The synthesis of head-to-tail (H–T) dimers of 3-substituted thiophenes by the hypervalent iodine(III)-induced oxidative biaryl coupling reaction

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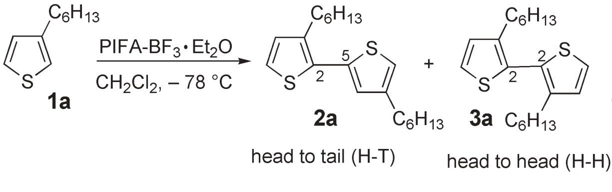
The head-to-tail (H–T) dimers could be obtained selectively by the oxidative coupling reaction of 3-substituted thiophenes using a combination of hypervalent iodine(III) reagents and trimethylsilyl trifluoromethanesulfonate.

Recently, the oligo- and poly-(3-alkylthiophene) derivatives have received considerable attention due to their useful physical behavior such as electrical conductivity, electroluminescence and in organic thin film transistors (TFTs).[1] 2,2′-Bithiophenes are one of the most important class of compounds for synthesizing oligo- and poly-thiophenes, which makes them attractive synthetic targets in modern organic synthesis.[2–4] Among them, the head-to-tail (H–T) dimers of the 3-alkylthiophenes have been the focus of much attention as useful precursors of high-quality electro-conductive materials due to their excellent degree of co-planarity in their oligomer forms.[1,5,6] A transition metal-catalyzed stepwise methodology *via* the condensation of metallated thiophenes and/or thienyl halides might be reliable for the selective construction of H–T dimers, despite the need for the pre-functionalization of a reactive functionality such as a halogen or metal into the thiophenes.[2,3] In contrast, relatively few examples have been reported about the direct synthesis of the 2,2′-bithiophenes from thiophenes themselves, which provided no H–T dimers but exclusively head-to-head (H–H) dimers.[4] To the best of our knowledge, no reports of the selective H–T dimer formation have appeared.

Oxidative biaryl coupling reactions using hypervalent iodine(III) reagents[7] are recognized as alternative methods to that using heavy-metal oxidizers.[8] We recently reported a phenyliodine bis(trifluoroacetate) (PIFA)-induced oxidative biaryl coupling reaction of thiophenes,[9] in which its mild oxidation ability is important for preventing any further undesired reaction of the products (eqn. (1)).[10] Herein, we report the PIFA-induced oxidative biaryl coupling reaction of various 3-substituted thiophenes using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a Lewis acid, selectively enabling the direct formation of the H–T dimers.



(1)

As previously reported, 3-hexylthiophene (**1a**) gave 2,2′-bithiophenes (**2a** and **3a**) in 68% yield as a mixture in the ratio 46:54 using a combination of PIFA and $BF_3·Et_2O$ at −78 °C (Table 1, entry 1).[9] The reaction conditions such as temperature or concentration did not effect this selectivity. Next, we examined the distribution of the reaction product[11] using several hypervalent iodine(III) reagents with different electrical and steric properties, but they also gave almost the same result in selectivities and only varied in product yields (Table 1, entries 2–4).

However, surprisingly, we found that Lewis acids, which were originally added for the purpose of activating the hypervalent iodine(III) reagents, remarkably affected the selectivity of the dimers. Thus, by changing $BF_3·Et_2O$ to $B(C_6F_5)_3$, the dimers were obtained in 66% yield with the slightly preferential formation of the H–T dimer **2a** (Table 1, entry 5). To confirm the difference among the Lewis acids used, extensive numbers of Lewis acids were examined (Table 1, entries 6–10).[12] Among them, the relatively weak Lewis acid, TMSOTf, gave the best result in terms of selectivity. Thus, the H–T dimer of 3-hexylthiophene was obtained as almost the sole product (Table 1, entry 10). On the other hand, the reaction was quite sluggish in the presence of Brønsted acids such as TfOH, CF_3CO_2H and HBF_4. By using **4d**, dimers were obtained in good yield with acceptable selectivity (Table 1, entry 11).

Selectivities were generally observed for various 3-substituted thiophenes (Table 2).† Similarly, alkyl thiophenes **1b** and **1c** having a higher *n*-heptyl or *n*-octyl group also gave the desired H–T dimers with no marked change in the selectivity (Table 2, entries 3 and 4). The smaller the alkyl substituent was, the lower the selectivity (Table 2, entry 5). Bulkier substituents did not affect the

Table 1 Effect of the Lewis acids in oxidative biaryl coupling reaction of **1a** (eqn. (1))

Entry[a]	$ArI(OCOCF_3)_2$	Lewis acid	Time/h	Yield[b] (%)	**2a**:**3a**[c]
1	Ar = C_6H_5 (**4a**)	$BF_3·Et_2O$	6	68	46:54
2	Ar = C_6F_5 (**4b**)	$BF_3·Et_2O$	3	74	52:48
3	Ar = 4-MeC_6H_4 (**4c**)	$BF_3·Et_2O$	3	34	45:55
4	Ar = 2-MeC_6H_4 (**4d**)	$BF_3·Et_2O$	3	73	44:56
5	**4a**	$B(C_6F_5)_3$	3	66	62:38
6	**4a**	BBr_3	1.5	48[d]	89:11
7	**4a**	Bu_2BOTf	1.5	71	64:36
8	**4a**	TMSBr	3	—[e]	—
9	**4a**	TBSOTf	3	19	82:18
10	**4a**	TMSOTf	3	41	94:6
11	**4d**	TMSOTf	3	72 (90)[f]	81:19

[a] The molar ratio of **1a**, **4a–d**, and Lewis acids is 3:1:2. [b] Isolated yields based on **4a–d**. [c] Determined by ^1H-NMR of the isolated product mixture. [d] The brominated 2,2′-bithiophenes were also obtained. [e] No reaction. [f] Isolated yield based on consumed **1a**.

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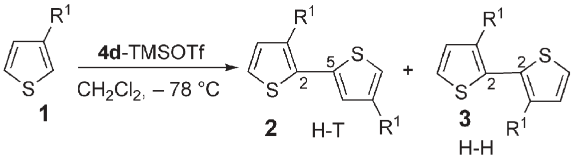
Table 2 H–T dimer selective oxidative coupling reaction of 3-substituted thiophenes (**1**)



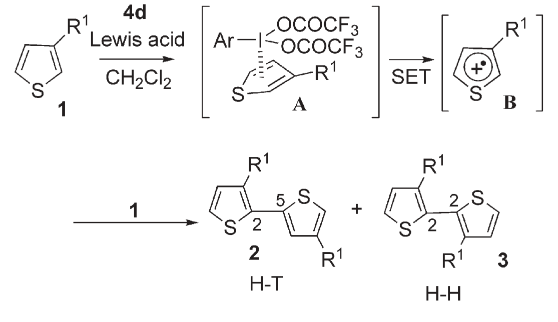
Entry[a]	Substrate	R^1	Yield[b] (%)	Product
1[c]	**1a**	*n*-Hexyl	41	**2a** + **3a** (94:6)
2	**1a**	*n*-Hexyl	72 (90)[d]	**2a** + **3a** (81:19)
3	**1b**	*n*-Heptyl	52	**2b** + **3b** (92:8)
4[c]	**1c**	*n*-Octyl	30	**2c** + **3c** (95:5)
5	**1d**	Methyl	72	**2d** + **3d** (80:20)
6	**1e**	*n*-Butyl	88	**2e** + **3e** (77:23)
7	**1f**	Isobutyl	98	**2f** + **3f** (87:13)
8[c]	**1h**	Cyclohexyl	67	**2h** + **3h** (90:10)
9	**1i**	$(CH_2)_6Br$	62	**2i** + **3i** (82:18)
10	**1j**	$SiMe_3$	46	**2j** + **3j** (1:99)

[a] The molar ratio of **1**, **4d** and TMSOTf is 3:1:2. [b] Isolated yield based on consumed **4a**,**d**. [c] **4a** was used instead of **4d**. [d] Isolated yield based on consumed **1a**.

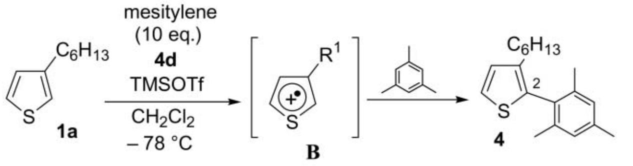
yields of the products, while higher selectivities were generally observed (Table 2, entries 7 and 8). The bromo group of **2i** may be useful for further functionalization of these dimers (Table 2, entry 9).[13] On the other hand, 3-trimethylsilylthiophene **1j** selectively gave the H–H dimer **3j** rather than the H–T dimer **2j** (Table 2, entry 10). This is probably due to the electronic character of the silyl group.

A plausible reaction mechanism is as follows (Scheme 1): cation radical **B** is initially formed from **1** with **4d**-Lewis acid *via* the CT-complex **A** during the reaction.[14] The radical **B** is thought to be confined in the coordination sphere of iodine(III).[15] Then, **B** reacts with a neutral molecule of **1** followed by the one-electron oxidation and deprotonation to give a mixture of the H–T dimer **2** and H–H dimer **3**.

The selectivities of products are determined in the last step. The selective couplings of the 2-position of the cation radical intermediate **B** and the 5-position of **1** accounts for the formation of the observed H–T linked 2,2′-bithiophene products. The following experiment and our previous results on the functionalization of thiophenes[16] support this explanation. Thus, during the biaryl coupling reaction of 3-hexylthiophene **1a** and mesitylene, the C–C bond formation preferentially occurred at the 2-position of 3-hexylthiophene (Scheme 2).



Scheme 1 Reaction mechanism.



Scheme 2 Biaryl coupling reaction of 3-hexylthiophene with mesitylene.

In summary, we have developed an unprecedented oxidative coupling reaction of alkyl thiophenes selectively leading to the corresponding H–T dimer of 2,2′-bithiophenes by choosing a suitable Lewis acid and hypervalent iodine(III) reagent. This is the first example for controlling the selectivity of the oxidative biaryl coupling reaction products. It is postulated that the *end-free* 2,2′-bithiophenes could be easily functionalized at these *end-free* sites as well as being converted to the corresponding high-quality oligo- and poly-thiophenes. Therefore, the present reaction provides a novel direct route to various 2,2′-bithiophenes. Further applications of these products are currently under way in our laboratory.

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Notes and references

† Typical experimental procedure is as follows: TMSOTf (0.36 mL, 2.0 mmol) and PIFA (430 mg, 1.0 mmol) were sequentially added to a stirred solution of 3-hexylthiophene (**1a**) (0.5 g, 3.0 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C under a nitrogen atmosphere. The mixture was stirred for 3 h under the same reaction condition. An aqueous work-up with saturated $NaHCO_3$ at 0 °C followed by column chromatography (SiO_2/*n*-hexane) gave the corresponding 2,2′-bithiophenes **2a** and **3a** in 41% yield. Identification and isolation of the two regioisomers, H–T and H–H, were performed by a previously reported procedure.[11]

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