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Metal-Free Regioselective Oxidative Biaryl Coupling Leading to Head-to-Tail Bithiophenes: Reactivity Switching, a Concept Based on the Iodonium(III) Intermediate

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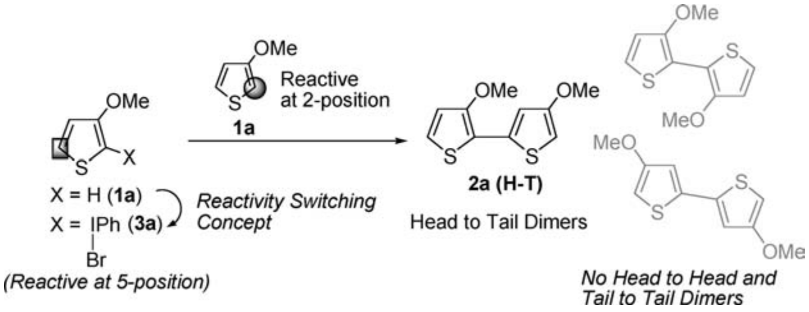
ABSTRACT



A new synthetic concept for obtaining unsymmetrical biaryl coupling products by an oxidative method is reported. Our synthetic strategy casts light on the reaction intermediate for switching the reactivity of 3-substituted thiophenes. On the basis of this strategy, a novel direct method for the synthesis of head-to-tail bithiophenes using hypervalent iodine(III) reagents has been developed.

Heteroaromatic biaryls have received considerable attention because of their importance as versatile building blocks in the synthesis of natural products, pharmaceuticals, agricultural chemicals, and electronic materials.[1] Bithiophenes, especially head-to-tail (H−T) dimers, in which two β-substituted thiophenes are coupled between the 2- and 5-positions of the thiophene ring, are useful precursors for the high quality of well-defined regioregular oligo- and polythiophenes and their derivatives.[2] Therefore, the development of a convenient regioselective synthesis of H−T dimers is important in organic chemistry.

Theoretically, the direct oxidative coupling reaction of thiophenes is conceptually attractive and convenient as a

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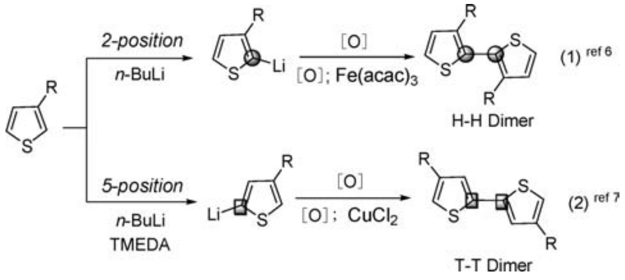
straightforward route to the synthesis of bithiophenes.[3,4] However, electrochemical oxidation or heavy metal oxidants not only for inducing oxidative coupling cannot be utilized for dimerization, but for oligomerization, due to the lower oxidation potential of the formed dimers compared to the corresponding initial monomers.[5] In addition, in the case of the coupling reaction of β-substituted thiophenes, the resulting coupling products were thought to be a mixture of three regioisomers, head-to-head (H−H), tail-to-tail (T−T), and H−T dimers. However, only the oxidative syntheses of symmetric H−H and T−T dimers have been accomplished to date. The regioselective oxidative syntheses of these dimers were typically realized through oxidative coupling of β-substituted thiophenes having metal functionalities at the 2-position or 5-position of the thiophene rings using a metal oxidant such as Fe or Cu oxidants (Scheme 1, eqs 1 and 2).[6,7] These methods, although widely employed, were not applicable to the synthesis of unsymmetric H−T dimers. This is because carbon−carbon bond formations should occur between the same metalated carbon atoms. Therefore, the H−T regioselective oxidative coupling reaction has not been reported, and their synthesis has been limited to transition-metal-catalyzed coupling reactions, that is, the reaction of halogenated and metalated thiophene derivatives.[8]

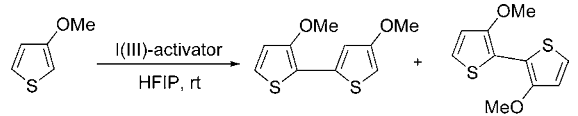
Scheme 1. General Methods for Oxidative Coupling Reaction of β-Substituted Thiophenes via Metalated Thiophenes



Herein, we describe a broadly applicable oxidative strategy that proceeds via iodonium intermediates, which show a unique reactivity at the 5-position, providing metal-free unsymmetrical oxidative coupling product H−T dimers.

We have previously reported the metal-free oxidative biaryl coupling reaction of aromatic compounds[9] induced by hypervalent iodine(III) reagents, such as $PhI(OCOCF_3)_2$ (PIFA), having useful oxidation abilities.[10] Recently, we have succeeded in applying our metal-free coupling reaction to alkylthiophenes and pyrroles.[11,12] Their mild oxidation abilities as oxidants led us to consider the regioselective synthesis of bithiophenes without using metal oxidants. First, we employed 3-methoxythiophene **1a** as a model substrate and examined the reaction conditions. According to our preliminary study, as expected, the use of BF_3•Et_2O and TMSOTf,[11] or TMSBr,[12] as the activators of PIFA in CH_2Cl_2 provided the coupling products in low yield, and the resulting products were a mixture of H−T dimer **2a (H−T)** and H−H dimer **2a (H−H)**. In contrast, when we performed the reaction in $(CF_3)_2CHOH$ (HFIP) in the presence of TMSBr, the H−T-linked coupling product **2a (H−T)** was obtained as the major regioisomer albeit in moderate yield (Table 1, entry 1). Addition of BF_3•Et_2O and TMSOTf, which was examined next, appeared to be less effective than TMSBr (entries 2 and 3). We also evaluated other iodine reagents, among which PhI(OH)OTs (HTIB) gave the best result in

Table 1. Coupling Reaction of 3-Methoxythiophene **1a**



1a **2a (H-T)** **2a (H-H)**

[Molar ratio ; Thiophene:I(III):activator = 2:1:2]

			yield[b] (%)	
entry	I(III)	activator	**2a (H−T)**	**2a (H−H)**
1[a]	PIFA	TMSBr	57	>5
2[a]	PIFA	BF_3•Et_2O	n.d.	n.d.
3[a]	PIFA	TMSOTf	n.d.	n.d.
4[a]	HTIB	TMSBr	64	>5
5[c]	HTIB	TMSBr	87	0

[a] Performed using **1a** (2 equiv), I(III) (1 equiv), and activator (2 equiv) in solvent. [b] Isolated yield. [c] TMSBr was added after thiophene **1a** reacted with PhI(OH)OTs in $(CF_3)_2CHOH$.

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this coupling reaction (entry 4).[13] Interestingly, we noticed the importance of premixing of thiophene **1a** and HTIB in the control of the regioselectivity. Thus, TMSBr was added to the stirred solution of 3-methoxythiophene **1a** and HTIB, and the yield and selectivity of the unsymmetrical coupling product **2a (H−T)** were complete at this stage (entry 5). The obtained H−T dimer **2a (H−T)** and related dimers should be potentially valuable when synthesizing H−T regioregular poly(3-alkoxythiophene)s, showing excellent conductivity, stability, and optical characteristics.[2] The observation described in Table 1 clearly indicated the importance of experimental procedure and the possibility of the existence of a reaction intermediate leading to the bithiophenes.

When 3-methoxythiophene **1a** reacted with HTIB in HFIP, the iodonium salt **3a-OTs** was rapidly yielded in nearly quantitative yields.[14] Surprisingly, the formed iodonium salt **3a-OTs** could selectively react at the 5-position of the thiophene ring with the 3-methoxythiophene **1a** at the 2-position.[15] Therefore, we considered that the realization of this unique unsymmetrical coupling reaction proceeded via the iodonium salts,[13] and a variety of H−T dimers might be synthesized using the thienyliodonium salts as the intermediates without formation of other regioisomers (Scheme 2). The strategy relies upon the use of iodonium intermediates **3-OTs** that activate the 5-position exclusively. Otherwise, H−H or T−T dimers would be obtained.

Scheme 2. Iodonium(III) Strategy for Switching the Reactivity of 3-Substituted Thiophenes

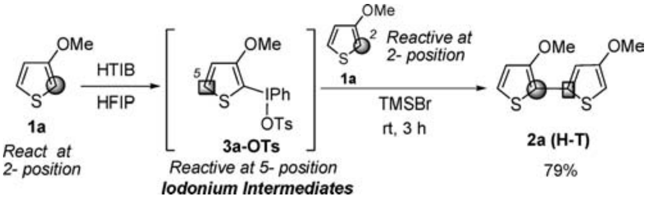
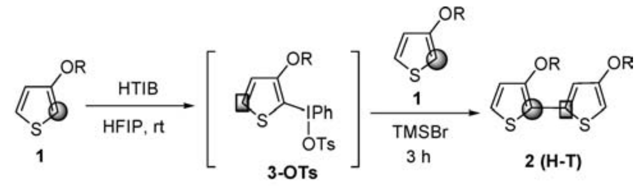


Table 2. Scope of 3-Alkoxylthiophenes **1**[a]



[Molar ratio ; Thiophene:HTIB:TMSBr = 2:1:2]

entry	R	yield[b] (%)
1	Me (**1a**)	85
2	Hex (**1b**)	84
3	butyl (**1c**)	75
4	isobutyl (**1d**)	73
5	cyclohexyl (**1e**)	70
6	$CH_2(CF_2)_5CF_3$ (**1f**)	75
7	$(CH_2)_2O(CH_2)_2OCH_3$ (**1g**)	72
8	Bn (**1h**)	61

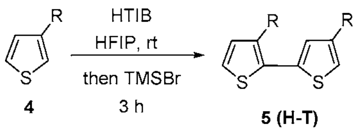
[a] Performed using **1** (2 equiv), HTIB (1 equiv), TMSBr (2 equiv) in HFIP at room temperature. [b] Isolated yield.

Relying on this strategy, we examined various 3-substituted alkoxythiophenes **1** to explore the scope of the substrates that could be used (Table 2). We noted that the reactions proceeded smoothly and gave the corresponding H−T bithiophenes **2 (H−T)** in high yield as the single isomer. The resulting bithiophenes, **2b (H−T)** and **2c (H−T)**, are useful precursors of conductive polymers (entries 2 and 3), such as the poly(3-butoxythiophene)s and poly(3-hexaloxythiophene)s. These are frequently used as a class of soluble, conjugated polymer with excellent stability in air.[2] The steric interaction affected neither the reactivity nor the selectivity, and the reaction of **1d** and **1e** gave the coupling products **2d (H−T)** and **2e (H−T)** in high yield. The fluoroalkyl-substituted thiophene **1f** also provided **2f (H−T)** as a single isomer in 75% yield.

The presence of some protecting groups such as 2-(2-methoxyethoxy)ethyl (MEET) and benzyl ethers was well tolerated, affording the corresponding coupling products **2g (H−T)** and **2h (H−T)** in good yield. In each case, phenyl group transfer from the salts **3-OTs** was not observed.

As illustrated in Scheme 3, the 3-alkylthiophenes **4** were also efficient substrates for the unsymmetrical oxidative coupling reaction, and the H−T bithiophenes **5 (H−T)** were obtained in high yield without reoptimization of the reaction conditions. Similarly, alkylthiophenes **4a−c** gave the unsymmetrical coupling biaryls **5a−c (H−T)** in excellent yield with a high degree of regioselectivity. Sterically hindered substrates **4d** and **4e** also coupled smoothly to give the expected coupling products, respectively, which indicated that the steric restriction was less influential in this strategy. The bromo group of **4f** was tolerable under the reaction conditions. In each case, the resulting coupling products were contaminated at less than 1% by other regioisomers.

Scheme 3. Scope of 3-Alkylthiophenes **4**



R = Me (**4a**); 87%, Butyl (**4b**); 88%
Hexyl (**4c**); 78%, Cyclohexyl (**4d**); 75%
i-Butyl (**4e**); 73%, $(CH_2)_6Br$ (**4f**); 72%

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(12) Regiopreference biaryl coupling reaction using hypervalent iodine(III) reagent with TMSBr in CH_2Cl_2 afforded a mixture of regioisomers: (a) Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007. (b) Dohi, T.; Morimoto, K.; Ito, M.; Kita, Y. *Synthesis* **2007**, 2913. (c) Dohi, T.; Morimoto, K.; Ogawa, C.; Fujioka, H.; Kita, Y. *Chem. Pharm. Bull.* **2009**, *57*, 710.

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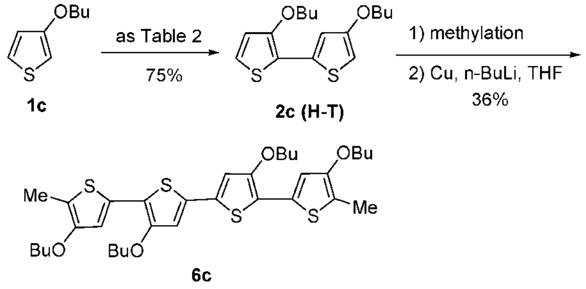
Synthesis of extended oligomers was carried out utilizing the H−T dimer product **2c (H−T)** (Scheme 4). Recently, oligothiophenes in their neutral form have been used to prepare electronic and electro-optical devices.[2] In these studies, practical synthesis of oligothiophenes with well-defined structures is highly important.[16] We envisaged a facile synthesis of extended regioregular oligomers by repeated oxidative coupling.

Scheme 4. Quaterthiophene **6c** from the H−T Dimer **2c (H−T)**



As a result, quaterthiophene **6c** was obtained in 51% yield when the Cu-mediated homocoupling of lithiated monomethylation product of **2c (H−T)** was carried out. This type of regioregular quarterthiophene **6c** having an oxygen substituent has never been reported. The measurement of the UV−vis absorption spectra of quarterthiophene **6c** shows 480 nm, the λ_{max} value of which shifted to red by 60 or 90 nm (see the Supporting Information), by comparison with the other reported quaterthiophenes.[16] This result reveals that the λ_{max} values of longer wavelength seem to be responsible for its high coplanarity to avoid steric repulsion between the OBu substituents.

In summary, a unique and selective oxidative coupling has been realized by the use of an iodonium(III)-mediated strategy. In combination with the unique reactivity of the thienyliodonium salts **3-OTs** and the high nucleophilicity of the 2-position of the β-substituted thiophenes, the reactions not only controlled the regioselectivity of the dimers but also provided a new direct synthetic route to H−T-linked bithiophenes without using transition-metal catalysts. The H−T dimers thus obtained are useful units for the synthesis of oligothiophenes having well-defined structures. Further studies on the application of this strategy are now in progress.

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Supporting Information Available: Experimental procedures, details for optimization of the reaction conditions, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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