# Regiocontrolled halogen dance of 2,5-dibromopyrroles using equilibrium between dibromopyrrolyllithiums

Okumi, Tatsuki

Mori, Atsunori

Okano, Kentaro

(Citation)
Chemical Communications,59(8):1046-1049

(Issue Date)
2023-01-25

(Resource Type)
journal article

(Version)
Accepted Manuscript

COMMUNICATION

# Regiocontrolled Halogen Dance of 2,5-Dibromopyrroles Using Equilibrium between Dibromopyrrolyllithiums

Tatsuki Okumi,[a] Atsunori Mori,[a,b] and Kentaro Okano*[a]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

**A regiocontrolled halogen dance reaction of 2,5-dibromopyrroles is described. An *N*,*N*-dimethylsulfamoyl group on the pyrrole nitrogen was especially effective for facilitating interconversion of the resulting 2,3- and 2,4-dibromopyrrolyllithiums, rendering the smooth halogen dance reaction. This method was applicable to the formal synthesis of atorvastatin.**

A variety of pyrroles with multiple substituents are found in pharmaceuticals, agrochemicals, natural products, and functional materials (Figure 1).[1] In addition to the classical Paal–Knorr synthesis, cyclization, cycloaddition, and multicomponent reactions have been developed to construct the pyrrole skeleton.[2,3] Direct functionalization of pyrrole has also been investigated;[4,5] however, there is room for improvement in the synthesis of multiply substituted pyrroles.

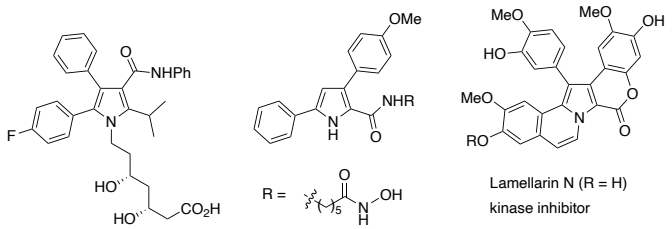
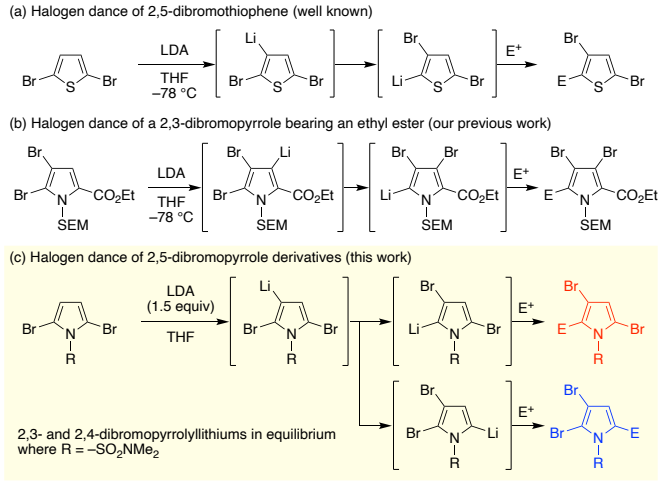



**Figure 1.** Representative biologically active pyrroles.

A halogen dance reaction, which is a formal exchange of a halogen atom and a lithium atom involved in halogenated aryllithium species, has the potential for constructing a densely functionalized aromatic ring.[6] Thiophenes are good substrate for the halogen dance reaction, and numerous examples have been reported.[7] Especially, 2,5-dibromothiophene is converted to the functionalized 2,4-dibromothiophene whose α- and β-bromo groups have different reactivities for further transformations (Scheme 1a).[8] We have recently reported the first example of the halogen dance reaction of an *N*-SEM-2,3-dibromopyrrole (SEM: 2-(trimethylsilyl)ethoxymethyl) bearing an ester group, which was applied to the total synthesis of lamellarins (Scheme 1b).[9] However, 2,3-dibromopyrroles are not available compared to 2,5-dibromopyrroles. Herein we report the effect of substituents on the pyrrole nitrogen on the halogen dance reaction of 2,5-dibromopyrroles, providing the corresponding 2,4-dibromopyrroles (Scheme 1c). In addition, the use of a 2,5-dibromopyrrole with an *N*,*N*-dimethylsulfamoyl group allowed the regiocontrolled synthesis of both 2,3- and 2,4-dibromopyrroles where the corresponding pyrrolyllithiums existed in equilibrium. This method provided direct access to isomeric dibromopyrroles in a regiocontrolled manner, which was utilized for the formal synthesis of atorvastatin.

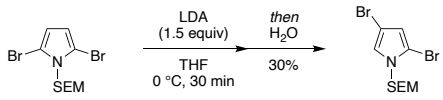



Scheme 1. Halogen dance of heteroaromatic compounds.

[a] *Department of Chemical Science and Engineering, Kobe University, 1-1 Rokkodai, Nada, Kobe 657-8501, Japan. E-mail: okano@harbor.kobe-u.ac.jp*
[b] *Research Center for Membrane and Film Technology, Kobe University, 1-1 Rokkodai, Nada, Kobe 657-8501, Japan.*

† Electronic Supplementary Information (ESI) available: experimental procedure, NMR spectra, and crystallographic data in CIF. See DOI: 10.1039/x0xx00000x

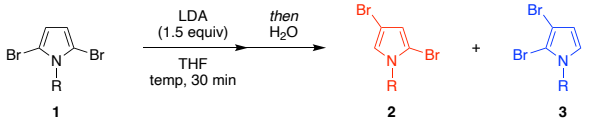
We began our investigation by conducting the halogen dance of *N*-SEM-2,5-dibromopyrrole (**1a**) at −78 °C which resulted in full recovery of **1a**, although the halogen dance of 2,5-dibromothiophene is reported to give 2,4-dibromothiophene in nearly quantitative yield under the same reaction conditions.[8] When the reaction was performed at 0 °C, 2,5-dibromopyrrole **1a** was completely consumed to afford 2,4-dibromopyrrole **2a** in 30% isolated yield with generation of several unidentified byproducts (Scheme 2).




Scheme 2. Halogen dance of *N*-SEM-2,5-dibromopyrrole.

We then aimed to improve the yield of 2,4-dibromopyrrole by investigating various *N*-substituted pyrroles (Table 1). In the case of dibromopyrrole bearing an ethyl group **1b** or a phenyl group **1c**, the corresponding products **2b** and **2c** were obtained at 0 °C in 36% and 60% yields, respectively (entries 1 and 2). These 2,5-dibromopyrroles were successfully converted into the corresponding 2,4-dibromopyrroles, but the yields were not satisfactory. In addition, the ethyl and phenyl groups on the pyrrole nitrogen were difficult to be transformed. The electron-withdrawing groups were next examined. Although *N*-tosylated dibromopyrrole **1d** decomposed at 0 °C, the reaction was performed at −78 °C to provide 2,4-dibromopyrrole **2d** in 59% yield associated with 2,3-dibromopyrrole **3d** (entries 3 and 4). These results indicate that the tosyl group facilitated deprotonation at −78 °C. Worthy of note is that 2,5-dibromopyrrole **1d** was converted into two isomeric dibromopyrroles **2d** and **3d** in contrast to the well reported halogen dance reaction of 2,5-dibromothiophene yielding the 2,4-dibromothiophene derivative exclusively.[10] *N*-Boc-dibromopyrrole **1e** underwent the halogen dance at −78 °C to give 2,4-dibromopyrrole **2e** in 48% isolated yield (entry 5). Bromopyrroles **1f** and **1g** bearing a benzenesulfonyl group and a 2,4,6-triisopropylbenzenesulfonyl (Trisyl) group were converted into **2f** and **2g** in 60% and 58% yields, respectively, while unidentified byproducts were obtained from pyrrole **1h** having a 2-nitrobenzenesulfonyl (Ns) group (entries 6–8). After extensive optimization, dibromopyrrole **1i** having an *N*,*N*-dimethylsulfamoyl group,[11] which has been rarely used as a protective group for pyrroles, underwent halogen dance to exclusively afford 2,4-dibromopyrrole **2i** (CCDC 2184814†) in 76% isolated yield, with the ratio 87:6 of **2i** and **3i** (entry 9).

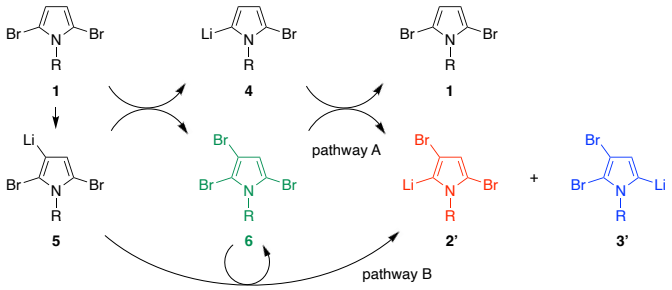
Table 1. Halogen dance of *N*-substituted 2,5-dibromopyrroles[a]




| entry | | R | temp (°C) | **2** (%)[b] | **3** (%)[b] |
|---|---|---|---|---|---|
| 1 | **1b** | Et | 0 | 36 (29[d]) | –[c] |
| 2 | **1c** | Ph | 0 | 60 (46[d]) | –[c] |
| 3 | **1d** | Ts | 0 | –[e] | –[c] |
| 4 | **1d** | Ts | −78 | 59 (54[d]) | 9 |
| 5 | **1e** | Boc | −78 | 57 (48[d]) | 7 |
| 6 | **1f** | $SO_2Ph$ | −78 | 60 (–[f]) | 11 |
| 7 | **1g** | Trisyl | −78 | 58 (55[d]) | 29 |
| 8 | **1h** | Ns | −78 | –[c] | –[c] |
| 9 | **1i** | $SO_2NMe_2$ | −78 | 87 (76[d]) | 6 |

[a]Reaction conditions: dibromopyrrole **1** (1.0 equiv, 0.30 mmol), LDA (1.5 equiv, 0.45 mmol), THF, 30 min, then $H_2O$. [b]The yield was determined from the $^1$H NMR spectrum of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. [c]Not detected in the crude $^1$H NMR spectrum. [d]Isolated yield. [e]Complex mixture. [f]Decomposed during purification.

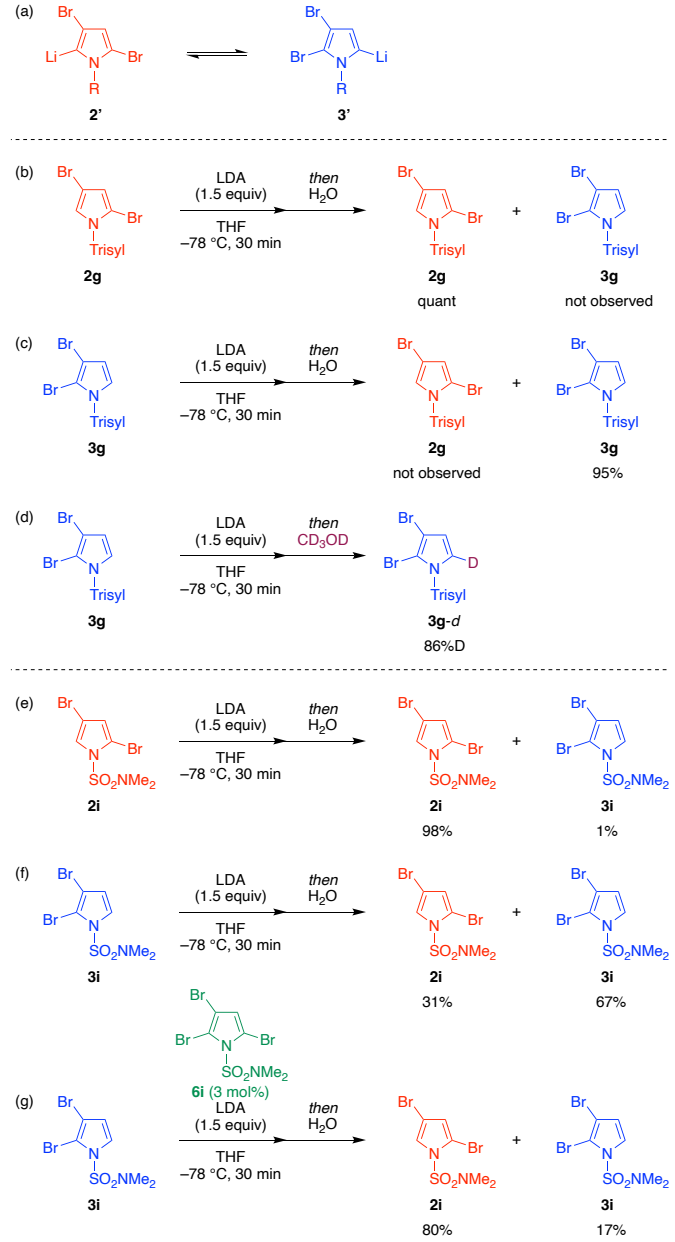
The results obtained by using the *N*,*N*-dimethylsulfamoyl group prompted us to investigate the mechanistic features of the halogen dance. We noticed a significant difference in the ratio between 2,4-dibromopyrrole **2** and 2,3-dibromopyrrole **3** (entries 7 and 9 in Table 1), although the total yield of **2** and **3** in entry 7 were comparable to that in entry 9. On the basis of literature precedent[6,12] and the experimental results that 2,3-dibromopyrroles **3** were observed in both cases, we assumed two possible reaction pathways to provide pyrrolyllithiums **2'** and **3'** which were generated from pyrrolyllithium **4** (pathway A) or **5** (pathway B), as shown in Scheme 3. In pathway A, 2,5-dibromopyrrole **1** undergoes deprotolithiation by LDA to provide 3-lithiopyrrole **5**, which reacts with another molecule of **1** to generate tribromopyrrole **6** and pyrrolyllithium **4** through halogen–lithium exchange. Pyrrolyllithium **4** thus formed is converted into pyrrolyllithium **2'** or **3'** through halogen–lithium exchange with tribromopyrrole **6**. In pathway B, pyrrolyllithium **2'** or **3'** is formed by halogen–lithium exchange of the primarily formed pyrrolyllithium **5** with tribromopyrrole **6**.




Scheme 3. Two possible halogen dance pathways.

The observed selectivity may be governed by regioselectivity in the halogen–lithium exchange of pyrrolyllithium **4** or **5** with tribromopyrrole **6**; however, each regioselectivity in the halogen–lithium exchange is difficult to estimate experimentally. We then investigated another factor influencing the selectivity, namely, isomerization between pyrrolyllithiums **2'** and **3'** (Scheme 4a). In the case of *N*-trisylpyrrole **1g**, dibromopyrroles **2g** and **3g** were not isomerized to each other under the reaction conditions,

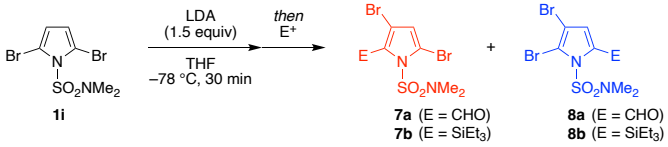
resulting in recovery of each starting material (Schemes 4b and 4c). Quenching the reaction with $CD_3OD$ led to the formation of deuterated **3g**, which supported that **3g** was deprotonated to generate pyrrolyllithium **3g'** (Scheme 4d). In contrast, *N*-sulfamoyl-2,3-dibromopyrrole **3i** was indeed converted to 2,4-dibromopyrrole **2i** in 31% yield, while almost all of **2i** was not isomerized to **3i** (Schemes 4e and 4f). Furthermore, 3 mol% tribromopyrrole **6i** facilitated the isomerization (Scheme 4g).[13] These results indicated that 2,4-dibromopyrrolyllithium **2'** is thermodynamically more stable than 2,3-dibromopyrrolyllithium **3'** and that the dimethylsulfamoyl group promotes isomerization of **3i'** to **2i'**, which is consistent with the observed results. The nitrogen atom of the sulfamoyl group could coordinate to the lithium, which enhanced the reactivity of the pyrrolyllithiums to facilitate the isomerization.




Scheme 4. Isomerization of 2,4- and 2,3-dibromopyrrolyllithiums facilitated by the dimethylsulfamoyl group.

This equilibrium was applicable to the regiocontrolled synthesis of both 2,4- and 2,3-dibromopyrroles from 2,5-dibromopyrrole **1i** through the halogen dance reaction and subsequent electrophilic trapping, simply by choosing an appropriate set of electrophiles (Table 2). After the halogen dance reaction was performed under the optimal conditions, the reaction mixture was treated with formic acid ethyl ester to afford dibromopyrrole **7a** in 66% yield as a major product (entry 1). In contrast, the use of DMF instead of formic acid ethyl ester provided the other isomer, dibromopyrrole **8a**, in 49% yield (entry 2).[14] These results strongly supported the existence of the equilibrium between dibromopyrrolyllithiums **2i'** and **3i'**. On the basis of the results in Table 1, it is reasonable that 2,4-dibromopyrrolyllithiums **2i'**, which was the major isomer in the reaction mixture, was converted into 2,4-dibromopyrrole **7a**. The minor 2,3-dibromopyrrolyllithium **3i'** must be thermodynamically unstable based on Scheme 4 and would be more reactive owing to the sterically less congested reaction site. In the case of less electrophilic DMF used as the formylating reagent, the minor but more reactive 2,3-dibromopyrrolyllithium **3i'** would be preferentially transformed into dibromopyrrole **8a**, with the interconversion of dibromopyrrolyllithium **2i'** to **3i'**. Similarly, the selectivity of the reaction with highly reactive TESOTf was governed by the ratio of the pyrrolyllithiums in equilibrium to provide 2,4-dibromopyrrole **7b** in 91% yield, whereas less electrophilic TESCl reacted only with more reactive pyrrolyllithium **3i'** to give 2,3-dibromopyrrole **8b** in 96% yield (entries 3 and 4).[15] Compared with the work by Iwao[5b] in which the equilibrium occurred through deprotonation, this equilibrium took place faster through the halogen–lithium exchange with catalytic amount of tribromopyrrole **6**,[16] achieving the extremely high selectivity of **7**/**8**.

Table 2. Regiocontrolled synthesis of 2,4- and 2,3-dibromopyrroles[a]

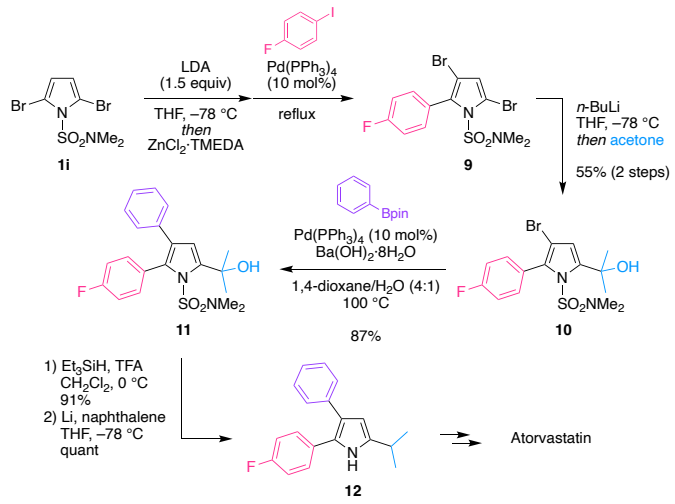



| entry | $E^+$ | E | **7** (%)[b] | **8** (%)[b] |
|---|---|---|---|---|
| 1 | $HCO_2Et$ | CHO | 66 (64[c]) | 5 |
| 2 | DMF | CHO | –[d] | 49 (39[c]) |
| 3 | TESOTf | $SiEt_3$ | 91 (89[c]) | 3 |
| 4 | TESCl | $SiEt_3$ | 2 | 96 (76[c]) |

[a]Reaction conditions: 2,5-dibromopyrrole **1i** (1.0 equiv, 0.30 mmol), LDA (1.5 equiv, 0.45 mmol), THF, 30 min, then $E^+$ (1.8 equiv, 0.54 mmol). [b]The yield was determined from the $^1H$ NMR spectrum of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. [c]Isolated yield. [d]Not observed.

To demonstrate the utility of the halogen dance reaction of 2,5-dibromopyrrole, we synthesized the substituted pyrrole as the synthetic intermediate of atorvastatin[17] (Scheme 5). The halogen dance reaction of 2,5-dibromopyrrole **1i** proceeded

smoothly, and the resulting 2,4-pyrrolyllithium was transformed into arylated dibromopyrrole **9** by Negishi coupling. Selective halogen–lithium exchange at the α position followed by electrophilic trapping with acetone provided the tertiary alcohol **10** in 55% yield over two steps. Subsequent Suzuki–Miyaura coupling of the bromopyrrole gave diarylated pyrrole **11**. Removal of the hydroxy group and the sulfamoyl group provided the substructure of the cholesterol-lowering medicine atorvastatin **12**.[3b,3c,18]




Scheme 5. Formal synthesis of atorvastatin through halogen dance.

In summary, the halogen dance reaction of 2,5-dibromopyrrole derivatives has been developed. Among various substituents on the pyrrole nitrogen tested, the *N*,*N*-dimethylsulfamoyl group was especially suitable for the regiocontrolled synthesis of the 2,4-dibromopyrroles. Several control experiments supported the existence of equilibrium between the corresponding pyrrolyllithiums bearing the *N*,*N*-dimethylsulfamoyl group, which allowed the synthesis of both 2,4- and 2,3-dibromopyrroles in a regiocontrolled manner by employing the appropriate set of electrophiles. This work provides a new concept toward the synthesis of multiply functionalized pyrroles.

This work was financially supported by JSPS KAKENHI (JP19H02717). This work was performed under the Cooperative Research Program of "Network Joint Research Center for Materials and Devices". We thank Professor Shigeki Mori (Ehime University) and Ms. Rimi Konishi (Ehime University) for the X-ray crystallographic analyses. We thank Iain Mackie, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

## Conflicts of interest

The authors declare no conflicts of interest.

## Notes and references

1 (a) N. Jeelan Basha, S. M. Basavarajaiah and K. Shyamsunder, *Mol. Divers.*, 2022, **26**, 2915–2937; (b) T. Fukuda, F. Ishibashi and M. Iwao, in *The Alkaloids: Chemistry and Biology*, ed. H.-J. Knölker, Academic Press, 2020, vol. 83, pp. 1–112; (c) Y. Ding, Y. Tang, W. Zhu and Y. Xie, *Chem. Soc. Rev.*, 2015, **44**, 1101–1112.

2 For a recent review, see: S. C. Philkhana, F. O. Badmus, I. C. Dos Reis and R. Kartika, *Synthesis*, 2021, **53**, 1531–1555.

3 For selected recent examples, see: (a) H. C. Chiu and I. A. Tonks, *Angew. Chem. Int. Ed.*, 2018, **57**, 6090–6094; (b) A. Kondoh, A. Iino, S. Ishikawa, T. Aoki and M. Terada, *Chem. Eur. J.*, 2018, **24**, 15246–15253; (c) P. K. Mishra, S. Verma, M. Kumar and A. K. Verma, *Org. Lett.*, 2018, **20**, 7182–7185; (d) B. Prabagar, R. K. Mallick, R. Prasad, V. Gandon and A. K. Sahoo, *Angew. Chem. Int. Ed.*, 2019, **58**, 2365–2370; (e) J.-K. Li, B. Zhou, Y.-C. Tian, C. Jia, X.-S. Xue, F.-G. Zhang and J.-A. Ma, *Org. Lett.*, 2020, **22**, 9585–9590.

4 For selected reviews, see: (a) L. I. Belen'kii, T. G. Kim, I. A. Suslov and N. D. Chuvylkin, *Russ. Chem. Bull.*, 2005, **54**, 853–863; (b) B. Borah, K. D. Dwivedi and L. R. Chowhan, *Asian J. Org. Chem.*, 2021, **10**, 2709–2762.

5 For selected examples via pyrrolyllithium species, see: (a) M. G. Banwell, B. L. Flynn, E. Hamel and D. C. R. Hockless, *Chem. Commun.*, 1997, 207–208; (b) T. Fukuda, T. Ohta, E.-i. Sudo and M. Iwao, *Org. Lett.*, 2010, **12**, 2734–2737.

6 For selected reviews, see: (a) J. F. Bunnett, *Acc. Chem. Res.*, 1972, **5**, 139–147; (b) M. Schnürch, M. Spina, A. F. Khan, M. D. Mihovilovic and P. Stanetty, *Chem. Soc. Rev.*, 2007, **36**, 1046–1057; (c) W. Erb and F. Mongin, *Tetrahedron*, 2016, **72**, 4973–4988; (d) K. Inoue and K. Okano, *Asian J. Org. Chem.*, 2020, **9**, 1548–1561.

7 J. Fröhlich, *Bull. Soc. Chim. Belg.*, 1996, **105**, 615–634.

8 (a) S. Kano, Y. Yuasa, T. Yokomatsu and S. Shibuya, *Heterocycles*, 1983, **20**, 2035–2037; (b) H. Fröhlich and W. Kalt, *J. Org. Chem.*, 1990, **55**, 2993–2995; (c) K. Okano, K. Sunahara, Y. Yamane, Y. Hayashi and A. Mori, *Chem. Eur. J.*, 2016, **22**, 16450–16454.

9 (a) D. Morikawa, K. Morii, Y. Yasuda, A. Mori and K. Okano, *J. Org. Chem.*, 2020, **85**, 8603–8617; (b) K. Morii, Y. Yasuda, D. Morikawa, A. Mori and K. Okano, *J. Org. Chem.*, 2021, **86**, 13388–13401; (c) Y. Okui, Y. Yasuda, A. Mori and K. Okano, *Synthesis*, 2022, **54**, 2647–2660.

10 To the best of our knowledge, there are no reported examples of 2,5-dibromothiophene undergoing the halogen dance to provide 2,3-dibromothiophene derivatives.

11 (a) J.-H. Liu, Q.-C. Yang, T. C. W. Mak and H. N. C. Wong, *J. Org. Chem.*, 2000, **65**, 3587–3595; (b) B. Jolicoeur, E. E. Chapman, A. Thompson and W. D. Lubell, *Tetrahedron*, 2006, **62**, 11531–11563; (c) W. Ishiga, M. Ohta, T. Kodama and M. Tobisu, *Org. Lett.*, 2021, **23**, 6714–6718.

12 L. Jones and B. J. Whitaker, *J. Comput. Chem.*, 2016, **37**, 1697–1703.

13 In the case of *N*-trisyl-2,3-dibromopyrrole **3g**, the use of 3 mol% tribromopyrrole **6g** did not promote isomerization of **3g'** to **2g'**.

14 The structures of compounds **7a** and **8a** were determined by HMBC experiments.

15 The structures of compounds **7b** and **8b** were determined by NOE experiments.

16 Recently, Bandar and co-workers have reported that brominated or iodinated thiophenes could be used as a halogen-transfer reagent for synthesizing a series of *N*-heteroaryl halides: T. R. Puleo, D. R. Klaus and J. S. Bandar, *J. Am. Chem. Soc.*, 2021, **143**, 12480–12486.

17 B. D. Roth, in *Progress in Medicinal Chemistry*, eds. F. D. King, A. W. Oxford, A. B. Reitz and S. L. Dax, Elsevier, 2002, vol. 40, pp. 1–22.

18 T. J. Donohoe, N. J. Race, J. F. Bower and C. K. A. Callens, *Org. Lett.*, 2010, **12**, 4094–4097.