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

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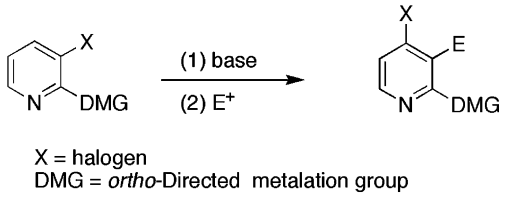
Abstract—Metalation–alkylation of 2-bromothiophene **1** when conducted at low temperature led to the 5-alkylated 2-bromo products **2**. While, at room temperature, the same sequential reactions afforded the original dibromo-alkylated thiophenes **3** following an unprecedented halogen transfer-based halogen dance process in highly regiocontrolled and ordered way.

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.

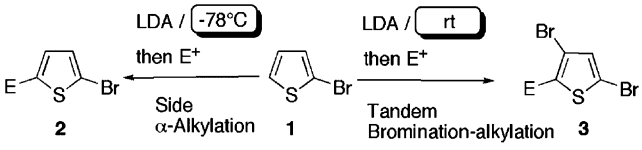
In connection with our ongoing project aimed at using 2-bromothiophene **1** as a starting point to prepare various probe-like *C*-nucleosides following their incorporation into oligonucleotides,[5] we have envisioned the possibility of preparing new functionalized thiophene *C*-nucleosides following post-synthetic transformations of their brominated derivatives.



Scheme 1. Typical example of the halogen dance reaction.

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 °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



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

Keywords: Regiocontrolled halogen transfer cascade; Halogen dance; Tandem process; X-philic reaction.
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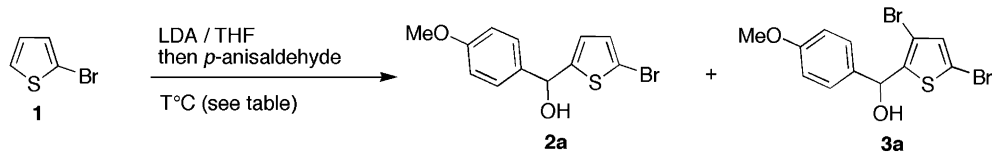
Table 1.



Entry[a]	*T* (°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 ^{1}H NMR and HPLC analysis.
[c] Combined yields.

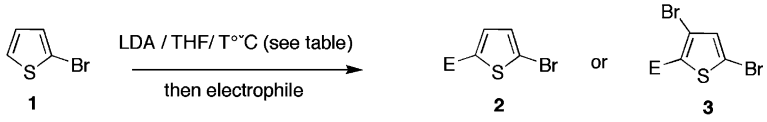
steps at 0 °C or at room temperature, the 3,5-dibromo adduct **3a** was isolated as a sole product of the reaction (entries 3 and 4). This derivative was obtained in high yield when the reaction was conducted with 2 equiv of **1**. At −20 °C, both compounds **2a** and **3a** were formed in nearly 1:1 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). ^{1}H 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 ^{1}H and ^{13}C NMR spectra of compound **3e**[8] are in accordance with those previously described,[7a] and hence argue for the proposed structures.

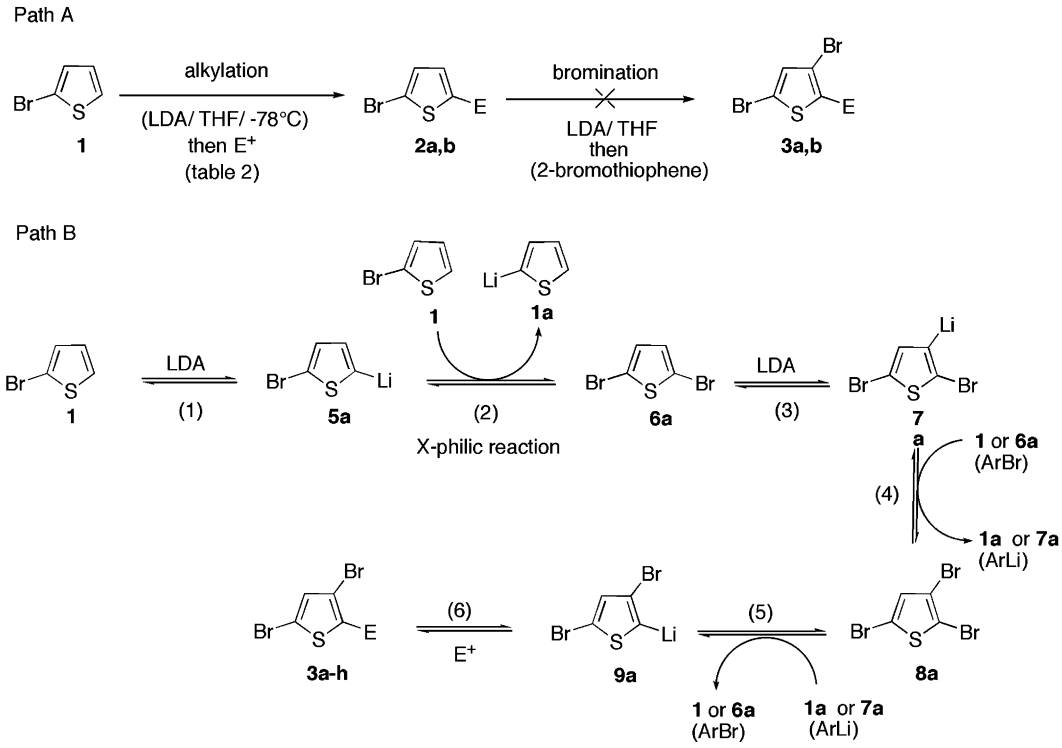
Concerning the mechanism of formation of the dibromo-derivatives **3a**–**g**, and considering the fact that **1** is the unique source of bromine, two different reaction pathways depicted in Scheme 3 appear to be probable.

Table 2.



Entry[a]	E^+	*T* (°C)	**2** or **3**	Yield[b] (%)
1	*p*-OMe–PhCHO	−78	**2a**	95
2	—	Rt	**3a**	92
3	$PhCH_2CH_2CHO$	−78	**2b**	91
4	—	0 or rt	**3b**	90
5	*i*-Pr–CH_2CHO	−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_3SnCl	Rt	**3f**	87
12	ICH_2CH_2I (I^+)	Rt	**3g**	90

[a] Conditions: **1** (2.2 equiv), LDA (2.2 equiv), electrophile (1 equiv).
[b] Yields based on pure isolated products.



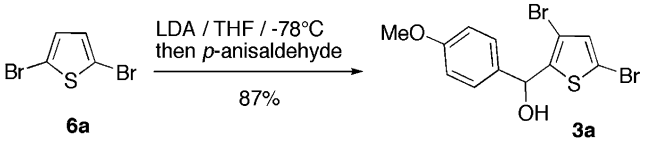
Scheme 3. Thermodynamic controlled halogen dance reaction via halogen transfer cascade, a possible reaction sequence.

Formation of **3** could have resulted from a subsequent bromination process of **2** (path A). In this sequence, **1** is supposed to be the brominating agent. Path B consists of a halogen transfer cascade starting from the 2-bromo-5-lithiothiophene **5a** leading to the key dibromo-lithiated specie **9a** precursor of products **3a–g**.

Pathway A could be ruled out by the almost quantitative recovery of **2a** or **2b** when these derivatives were submitted to LDA at rt and then quenched with **1**. Moreover, the use of an excess of LDA at rt or at −78 °C did not change the issue of these reactions.

Pathway B could take place according to a thermodynamic controlled process. Thus, deprotonation of **1** by LDA could result in the lithiated species **5a** (Eq. 1), which underwent halogenation with an other molecule of **1** according to an X-philic like process (Eq. 2) to give the dibromothiophenes **6a**.[9] Similarly, **6a** would then provide (Eqs. 3 and 4: metalation–halogen transfer) the tribromothiophene intermediate **8a**, which, after a third regioselective Li–Br exchange (Eq. 5), is converted into the more stable lithiated dibromothiophene **9a**,[10] precursor of the isolated products **3** (Eq. 6). It is worth noting that the overall process involves two metalations, three halogen transfers, and finally the alkylation step.

To provide further support for path B sequences, additional experiments were undertaken. First, as illustrated in Scheme 4 and in line with literature,[7] we showed that compound **3a** was also obtained from the dibromothiophene **6a** (which was supposed to be formed as intermediate) when submitted to LDA at −78 °C and then trapped with *p*-anisaldehyde, respectively.



Scheme 4. Synthesis of **3a** from intermediate **6a**.

Second, the presence of thiophene (NMR and GC) after hydrolysis of the reaction medium confirms that **1** is a bromine donor in the reaction sequence. However, the fate of the 2-lithiated thiophene, and more particularly the non-detection of alkylated thiophenes therefrom, remains unresolved.[11]

Third, the proposed mechanism for the conversion of **1** into **3**, which involves 2 equiv of **1** and LDA seems also to be supported by our experimental results since the best yields were obtained with a very close stoichiometry of LDA and **1** (⩾2 equiv) with respect to the electrophile (1 equiv). Finally, the conversion (**1** to **3**) likely occurs through the thermodynamic controlled B sequence, starting from **5a**. Indeed, as attested by experiences 5 and 6 in Table 1: (i) **5a** (generated at −78 °C) evolves to **9a** when the reaction temperature was increased from −78 °C to rt (entry 5) and, (ii) **9a** (generated at rt) remains intact when the reaction temperature was decreased from rt to −78 °C indicating that the lithiated dibromothiophene **9a** is particularly stable (entry 6).

In conclusion, we have discovered a new halogenation/alkylation tandem reaction, which allows access from 2-bromothiophene to functionalized dibromothiophenes. The process most probably involves an original

halogen transfer cascade in highly regiocontrolled and ordered fashion. Interestingly, the methodology is highly convenient since the reactions are achieved at rt, proceed in high yields and within short times. Moreover, only thiophene and diisopropylamine volatile materials are generated with the target compound. Further studies on the scope of this reaction, its limitations, and applications are currently under progress.

Acknowledgements

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References and notes

1. For reviews on the halogen dance reaction, see: (a) Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139–147; (b) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187–304; (c) Fröhlich, J. In *Progress in Heterocyclic Chemistry*; Suschitzky, H, Scriven, E. F. V., Eds.; Oxford: New York, 1994; 6, pp 1–35; (d) Fröhlich, J. *Bull. Soc. Chim. Belg.* **1996**, *105*, 615–634; For recent examples, see: (e) Arzel, E.; Rocca, P.; Grellier, P.; Labaeïd, M.; Frappier, F.; Guéritte, F.; Gaspard, C.; Marsais, F.; Godard, A.; Quéguiner, G. *J. Med. Chem.* **2001**, *44*, 949–960; (f) Mongin, F.; Marzi, E.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 2771–2777; (g) Lazaar, J.; Rebstock, A.-S.; Mongin, F.; Godard, A.; Trécourt, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2002**, *58*, 6723–6728; (h) Toudic, F.; Ple, N.; Truck, A.; Quéguiner, G. *Tetrahedron* **2002**, *58*, 283–293; (i) Eskildsen, J.; Østergaard, N.; Vedso, P.; Begtrup, M. *Tetrahedron* **2002**, *58*, 7635–7644; (j) Sammakia, T.; Stangeland, E. L.; Whitcomb, M. C. *Org. Lett.* **2002**, *4*, 2385–2388; (k) Stangeland, E. L.; Sammakia, T. *J. Org. Chem.* **2004**, *69*, 2381–2385.
2. (a) Bohlmmann, F.; Zdero, C. In *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives*; Gronowitz, S., Ed.; John Wiley & Sons: New York, 1985; 44, pp 261–323; (b) Pelkey, E. T. *Prog. Heterocycl. Chem.* **1998**, *10*, 87–108.
3. Press, J. B. In *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives*; Gronowitz, S., Ed.; John Wiley & Sons: New York, 1991; 44, pp 397–502.
4. (a) *Handbook of Oligo and Polythiophenes*; Fichou, D., Ed.; Wiley-VCH: New York, 1999; (b) Roncali, J. *Chem. Rev.* **1992**, *92*, 711–738; (c) Katz, H. E.; Bao, Z.; Gilat, S. L. *Acc. Chem. Res.* **2001**, 359–369; (d) Facchetti, A.; Yoon, M.-H.; Stern, C. L.; Katz, H. E.; Marks, T. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3900–3903.
5. (a) Guianvarc'h, D.; Fourrey, J.-L.; Maurisse, R.; Sun, J. S.; Benhida, R. *Org. Lett.* **2003**, *4*, 4209–4212; (b) Guianvarc'h, D.; Fourrey, J.-L.; Maurisse, R.; Sun, J. S.; Benhida, R. *Bioorg. Med. Chem.* **2003**, *11*, 2751–2759.
6. *Adduct* **2a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.31 (d, 2H, J = 8.71 Hz, Ph), 6.91 (m, 3H, *CH*–CBr and Ph), 6.58 (dd, 1H, J = 3.79, 0.88 Hz, *CH*–CH–CBr), 5.83 (s, 1H, *CH*–OH), 3.83 (s, 3H, OMe), 3.42 (s, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.40 (*C*–OCH_3), 150.16 (C–S), 134.77 (*C*–CHOH), 129.42 (*CH*–CBr), 127.70 (Ph), 124.86 (*CH*–CH–CBr), 113.97 (Ph), 112.03 (CBr), 72.04 (CHOH), 55.31 (CH_3). MS (ESI+) *m*/*z* (rel intensity) 320.7–322.7 (91, 100, MNa^+).
Adduct **3a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18 (d, 2H, J = 8.72 Hz, Ph), 6.72 (m, 3H, CH and Ph), 5.78 (s, 1H, *CH*–OH), 3.64 (s, 3H, OMe), 3.50 (s, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.37 (*C*–OCH_3), 144.86 (C–S), 133.59 (*C*–CHOH), 131.96 (CH), 127.69 (Ph), 113.96 (Ph), 112.25 (CBr–S), 106.66 (*CBr*–C–S), 71.30 (CH–OH), 55.27 (CH_3). MS (ESI+) *m*/*z* (rel intensity) 398.5–400.5–402.5 (51, 100, 46, MNa^+).
7. (a) Sauter, F.; Fröhlich, H.; Kalt, W. *Synthesis* **1989**, 771–773; (b) Fröhlich, H.; Kalt, W. *J. Org. Chem.* **1990**, *55*, 2993–2995; (c) Lukevics, E.; Arseyan, P.; Belyakov, S.; Popelis, J.; Pudova, O. *Tetrahedron Lett.* **2001**, *42*, 2039–2041.
8. *Adduct* **3e**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15–2.30 (m, 10H, CH_2), 2.44 (br s, 1H, OH), 6.87 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.75 (CH_2), 25.04 (C–OH), 36.30 (CH_2), 74.16 (CH_2), 102.78 (*CBr*–C=S), 110.12 (BrC=S), 134.29 (*CH*–CBr), 149.75 (C=S). Reported **3e** (Ref. 9) ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15–2.34 (m, 10H, CH_2), 2.33 (br s, 1H, OH), 6.88 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.6 (CH_2), 24.9 (C–OH), 36.2 (CH_2), 73.9 (CH_2), 102.6 (*CBr*–C=S), 109.9 (BrC=S), 134.0 (*CH*–CBr), 149.5 (C=S).
9. Zefirov, N. S.; Makhon'Kov, D. *Chem. Rev.* **1982**, *82*, 615–624.
10. The dibromo-lithiated thiophene **9a** is stabilized by both sulfur and bromine atoms. For the use of a bromine as *ortho*-directing group, see: (a) Lulinski, S.; Serwatowski, J. *J. Org. Chem.* **2003**, *68*, 5384–5387; (b) Lulinski, S.; Serwatowski, J. *J. Org. Chem.* **2003**, *68*, 9384–9388; (c) Gohier, F.; Mortier, J. *J. Org. Chem.* **2003**, *68*, 2030–2033; For reviews on directed *ortho*-metalation and complex-induced proximity effect, see: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933; (b) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206–2225.
11. One plausible explanation is that **1a** is probably protonated by the diisopropylamine generated in the medium.