COMMUNICATION

A novel and direct synthesis of alkylated 2,2′-bithiophene derivatives using a combination of hypervalent iodine(III) reagent and BF₃·Et₂O

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A novel nonmetallic oxidative coupling of alkylthiophene derivatives leading to the corresponding 2,2′-bithiophene derivatives using a combination of a hypervalent iodine(III) reagent, phenyliodine bis(trifluoroacetate) (PIFA), and BF₃·Et₂O was developed.

The oligo- and poly-(3-alkylthiophene) derivatives have recently received considerable attention due to their useful physical properties such as electrical conductivity and electroluminescence.[1] 2,2′-Bithiophene is one of the most important precursors of oligo- and poly-thiophenes since it can be polymerized under mild conditions due to its lower oxidation potential compared to thiophene itself, and predominantly yields higher quality α-linked polymer compared to that prepared from thiophene monomer by inhibiting the formation of α,β-defects.[1b] Therefore, there have been a number of reports on the preparation of 2,2′-bithiophenes, but these methodologies have been limited to transition metal catalyzed coupling reactions. Namely, reactions such as Ullmann, Suzuki, Stille, Negishi, Kumada–Tamao, and the related coupling reactions *via* halogenation or metallation of thiophene derivatives have been the most reliable methods.[2] On the other hand, oxidative coupling of thiophenes seems to be a direct and convenient route to the preparation of bithiophenes, yet, to the best of our knowledge, there have been no reports on the oxidative dimerization of thiophenes due to the lower oxidation potential of the bithiophene compared to the corresponding thiophene, unless the thiophene itself was activated as its anion form by treatment with strong base.[3] That is, the dimer, which is more easily oxidized than the monomer, always undergoes further coupling to afford the polythiophene through successive steps.[4] Therefore, typical oxidative coupling methods using electrochemical oxidation [1a] or metal oxidants such as Fe(III),[1] Tl(III),[4,5a,b] Ru(III),[5c] and Mo(V)[5c] have not been utilized for dimerization, but for oligomerization or polymerization of alkyl thiophene derivatives.

Over the last decade, the use of hypervalent iodine(III) reagents has gained importance as a safe alternative to heavy metal reagents for performing a variety of organic transformations.[6] In our ongoing studies on hypervalent iodine chemistry, we have recently developed mild and high yielding oxidative biaryl coupling reactions of phenol ethers or alkylarenes *via* aromatic cation radical intermediates using a combination of either phenyliodine(III) bis(trifluoroacetate) (PIFA) and BF₃·Et₂O or PIFA and heteropolyacid.[7] As a novel and useful extension of our studies on biaryl synthesis, we report herein the first facile and direct oxidative coupling reaction of alkyl thiophene derivatives leading to the corresponding bithiophenes using PIFA-BF₃·Et₂O without any activation of thiophene monomers.

We first examined the dimerization of 3-hexylthiophene (**1a**) using PIFA-BF₃·Et₂O. At room temperature, only a complex mixture was obtained. However, surprisingly, 2,2′-bithiophenes (**2a** and **3a**) were mainly obtained at lower temperatures. Furthermore, both the reaction temperature and the molar ratio of **1a** and PIFA remarkably affected the yield of the dimer (**2a** and **3a**), bithiophenes were obtained in 72% yield (by GC) when the reaction was carried out following the typical procedure described in the Notes and references section† (entries 1–4, Table 1). On the other hand, no reaction occurred in the absence of additives, in the presence of heteropolyacid (H₃[PW₁₂O₄₀]), or in (CF₃)₂CHOH (entries 5–7, Table 1). To confirm the differences among the oxidants, typical metal-induced reaction conditions including the variations in both temperature and equivalents of the reagents were also re-examined. As a result, in all cases, no dimer was obtained even when the reaction was carried out at a temperature lower than those reported for entries 8–12 in Table 1.

This reaction was applicable to various alkylated bithiophene syntheses. The results are summarized in Table 2. Although the regioselectivity† [head to head (H-H) isomer **2** and head to tail (H-T) isomer **3**] of bithiophenes was not observed, the corresponding 2,2′-bithiophenes were obtained exclusively in moderate to good yields without forming 2,3′-linked bithiophenes and polymers (entries 1 and 3–6, Table 2). Similarly, the coupling reactions of di- or tri-alkyl thiophenes (**1f–h**) also proceeded smoothly to afford end-capped bithiophenes (**2f–h**) in moderate yields (entries 7–9, Table 2).

A plausible reaction mechanism is shown in Scheme 1. Cation radical **B** is initially formed from **1** with PIFA-BF₃·Et₂O *via* CT-complex **A** under the reaction conditions in a manner analogous to those of our previously developed PIFA-induced reactions[7,8] or typical heavy metal oxidations[5] yielding aro-
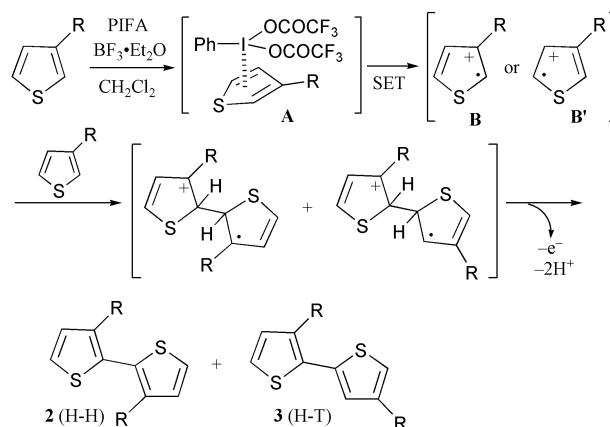

Scheme 1 A plausible reaction mechanism.

Table 1 Oxidative coupling reaction of **1a**
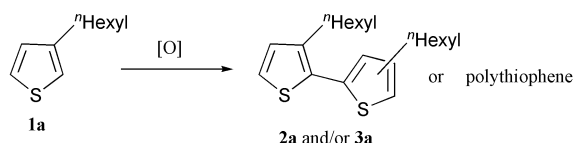
Entry	Reagents and solvents (0.4 M: concentration of oxidant)	T/°C	Time	Yield (%)[a]
1[f]	PIFA-BF$_3$·Et$_2$O, CH$_2$Cl$_2$	0	3 h	7(10[b])
2[f]	PIFA-BF$_3$·Et$_2$O, CH$_2$Cl$_2$	−40	3 h	26(37[b])
3[f]	PIFA-BF$_3$·Et$_2$O, CH$_2$Cl$_2$	−78	6 h	55(68[b])
4[g]	PIFA-BF$_3$·Et$_2$O, CH$_2$Cl$_2$	−78	6 h	72(68[c])
5[f]	PIFA, CH$_2$Cl$_2$	−78~rt	12 h	n.r.[d]
6[f]	PIFA, (CF$_3$)$_2$CHOH	0~rt	12 h	n.r.[d]
7[f]	PIFA-H$_3$[PW$_{12}$O$_{40}$], CH$_3$CN	−20~rt	12 h	n.r.[d]
8	FeCl$_3$, CH$_2$Cl$_2$	−78	12 h	n.r.[d]
9	FeCl$_3$, CHCl$_3$	0	3 h	n.d.[e]
10	Tl(OCOCF$_3$)$_3$-BF$_3$·Et$_2$O, CH$_2$Cl$_2$	−78	30 min	n.d.[e]
11	Tl(OCOCF$_3$)$_3$, CF$_3$CO$_2$H (TFA)	0	30 min	n.d.[e]
12	Tl(OCOCF$_3$)$_3$, (CF$_3$)$_2$CHOH-TFA	0	10 min	n.d.[e]

[a] GC yields based on consumed PIFA. [b] Yields based on the reacted substrate. [c] Isolated yield. [d] No reaction. [e] Dimer was not detected, but the polymer was formed immediately. [f] The molar ratio of **1a**, PIFA, and BF$_3$·Et$_2$O is 2 : 1 : 2. [g] The molar ratio of **1a**, PIFA, and BF$_3$·Et$_2$O is 3 : 1 : 2.

Table 2 Oxidative coupling reaction of alkylthiophenes (**1**) with PIFA-BF$_3$·Et$_2$O
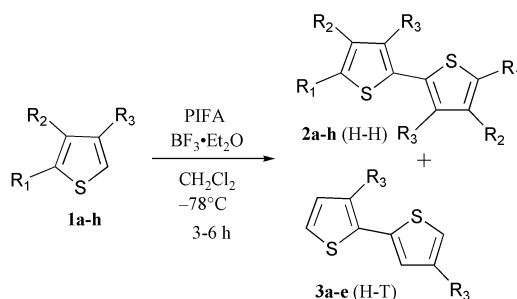
Entry	Substrate	R$_1$	R$_2$	R$_3$	Product	Yield (%)[a]
1[e]	**1a**	H	H	^{n}Hexyl	**2a** + **3a** (54 : 46)	72 (68[b])
2[e]	**1a**	H	H	^{n}Hexyl	—	n.r.[c]
3[e]	**1b**	H	H	Me	**2b** + **3b** (40 : 60)	50
4[e]	**1c**	H	H	^{n}Bu	**2c** + **3c** (43 : 57)	67
5[e]	**1d**	H	H	^{n}Octyl	**2d** + **3d** (50 : 50)	66
6[e]	**1e**	H	H	Cyclopentyl	**2e** + **3e** (42 : 58)	55
7[f]	**1f**	Me	H	Me	**2f**	44 (65[d])
8[f]	**1g**	Me	H	^{n}Hexyl	**2g**	45 (68[d])
9[f]	**1h**	Me	Me	Me	**2h**	36 (65[d])

[a] GC yields based on consumed PIFA. [b] Isolated yield. [c] No reaction (in the presence of galvinoxyl). [d] Yield based on consumed substrate. [e] The molar ratio of **1a**, PIFA, and BF$_3$·Et$_2$O is 3 : 1 : 2. [f] The molar ratio of **1a**, PIFA, and BF$_3$·Et$_2$O is 2 : 1 : 2.

matic cation radicals. Then, the radical cation (**B** or **B′**) reacts with a neutral molecule of **1** followed by one electron oxidation and deprotonation to give a mixture of H-H dimer **2** and H-T dimer **3**. Formation of **B** was supported by effective inhibition of the reaction of **1a** to form **B** in the presence of galvinoxyl, which is an efficient radical scavenger (entry 2, Table 2). A detailed mechanism for yielding predominantly dimers only when using PIFA (Table 1) is still unclear, but, the longer life time of CT-complex **A** and/or cation radical **B** induced by PIFA-BF$_3$·Et$_2$O at −78 °C compared to those by heavy metal oxidants seems to be an important factor.

In conclusion, we have developed an efficient nonmetallic oxidative coupling reaction of alkyl thiophenes leading to the corresponding 2,2′-bithiophenes using PIFA-BF$_3$·Et$_2$O. It was difficult to obtain bithiophene selectively by the conventional oxidative methods since further oxidation of bithiophenes to polythiophenes readily occurs. Therefore, the present reaction provides a novel and direct route to bithiophenes without introducing any directing groups into the thiophene monomers

before the coupling reaction. Detailed mechanistic studies of this reaction and a selective synthesis of regioregular bithiophenes improving this methodology are now underway.

Acknowledgements

Notes and references

† Typical experimental procedure: BF$_3$·Et$_2$O (1.01 mL, 8.0 mmol) and PIFA (1.72 g, 4.0 mmol) were added sequentially to a stirred solution of ^{n}hexylthiophene (**1a**, 2.0 g, 12.0 mmol) in CH$_2$Cl$_2$ (10 mL) at −78 °C under a nitrogen atmosphere. The mixture was stirred for 6 h under the same reaction conditions. Aqueous work-up with saturated NaHCO$_3$ at

0 °C followed by column chromatography (SiO$_2$/*n*-hexane) gave the corresponding bithiophene compound **2a** and/or **3a** in 68% yield. Identification and isolation of the two regioisomers, H-H and H-T, were performed by the previously reported procedure.[9]

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