Multiple Alkylation of Thiophene Derivatives with Simple and Extended Diarylcarbenium Ion Pools

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Key Words

Diarylcarbenium ion, Electrochemical oxidation, Thiophene, Alkylation

Abstract

The reactions of thiophene derivatives, bithiophene and terthiophene with an electrochemically generated diarylcarbenium ion pool afforded multiple alkylation products. Extended diarylcarbenium ion pools afforded dendritic molecules by the multiple alkylation of bithophene and terthiophene.

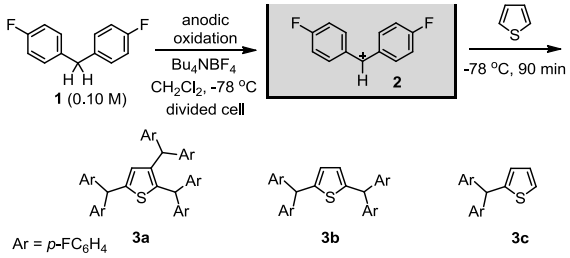
Conducting multiple reactions in one operation has received signficant research interest because it serves as a powerful method for time-efficinet construction of relatively large molecules of interesting functions or biological activities. Recently, transition metal-mediated[1] and catalyzed[2,3] reactions have been developed as powerful tools for preparing novel multi-substituted aromatics such as fullerene and thiophene derivatives. Although conventional Friedel-Crafts type electrophilic multiple reactions are also effective in some cases,[4] selective activation of precursors of electrophiles in the presence of nucleophilic aromatics is still a problem.

We have developed the cation pool method that involves electrochemical oxidative generation[5] and accumulation of organic cations[6,7] which react with various nucleophiles very quickly.[8-11] For example, diarylcarbenium ion pools[12-20] reacted with 1-(trimethylsilyl)-1,1-diphenylmethane and synthesis of dendrimers[21,22] and dendronized polymers[23] has been easily accomplished by repeating this reaction. This finding prompted us to examine multiple alkylation of oligothiophenes,[24-26] which serve

as electronically interesting structures, with simple and extended diarylcarbenium ions. Moreover, oligothiophenes with dendritic substituents have already been reported to show unique redox behavior because of their huge dendritic substituents.[27,28] Herein we report the results of this study.

At first, multiple alkylation of thiophene with diarylcarbenium ions was examined (Table 1). Diarylcarbenium ion **2** was prepared by the low-temperature electrochemical oxidation of di(*p*-fluorophenyl)methane (**1**).[29] The subsequent reaction of **2** with thiophene in the same pot afforded tri-, di-, and mono-substituted products **3a-c** as a mixture. A significant amount of 2,5-di-alkylated thiophene **3b** was obtained by the action of 0.2 equiv. of diarylcarbenium ion **2** (entry 1). Although the ratio of tri-alkylated thiophene **3a** increased with an increase in the amount of diarylcarbenium ion **2** (entries 2-4), the tetra-alkylated product of thiophene was not detected under conditions as shown in Table 1.

Table 1. Multiple alkylation of thiophene with diarylcarbenium ion **2** generated from **1.**[a]



entry	molar ratio **1**:thiophene	yields **3a** (%)	**3b** (%)	**3c** (%)
1[b]	1:5	0	40	47
2[c]	1:1	trace	44	11
3	2:1	27	55	trace
4	5:1	58	24	0

[a] Reaction conditions: diarylmethane **1** (0.4 – 0.8 mmol), electricity (2.5 F/mol), thiophene (2.0 – 0.16 mmol) in 0.3 M Bu_4NBF_4/CH_2Cl_2 (8.0 mL). [b] Yields based on diarylmethane **1**. [c] NMR yields based on 1,1,2,2-tetrachloroethane as an internal standard.

Next, we examined the reaction of diarylcarbenium ion **2** (5.0 equiv) with 2,2'-bithiophene. Mono- and multiple alkylation products were obtained as a mixture (Figure 1). NMR and MS analyses indicated that the major product was tetrakis(diarylmethyl) substituted bithiophene **4a**. The X-ray single crystal structure analysis of **4a** revealed that di(*p*-fluorophenyl)methyl groups were introduced at 3-, 3'-, 5-, and 5'-positions (Figure 1).[30] Because of the steric hindrance of four bulky substituents, two thiophene rings of **4a** are not in the same plane.

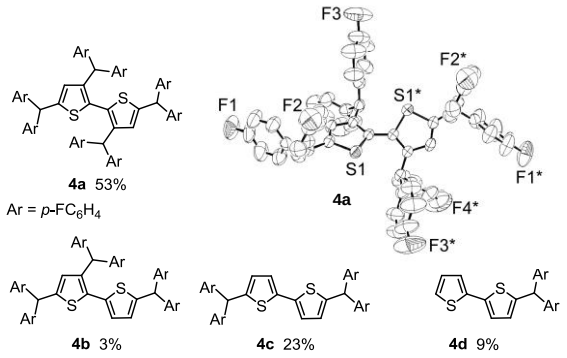


Figure 1. Structures of multiple alkylation products and ORTEP drawing of tetra-alkylated product **4a** (30% probability thermal ellipsoids). Hydrogen atoms are omitted for clarity.

The multiple alkylation reactions of 3,3'-bitihophene, 1,3,5-tris(2'-thienyl)benzene,[31] and 1,3,5-tris(3'-thienyl)benzene[31] were also studied (Figure 2). The reaction of 3,3'-bithiophene with 6 equiv of diarylcarbenium ion **2** afforded tetra-alkylated product **5** in 95% yield. Though the reaction of 1,3,5-tris(2'-thienyl)benzene with diarylcarbenium ion **2** (3~10 equiv) afforded a complex mixture including a small amount of tri-alkylated product,[32] the reaction of 1,3,5-tris(3'-thienyl)benzene with 10 equiv of diarylcarbenium ion **2** gave the

hexa-alkylated product **6** as a sole product in 76% yield.

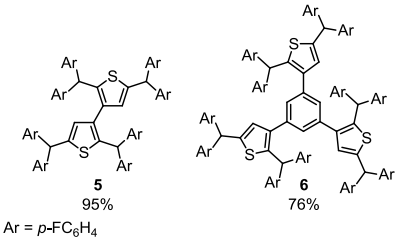


Figure 2. Structures of multiple alkylation products of 3,3'-bithiophene and 1,3,5-tris(3'-thienyl)benzene.

The multiple alkylation of terthiophene is interesting (Figure 3).[24] The reaction of diarylcarbenium ion **2** (5.0 equiv) with commercially available 2,2':5',2"-terthiophene afforded tetra-, tri-, and di-alkylated products **7a-c** as a mixture together with the mono-alkylated product and unchanged terthiophene. The yield of tetra-alkylated product **7a** was the lowest among them (6%). This sharply contrasts to the fact that tetra-alkylated products were obtained as major products in cases of 2,2'- and 3,3'-bithiophenes. Lower nucleophilicity of terthiophene due to a larger π-conjugation seems to be responsible. On the other hand, these results also suggest higher nucleophilicity of 5 and 5" positions than other positions of 2,2':5',2"-terthiophene.

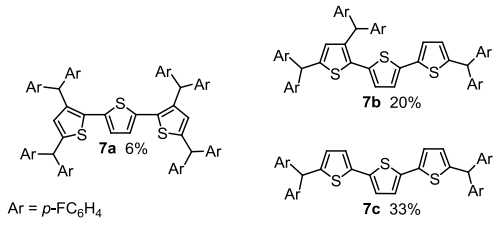
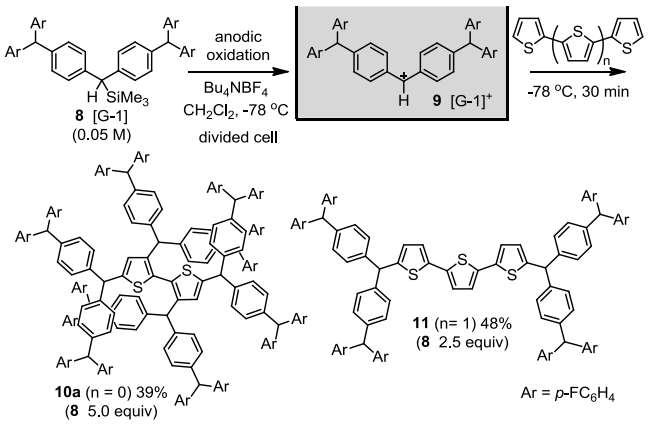


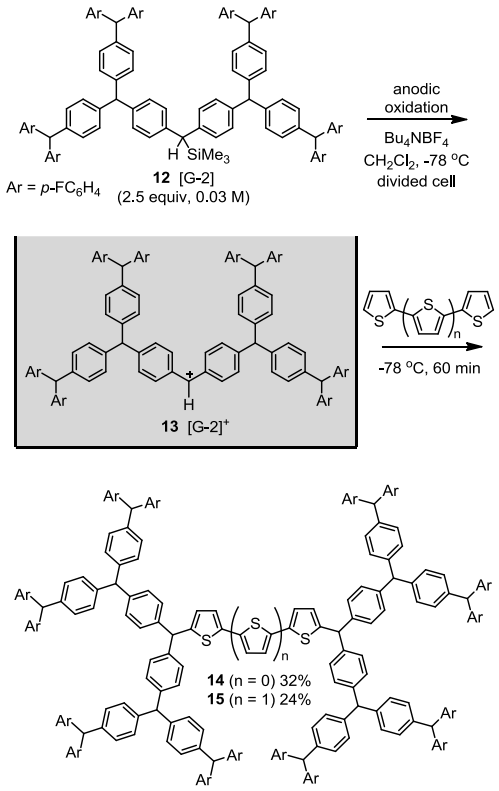
Figure 3. Structures of multiple alkylation products of terthiophene.

We also examined the multiple alkylation of 2,2'-bithiophene and 2,2':5',2"-terthiophene with the extended diarylcarbenium ion pool (Scheme 1). The extended diarylcarbenium ion pool $[G\text{-}1]^+$ was prepared by the low-temperature electrochemical oxidation of the corresponding precursor **8** [G-1] (the 1st generation of dendritic diarylmethane). The reaction of **9** $[G\text{-}1]^+$ (5.0 equiv) with 2,2'-bithiophene gave tetra-substituted product **10a** as a major product in 39% yield together with di- and tri-substituted products **10b**, **10c** in 19% and 13% yields, respectively. Although the yield of tetra-alkylated product **10a** is lower than that of tetra-alkylated product **4a** (Figure 1) presumably because of the steric reason, tetra-substituted products are obtained as major products in both cases. Taking advantage of the higher nucleophilicity of 5 and 5" positions than other positions of 2,2':5',2"-terthiophene, we examined regioselective dialkylation of terthiophene with **9** $[G\text{-}1]^+$. The reaction of extended diarylcarbenium ion **9** $[G\text{-}1]^+$ (2.5 equiv) with terthiophene afforded dialkylated product **11** as a major product, although the yield is still moderate (Scheme 1). These results indicate that reactivity of both diarylcarbenium ion **2** and that of the 1st generation of dendritic diarylcarbenium ion **9** $[G\text{-}1]^+$ are similar.



Scheme 1. Major multiple alkylation products of bithiophene and terthiophene with the first generation diarylcarbenium ion $[G\text{-}1]^+$.

Finally, we performed the regioselective dialkylation of bithiophene and terthiophene by using extended diarylcarbenium ion pools in order to demonstrate a potential of the present method for construction of dendritic molecules (Scheme 2).[27,28] The anodic oxidation of the cation precursor **12** [G-2] (the 2nd generation dendritic diarylcarbenium ion precursor) was performed under the standard cation pool conditions. The resulting extended diarylcarbenium ion **13** $[G\text{-}2]^+$ afforded di-alkylated products of bithiophene **14** and terthiophene **15** in 32% and 24% yields, respectively, although further optimization of reaction condition is required (**14** FAB-MS: *m/z* calcd for $C_{190}H_{130}F_{16}S_2$: 2778.9358, found: 2778.9375, **15** FAB-MS: *m/z* calcd for $C_{194}H_{132}F_{16}S_3$: 2860.9236, found: 2860.9180).



Scheme 2. Dialkylation of terthiophene by the further extended diarylcarbenium ion.

In summary, we have developed an efficient method for multiple alkylation of thiophene derivatives using electrochemically generated diarylcarbenium ion pools. The combination of the extended diarylcarbenium ions with bithiophene and terthiophene paved the way for rapid construction of molecules consisting of conjugated thiophenes and dendritic structures. The scope and limitations of the present method and its applications to synthesis of molecules having interesting functions are under investigation in our laboratory.

Acknowledgements

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29 The anodic oxidation was carried out in 0.3 M Bu_4NBF_4/CH_2Cl_2 (8.0 mL for both chamber) using a divided cell equipped with a carbon felt anode and a platinum plate cathode. In the anodic and cathodic chamber 4,4'-Difluorodiphenylmethane (**1**) (0.92 mmol) and TfOH (70 μL) were placed, respectively, and the constant current electrolysis (20 mA, 2.5 F/mol-**1**) was carried out at -78 °C. After the electrolysis, thiophene (0.17 mmol) was added to the anodic chamber and the reaction mixture was stirred for another 90 min. Then Et_3N was added and the reaction mixture was filtered through a short column of silica gel (d: 2 cm, h: 3 cm). After removal of solvent, the crude product was purified with preparative GPC to obtain **3a** and **3b** in 58% (56 mg, 0.096 mmol) and 24% (17 mg, 0.040 mmol) yields, respectively.

30 CCDC 745439 contains crystallographic data for **4a**.

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