## 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).<sup>1</sup> 2,2'-Bithiophenes are one of the most important class of compounds for synthesizing oligoand poly-thiophenes, which makes them attractive synthetic targets in modern organic synthesis.<sup>2-4</sup> Among them, the headto-tail (H-T) dimers of the 3-alkylthiophenes have been the focus of much attention as useful precursors of high-quality electroconductive materials due to their excellent degree of co-planarity in their oligomer forms.<sup>1,5,6</sup> 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.<sup>2,3</sup> 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.<sup>4</sup> 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<sup>7</sup> are recognized as alternative methods to that using heavy-metal oxidizers.<sup>8</sup> We recently reported a phenyliodine bis(trifluoroacetate) (PIFA)-induced oxidative biaryl coupling reaction of thiophenes,<sup>9</sup> in which its mild oxidation ability is important for preventing any further undesired reaction of the products (eqn. (1)).<sup>10</sup> 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.



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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  $BF_3 \cdot Et_2O$  at -78 °C (Table 1, entry 1).<sup>9</sup> The reaction conditions such as temperature or concentration did not effect this selectivity. Next, we examined the distribution of the reaction product<sup>11</sup> 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<sub>3</sub>·Et<sub>2</sub>O to B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>, 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).<sup>12</sup> 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<sub>3</sub>CO<sub>2</sub>H and HBF<sub>4</sub>. 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 <sup>a</sup>	ArI(OCOCF <sub>3</sub> ) <sub>2</sub>	Lewis acid	Time/h	$\operatorname{Yield}^{b}(\%)$	<b>2a:3a</b> <sup>c</sup>
1	$Ar = C_6 H_5 (4a)$	BF <sub>3</sub> ·Et <sub>2</sub> O	6	68	46:54
2	$Ar = C_6 F_5 (4b)$	$BF_3 \cdot Et_2O$	3	74	52:48
3	$Ar = 4 - MeC_6H_4 (4c)$	BF <sub>3</sub> ·Et <sub>2</sub> O	3	34	45:55
4	$Ar = 2 - MeC_6H_4 (4d)$	BF <sub>3</sub> ·Et <sub>2</sub> O	3	73	44:56
5	4a	$B(C_{6}F_{5})_{3}$	3	66	62:38
6	4a	BBr <sub>3</sub>	1.5	$48^d$	89:11
7	4a	Bu <sub>2</sub> BOTf	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) <sup>f</sup>	81:19

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

* `/							
	R <sup>1</sup> <b>4d</b> -TM: CH <sub>2</sub> Cl <sub>2</sub> , -	SOTf - 78 °C	R <sup>1</sup> 5 8 + H-T R <sup>1</sup>	$ \begin{array}{c}                                     $			
Entry <sup>a</sup>	Substrate	$\mathbb{R}^1$	$\operatorname{Yield}^{b}(\%)$	Product			
1 <sup>c</sup>	1a	n-Hexyl	41	<b>2a</b> + <b>3a</b> (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 <sup>c</sup>	1h	Cyclohexyl	67	2h + 3h (90:10)			
9	1i	(CH <sub>2</sub> ) <sub>6</sub> Br	62	2i + 3i (82:18)			
10	1j	SiMe <sub>3</sub>	46	2j + 3j (1:99)			

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



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).<sup>13</sup> 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.<sup>14</sup> The radical **B** is thought to be confined in the coordination sphere of iodine(III).<sup>15</sup> 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<sup>16</sup> 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<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub> at 0 °C followed by column chromatography (SiO<sub>2</sub>/*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.<sup>11</sup>

- Recent reviews, see: (a) J. Roncali, Chem. Rev., 1992, 92, 711; (b) Electronic Materials: The Oligomer Approach, ed. K. Müllen and G. Wegner, Wiley-VCH, Verlag GmbH, 1998; (c) R. D. McCullough, Adv. Mater., 1998, 10, 93; (d) R. L. Elsenbaumer, K.-Y. Jen, G. G. Miller, H. Eckhardt, L. W. Shacklette and R. Jow, Electronic Properties of Conjugated Polymers, ed. H, Kuzmany, M. Mehring and S. Roth, Springer Series in Solid State Sciences, Springer-Verlag, Berlin, 1987, vol, 76, p. 400; (e) N. J. L. Guernion and W. Hayes, Curr. Org. Chem., 2004, 8, 637.
- 2 Pre-treatment with strong bases: (a) J. Kagan and S. K. Arora, *Heterocycles*, 1983, **20**, 1937; (b) H. Higuchi, T. Nakayama, H. Koyama, J. Ojima, T. Wada and H. Sasabe, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 2363, and references cited therein.
- 3 Transition metal-catalyzed coupling of thienyl halide: (a) J. M. Tour, *Chem. Rev.*, 1996, **96**, 537; (b) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359, and references cited therein.
- 4 Palladium-catalyzed direct homocoupling of thiophene: (a) T. Itahara, M. Hashimoto and H. Yumisashi, *Synthesis*, 1984, 255; (b) K. Masui, H. Ikegami and A. Mori, *J. Am. Chem. Soc.*, 2004, **126**, 5074.

- 5 (a) R. D. McCullough, R. D. Lowe, M. Jayaraman and D. L. Anderson, J. Org. Chem., 1993, 58, 904; (b) R. D. McCullough and S. P. Williams, J. Am. Chem. Soc., 1993, 115, 11608; (c) R. S. Loewe, P. C. Ewbank, J. Liu, L. Zhai and R. D. McCullough, Macromolecules, 2001, 34, 4324.
- 6 (a) T.-A. Chen and R. D. Rieke, J. Am. Chem. Soc., 1992, 114, 10087;
  (b) T.-A. Chen and R. D. Rieke, Synth. Met., 1993, 60, 175; (c) T.-A. Chen, X. Wu and R. D. Rieke, J. Am. Chem. Soc., 1995, 117, 233.
- 7 (a) Y. Kita, M. Gyoten, M. Ohtsubo, H. Tohma and T. Takada, Chem. Commun., 1996, 1481; (b) T. Takada, M. Arisawa, M. Gyoten, R. Hamada, H. Tohma and Y. Kita, J. Org. Chem., 1998, 63, 7698; (c) M. Arisawa, S. Utsumi, M. Nakajima, N. G. Ramesh, H. Tohma and Y. Kita, Chem. Commun., 1999, 469; (d) H. Tohma, H. Morioka, S. Takizawa, M. Arisawa and Y. Kita, Tetrahedron, 2001, 57, 345; (e) H. Hamamoto, G. Anilkumar, H. Tohma and Y. Kita, Chem. Commun., 2002, 450; (f) H. Hamamoto, G. Anilkumar, H. Tohma and Y. Kita, Chem. Eur. J., 2002, 8, 5377; (g) H. Tohma, M. Iwata, T. Maegawa and Y. Kita, Tetrahedron Lett., 2002, 43, 9241.
- 8 (a) P. J. Stang and V. V. Zhdankin, *Chem. Rev.*, 1996, 96, 1123; (b)
  Y. Kita, T. Takada and H. Tohma, *Pure Appl. Chem.*, 1996, 68, 627; (c)
  A. Varvoglis, *Hypervalent Iodine in Organic Synthesis*, Academic Press, San Diego, CA, 1997; (d) T. Kitamura and Y. Fujiwara, *Org. Prep. Proc. Int.*, 1997, 29, 409; (e) T. Wirth and U. H. Hirt, *Synthesis*, 1999, 1271; (f) V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2002, 102, 2523;

(g) Hypervalent Iodine Chemistry, ed. T. Wirth, Springer-Verlag, Berlin-Heidelberg, 2003.

- 9 H. Tohma, M. Iwata, T. Maegawa, Y. Kiyono, A. Maruyama and Y. Kita, Org. Biomol. Chem., 2003, 1, 1647.
- (a) R. M. Souto Maior, K. Hinkelmann, H. Eckert and F. Wudl, Macromolecules, 1990, 23, 1268; (b) K. Yoshino, S. Nakajima and R. Sugimoto, Jpn. J. Appl. Phys., 1987, 26, L1038; (c) L. Juliá, A. G. Davies, D. R. Rueda and F. J. B. Calleja, Chem. Ind., 1989, 78; (d) J. Tormo, F. J. Moreno, J. Ruiz, L. Fajarí and L. Juliá, J. Org. Chem., 1997, 62, 878; (e) F. Barbosa, L. Eberson, G. Gescheidt, S. Gronowitz, A. Hörnfeldt, L. Juliá and O. Persson, Acta. Chem. Scand., 1998, 52, 1275.
- 11 H. Higuchi, N. Hayashi, H. Koyama and J. Ojima, *Chem. Lett.*, 1995, 1115.
- 12 Lewis acids such as AlCl<sub>3</sub>, GaCl<sub>3</sub>, TiCl<sub>4</sub>, SnCl<sub>4</sub>, ZnBr<sub>2</sub>, FeCl<sub>3</sub>, Cu(OTf)<sub>2</sub> and MgBr<sub>2</sub> did not produce any 2,2'-bithiophenes.
- 13 (a) K. K. Stokes, K. Heuze and R. D. McCullough, *Macromolecules*, 2003, **36**, 7114; (b) M. Schaeferling and P. Baeuerle, *J. Mater. Chem.*, 2004, **14**, 1132.
- 14 Y. Kita, H. Tohma, K. Hatanaka, T. Takada, S. Fujita, S. Mitoh, H. Sakurai and S. Oka, *J. Am. Chem. Soc.*, 1994, **116**, 3684.
- 15 M. Kameyama, N. Kamigata and M. Kobayashi, J. Org. Chem., 1987, 52, 3312, and references cited therein.
- 16 T. Dohi, K. Morimoto, Y. Kiyono, H. Tohma and Y. Kita, Org. Lett., 2005, 7, 537.