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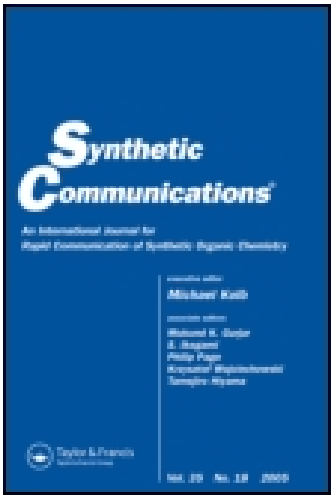

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Selective Metallation of 3-Halothiophenes: Practical Methods for the Synthesis of 2-Bromo-3-formylthiophene

Motohiro Sonoda [a], Shoko Kinoshita [a], Thanh Luu [a], Hiroshi Fukuda [a], Koji Miki [a], Rui Umeda [a] & Yoshito Tobe [a]

[a] Division of Frontier Materials Science, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka, Japan

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Selective Metallation of 3-Halothiophenes: Practical Methods for the Synthesis of 2-Bromo-3-formylthiophene

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Division of Frontier Materials Science, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka, Japan

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Abstract: Selective lithiation of 3-bromothiophene was accomplished under controlled conditions without formation of undesired thienyllithium compounds. A thienyl Grignard reagent derived from 2-bromo-3-iodothiophene was transformed into 2-bromo-3-formylthiophene in high selectivity by formylation with dimethylformamide (DMF) at optimal reaction temperature.

Keywords: 2-Bromo-3-formylthiophene, 2-bromo-3-iodothiophene, 3-bromothiophene, thienyl Grignard reagent, thienyllithium reagent

INTRODUCTION

Thiophene-based organic materials are an important class of compounds because they often show attractive properties that would lead to electronic, magnetic, and/or photochromic functional devices.[1] From this point of view, we recently reported the synthesis of bridged dithienylethene **1** as a key compound for photochromic or nonlinear optical materials via palladium (Pd)–catalyzed double-cyclization reactions of (*Z,Z*)-1,6-dithienyl-1,5-hexadien-3-ynes (**2**) (Scheme 1).[2]

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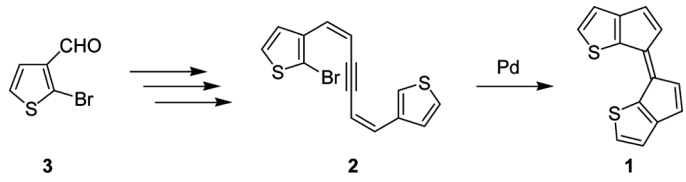
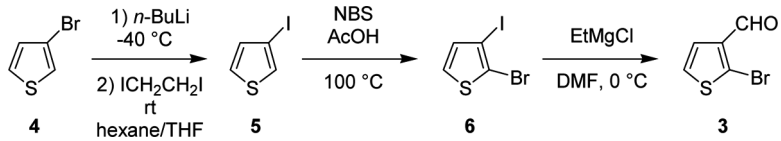
Address correspondence to Yoshito Tobe, Division of Frontier Materials Science, Graduate School of Engineering Science, Osaka University, 1-3 Machikaneyama Toyonaka, Osaka 560-8531, Japan. E-mail: tobe@chem.es.osaka-u.ac.jp



Scheme 1.



Scheme 2.

2-Bromo-3-formylthiophene (**3**), one of the building blocks for the construction of hexadienyne **2**, is often employed as a useful synthetic intermediate.[2,3] The synthesis of **3** consists of three steps; iodination of 3-lithiothiophene,[4] bromination of 3-iodothiophene (**5**),[5] and selective formylation of 2-bromo-3-iodothiophene (**6**) via generation of 2-bromothienylmagnesium chloride[6] (Scheme 2). In the course of our study, we observed that the iodination of 3-lithiothiophene caused bothersome contamination with inseparable by-products generated by migration of lithium to the 2- or 5-position of thiophene ring[5a,7] even when we employed the method disclosed by Wu et al. that was reported to give **5** selectively.[4] Moreover, we met with the same problem in the preparation of **3**; a considerable amount of isomeric products was formed in the formylation of 2-bromo-3-iodothiophene (**6**) because of the rearrangement of magnesium chloride on the thiophene ring, even though we followed the procedure reported by Christophersen et al.[6b] These products often create unavoidable trouble in the purification step. Christophersen also observed a small amount of by-product.[6b] Therefore, we intended to elaborate these processes to obtain pure products of **3** and **5** reproducibly, and we describe in detail here the successful practical method with high selectivity.

RESULTS AND DISCUSSION

As an initial step, the synthesis of 3-iodothiophene (**5**) was performed according to Wu et al.'s method.[4] A solution of *n*-butyllithium in hexane was added dropwise into a solution of 3-bromothiophene in hexane at

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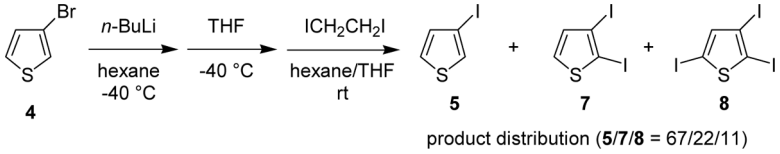
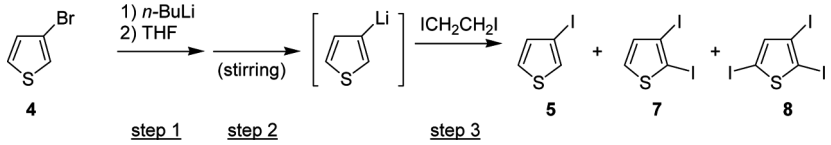


Scheme 3.

−40°C, and a small amount of THF was added for complete dissolution of 3-lithiothiophene. After the supplement of additional hexane with stirring, 1,2-diiodoethane, an electrophile, was added dropwise to the solution at room temperature to give a mixture of products: 3-diiodothiophene (**5**), 2,3-diiodothiophene (**7**),[8] and 2,3,5-triiodothiophene (**8**)[8a,9] (**5**/**7**/**8** = 67/22/11) (Scheme 3). The products were identified by ^{1}H NMR and GC/MS spectrometers. The product distribution was calculated based on the integration of the signals in ^{1}H NMR spectra.

Because this result was due to the instability of 3-lithiothiophene at such a high temperature,[7,10] we performed the reaction under the mild conditions offered by Gronowitz.[7a,b] Thus all reagents, *n*-butyllithium, THF, and 1,2-diiodoethane, were mixed at −70°C without warming. However, a mixture of **5, 7**, and **8** of similar composition was produced (**5**/**7**/**8** = 55/27/18). This result indicated that further improvement of the procedure for the selective lithiation of **4** was necessary. Then we examined the lithiation under various conditions (Scheme 4), and the results are summarized in Table 1. The result of run 1 was obtained by Gronowitz's method. When addition of 1,2-diiodoethane was carried out at 0°C after short stirring at room temperature (run 2), the product distribution remained almost unchanged (**5**/**7**/**8** = 61/24/15). Next, when the addition of 1,2-diiodoethane was conducted at −30°C after short stirring at −30°C, the yield of desired product **5** was slightly increased (**5**/**7**/**8** = 85/10/5) (run 3). In the case of the reaction at −10°C, the selectivity became slightly worse (**5**/**7**/**8** = 73/18/9) (run 4). It is interesting, however, to note that the formation of undesired product **8** completely vanished when the addition of *n*-butyllithium was performed in one portion, not dropwise, at −70°C (**5**/**7**/**8** = 75/25/0) (run 5). Finally, the



Scheme 4.

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Table 1. Reaction conditions of lithiation and distribution of products

Run	Addition of *n*-BuLi	Temperature (°C)			Distribution (%) (**5**/**7**/**8**)
		Step 1	Step 2	Step 3	
1	Dropwise	−70	−70	−70	55/27/18
2	Dropwise	−70	Rt	0	61/24/15
3	Dropwise	−70	−30	−30	85/10/5
4	Dropwise	−70	−10	−10	73/18/9
5	In one portion	−70	−10	−10	75/25/0
6	In one portion	−70	0	−70	100/0/0

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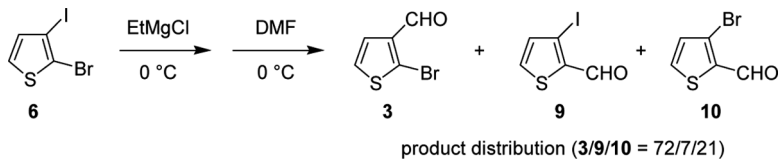
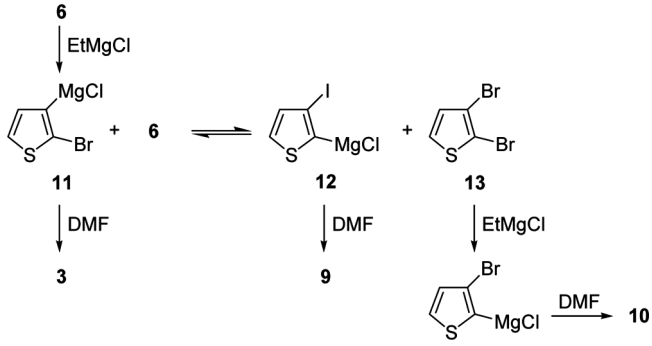
selectivity was dramatically improved when *n*-butyllithium was added in one portion, followed by stirring at 0°C for a short period before addition of 1,2-diiodoethane at −70°C, which exhibited excellent selectivity (**5**/**7**/**8** = 100/0/0) (run 6). It should be pointed out that **5** was reproducibly obtained by this procedure with good selectivity.

Next we embarked on a study of the last step, formylation of 2-bromo-3-iodothiophene (**6**), which was derived from **5** by bromination with *N*-bromosuccinimide.[5] According to the reported synthesis of 2-bromo-3-formylthiophene (**3**),[6] we generated 3-(2-bromothienyl)-magnesium chloride (**11**) by Grignard exchange reaction of **6** with ethylmagnesium chloride in THF at 0°C and treated it with DMF at the same temperature. After hydrolysis, the formylation product **3** was obtained as the major product accompanied by 2-formyl-3-iodothiophene (**9**)[3d,8c,11] and 2-formyl-3-bromothiophene (**10**)[12] (**3**/**9**/**10** = 72/7/21) (Scheme 5). The products were identified by ^{1}H NMR and GC/MS spectrometers. The product distribution was calculated based on the integration of the signals in ^{1}H NMR spectra.

This result also indicated that the procedure for the formylation of dihalothiophene **6** remained a matter of research. On lithiation of dihalothiophene, Gronowitz pointed out that facile migration of lithium often occurred from the 3- to 2-position of the thiophene ring, accompanying halogen–lithium exchange reaction.[7] This, together with the fact that a



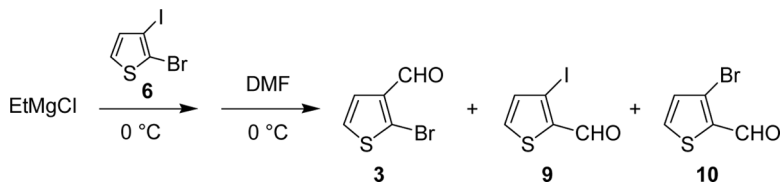
Scheme 5.



Scheme 6.

3-bromothiophene derivative **10** was formed, indicated that the similar migration occurred via halogen–magnesium exchange reaction when using ethylmagnesium chloride. Possible pathways for the formation of **9** and **10** are shown in Scheme 6, which include an undesired reaction of the generated Grignard reagent **11** with the starting thiophene **6** through halogen–metal exchange. The resulting 2-(3-iodothienyl)-magnesium chloride (**12**) and 2,3-dibromothiophene (**13**) are then converted to **9** and **10**, respectively, as shown.

To obtain **3** selectively, we examined the formylation of **6** under several conditions (Scheme 7). Representative results are summarized in Table 2. To suppress the reaction of **11** with the starting material **6, 6** was added dropwise to a solution of an equivalent or an excess amount of ethylmagnesium chloride in THF. When 1 eq of ethylmagnesium chloride was used, the selectivity was worse than those reported previously[6] (**3**/**9**/**10** = 50/15/35) (run 1). On the other hand, when 2 eq of ethylmagnesium chloride were used, the product distribution was considerably improved, giving **3** in high selectivity (**3**/**9**/**10** = 91/4/5) (run 2). The use of a further excess amount of ethylmagnesium chloride (3 eq), however, reduced the selectivity of the desired product (**3**/**9**/**10** = 77/8/15) (run 3). In summary, the procedure of run 2 reproducibly provides good selectivity of **3**.



Scheme 7.

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Table 2. Formylation of 2-bromo-3-iodothiophene

Run	EtMgCl	Yield (%)	Distribution (%) (**3**/**9**/**10**)
1	1 eq	74	50/15/35
2	2 eq	62	91/4/5
3	3 eq	48	77/8/15

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CONCLUSIONS

In conclusion, we have accomplished the practically useful and reproducible synthesis of 2-bromo-3-formylthiophene, which included the selective halogen–metal exchange reaction of 3-bromothiophene with butyllithium and that of 2-bromo-3-iodothiophene with a Grignard reagent under controlled conditions. These methods provide reliable access to the key compound for construction of various thiophene-based functional materials.

EXPERIMENTAL

General

^{1}H NMR (300 MHz) spectra were recorded on a Varian Mercury 300 spectrometer in $CDCl_3$ at 30°C. The chemical shifts of ^{1}H NMR signals are quoted relative to internal $CHCl_3$ ($\delta = 7.26$) or tetramethylsilane (TMS). Gas liquid chromatography (GLC) analysis of the products was performed with a Shimadzu GC-14B gas chromatograph equipped with a CBP1 capillary column (0.25 mm × 25 m). Preparative high-performance liquid-chromatographic (HPLC) separation was undertaken with a Jai LC-908 chromatograph using 600 mm × 20 mm Jaigel-1H and 2H gel permeation chromatography (GPC) columns with $CHCl_3$ as an eluent. All reagents were obtained from commercial suppliers and used as received. Solvents were dried (drying agent in parentheses) and distilled prior to use: THF (sodium benzophenone ketyl), DMF (CaH_2), and hexane (CaH_2).

3-Iodothiophene (5)

A 1.6 M solution of *n*-butyllithium in hexane (12.3 mL, 19.7 mmol) was added in one portion to a solution of 3-bromothiophene (1.74 mL, 18.4 mmol) in hexane (27.6 mL) at −70°C under an argon atmosphere.

Successively, a small amount of THF (2.7 mL), followed by hexane (9.3 mL), was added quickly. Then the mixture was stirred at 0°C for a short period of time and was recooled to −70°C. After an addition of 1,2-diiodoethane (6.00 g, 21.3 mmol) at −70°C, the reaction mixture was warmed to room temperature and stirred there for 1 h. A sat. sodium thiosulfate solution was poured into the reaction mixture. The organic layer was diluted with ethyl acetate, washed with brine, and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash chromatography (eluate: hexane) to afford **5** as a yellow oil (3.32 g, 86%): ^{1}H NMR ($CDCl_3$, 30°C) δ 7.41 (dd, $J = 3.0$, 1.8 Hz, 1H), 7.20 (dd, $J = 5.1$, 3.0 Hz, 1H), 7.10 (dd, $J = 5.1$, 1.8 Hz, 1H).

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2-Bromo-3-iodothiophene (6)

A mixture of **5** (2.44 g, 11.6 mmol), *N*-bromosuccinimide (2.21 g, 12.4 mmol), and acetic acid (10 mL) was stirred at 100°C for 1 h under an argon atmosphere. The reaction mixture was diluted with water and sat. $NaHCO_3$ and was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash chromatography (eluate: hexane) to afford **6** as a colorless oil (2.47 g, 74%): ^{1}H NMR ($CDCl_3$, 30°C) δ 7.23 (d, $J = 5.7$ Hz, 1H), 6.96 (d, $J = 5.7$ Hz, 1H).

2-Bromo-3-formylthiophene (3)

A solution of **6** (561 mg, 1.94 mmol) in THF (1.8 mL) was added dropwise into a 2.0 M solution of ethylmagnesium chloride in THF (1.9 mL, 3.8 mmol) at 0°C under an argon atmosphere. The mixture was stirred at 12°C for a short period of time, and then freshly distilled DMF (0.27 mL, 3.5 mmol) was added dropwise at 0°C. After stirring at room temperature for 1 h, the reaction mixture was diluted with sat. NH_4Cl and was extracted with ethyl acetate. Evaporation of the solvent followed by flash chromatography (eluate: hexane/ethyl acetate = 6/1) gave a mixture of products containing **3** (**3**/**9**/**10** = 91/4/5) as a yellow oil (230 mg, 62%). The products were identified by ^{1}H NMR and GC/MS spectrometers. The product distribution was calculated based on the integration of the signals in ^{1}H NMR spectra. The presence of by-products **9** and **10** was confirmed by comparison of the ^{1}H NMR spectra with the reported data.[8c,12c] Pure product **3** was obtained by subjection of the mixture to a recyclable preparative HPLC: ^{1}H NMR ($CDCl_3$, 30°C) δ 9.94 (s, 1H), 7.36 (d, $J = 6.0$ Hz, 1H), 7.28 (d, $J = 6.0$ Hz, 1H).

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