transformations of their brominated derivatives.

Herein we report on an unprecedented temperature-dependent regioselective process in the metalation–alkylation of **1** with diverse electrophiles. These metalation–alkylation reactions, when conducted at room temperature, led indeed to the original dibromo-alkylated thiophenes **3** (Scheme 2), while, when conducted at low temperature, they gave the 5-alkylated 2-bromo products **2**. The former derivatives resulted from an unexpected regiocontrolled halogen transfer-based halogen dance process.

Metalation of **1** using LDA in THF at $-78\text{ }^{\circ}\text{C}$ followed by addition of the *p*-anisaldehyde (used as a testing substrate) afforded product **2a** in 85% yield (Table 1, entry 1). Unexpectedly, the issue of this aldol-like condensation was found to be highly temperature dependent. Indeed, when we performed these metalation–alkylation

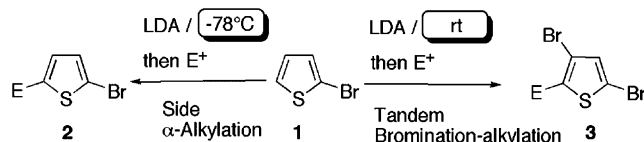


X = halogen
DMG = *ortho*-Directed metalation group

Scheme 1. Typical example of the halogen dance reaction.

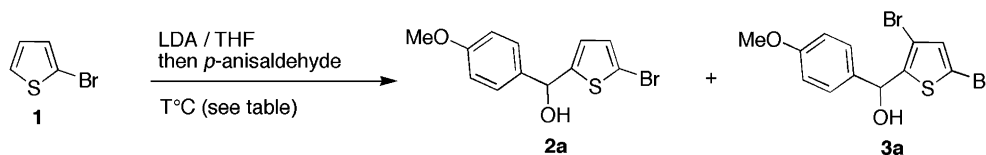
Keywords: Regiocontrolled halogen transfer cascade; Halogen dance; Tandem process; X-philic reaction.

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Scheme 2. Temperature-based regiocontrolled reactions with **1**.

Table 1.



Entry ^a	<i>T</i> (°C)	Ratio 2a / 3a ^b (%)	Yield ^c (%)
1	−78	100/0	85
2	−20	45/55	88
3	0	0/100	90
4	Rt	0/100	92
5	−78 °C then rt (0.5–2 h)	0/100	78
6	Rt then −78 °C (0.5–2 h)	0/100	76

^a *p*-Anisaldehyde (2 mmol), **1** (2.2 equiv), LDA (2.2 equiv).

^b Ratio based on ¹H NMR and HPLC analysis.

^c Combined yields.

steps at 0 °C or at room temperature, the 3,5-dibromo adduct **3a** was isolated as a sole product of the reaction (entries 3 and 4). This derivative was obtained in high yield when the reaction was conducted with 2 equiv of **1**. At −20 °C, both compounds **2a** and **3a** were formed in nearly 1:1 ratio (entry 2). The structure of **3a** was unambiguously confirmed by MS, NMR spectroscopy,⁶ and by comparison with the data of structurally related compounds.⁷

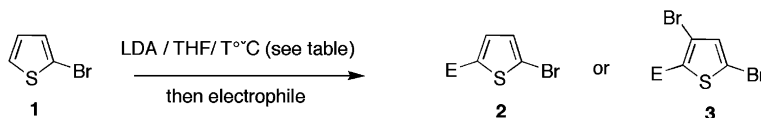
To get further information on the temperature effect, **1** was subjected to metalation at low temperature (LDA/−78 °C/30 min), then stirred at rt for 0.5–2 h before quenching with *p*-anisaldehyde (entry 5). ¹H NMR analysis clearly showed the formation of **3a** at the expense of **2a**, as a result of the evolution of the kinetic 2-bromo-5-lithiothiophene into a thermodynamically more stable intermediate most probably consisting into 2,4-dibromo-5-lithiothiophene (vide infra). Moreover, when

1 was subjected to metalation at rt (LDA/rt/30 min), cooled at −78 °C for 0.5–2 h, and then quenched with *p*-anisaldehyde (entry 6), only **3a** was formed.

The potential and general applicability of this novel tandem, temperature-regiocontrolled reaction is illustrated by the examples collected in Table 2. Indeed, aldehydes, ketones, and other electrophiles furnished high yields of derivatives **2** or **3** when the reaction was performed at −78 °C or at rt, respectively. Moreover, at rt, the tandem process was very rapid and did not exceed a few minutes. In addition, the ¹H and ¹³C NMR spectra of compound **3e**⁸ are in accordance with those previously described,^{7a} and hence argue for the proposed structures.

Concerning the mechanism of formation of the dibromo-derivatives **3a–g**, and considering the fact that **1** is the unique source of bromine, two different reaction pathways depicted in Scheme 3 appear to be probable.

Table 2.



Entry ^a	E ⁺	<i>T</i> (°C)	2 or 3	Yield ^b (%)
1	<i>p</i> -OMe-PhCHO	−78	2a	95
2	—	Rt	3a	92
3	PhCH ₂ CH ₂ CHO	−78	2b	91
4	—	0 or rt	3b	90
5	<i>i</i> -Pr-CH ₂ CHO	−78	2c	88
6	—	Rt	3c	90
7	Cyclopentanone	−78	2d	93
8	—	0 or rt	3d	91
9	Cyclohexanone	−78	2e	90
10	—	0 or rt	3e	87
11	Bu ₃ SnCl	Rt	3f	87
12	ICH ₂ CH ₂ I (I ⁺)	Rt	3g	90

^a Conditions: **1** (2.2 equiv), LDA (2.2 equiv), electrophile (1 equiv).

^b Yields based on pure isolated products.

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