Clean and Direct Synthesis of α,α’-Bithiophenes and Bipyroles by Metal-Free Oxidative Coupling Using Recyclable Hypervalent Iodine(III) Reagents

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The facile and clean oxidative biaryl coupling reaction of thiophenes and pyrroles has been achieved using the recyclable hypervalent iodine(III) reagents having adamantane or methane structures. These iodine(III) reagents could be recovered from the reaction mixtures by a simple solid–liquid separation, i.e., filtration.

Key words oxidative coupling; hypervalent iodine(III) reagent; recycling; heteroaromatic compound; biaryl

Biaryl compounds serve as key structures of bioactive natural products and chiral ligands for asymmetric reactions and as precursors of various organic materials due to their unique physical properties.1–3) These beneficial features make them attractive as synthetic targets in modern organic chemistry.4,5) A large number of the straightforward methods that involve the oxidative coupling processes of unfunctionalized aromatic compounds have been reported using oxidizing agents to produce these important biaryl compounds.6) Over the past decade, we originally developed a new oxidative biaryl coupling method using the hypervalent iodine(III) reagents, such as phenyliodine bis(trifluoroacetate) (PIFA),7) and have extended the method to work in alkylarenes,8) even in as phenyliodine bis(trifluoroacetate) (PIFA),7) and have extended the method to work in alkylarenes,8) even in heteroaromatic compounds, i.e., thiophenes9) and pyrroles.10) Our new biaryl coupling methods using the low toxic, safe and easy handling trivalent organoiodine oxidants have significant synthetic merits that avoid not only the pre-functionalization of aromatic compounds to the corresponding activated halide or metal forms, but also the use of toxic heavy-metal agent or metal catalyst.

The use of recyclable hypervalent iodine reagents, such as polymer-supported reagents, in the reactions should be a further promising and ecological approach for enhancing the practicability of the methods and for reducing the iodoarene wastes, as a result of the easy removal of the reagents from the reaction mixtures and their reuse.11) During the course of this study, poly[bis(trifluoroacetoxy)iodo]styrene (PBTIS) has already been applied to the oxidative biaryl coupling reactions of phenyl ethers and alkylarenes.12) However, we noted that the utilization of the polymer-supported reagent is not successful for the coupling reactions of heteroaromatic compounds, thiophenes and pyrroles, due to its low reactivity and insolubility in most organic solvent systems. Furthermore, PBTIS is sometimes degraded after repeated use.

We have succeeded in the practical oxidative coupling reactions of thiophenes and pyrroles using the non-polymer-supported recyclable iodine(III) reagents 1 (Fig. 1) that can directly provide useful classes of heteroaromatic biaryls.

Our recyclable hypervalent iodine(III) reagents 113) and 314) with an adamantane or methane core have several advantages over the conventional polymer-supported reagents in reactivity and recyclability; they typically show higher reactivities compared to the polymer-supported reagents and no degradation of their backbones after repeated use, which are derived from the well-defined tetrahedral structures. We thus initially attempted the biaryl coupling reaction of 3-hexylthiophene 5a using the recyclable reagent 1a based on the standard reaction conditions at −78 °C in CH2Cl2 in combination with the several Lewis acids, such as BF3·Et2O, TMSOTf, and TMSBr9,10) but unexpectedly, the product α,α’-bithiophene 6a was only obtained in low yields and large amounts of the starting 5a remained unchanged. We assumed that these results should be attributed to the low solubility of the reagent 1a in CH2Cl2 at −78 °C, and therefore, decided to examine the reactions at room temperature. Although the reactions of 5a using the reagent 1a in ordinary solvents, such as CH2Cl2, CH3CN and MeOH, were similarly not productive, the dimer 6a was formed exclusively as a single regiosomer in 69% yield when the reaction was carried out in a highly polar, but low nucleophilic 1,1,1,3,3,3-hexafluoroisopropanol (HFIP, (CF3)2CHOH) solvent in the presence of TMSBr (Chart 1). One of the important roles of the HFIP
solvent selected in the reactions is considered to be the enhancement of the reactivity of the reagent 1a to generate reactive aromatic cation intermediates of thiophene 5a.15,16 The use of trifluoroethanol (TFE) instead of HFIP or other Lewis acids such as BF3·Et2O and TMSOTf in HFIP resulted in no production of the desired coupling product, because formation of the diaryliodonium salts occurred.17 We also evaluated the reactivities of the related reagents 1b and 3b in the coupling reaction. The reagent 1b could work more effectively, giving the product 6a in higher yield than the reagent 1a and an alternative reagent having a methane core 3b. In contrast, the polymer-supported reagent, PBTIS, was still ineffective under the given conditions due to its low solubility in the HFIP solvent.

The oxidants 1a, b or 3b could be easily separated from the reaction mixtures as the corresponding reduced forms, i.e., the tetraiodide 2 (from 1a and 1b) or 4 (from 3b), by a simple solid–liquid separation. The procedure to recover the tetraiodides was started with the removal of the solvent under reduced pressure by a rotary evaporator. MeOH was then added to the resulting oily residues to precipitate the tetraiodide 2 or 4. As the tetraiodides are hardly soluble in MeOH, they were simultaneously precipitated as a white powder by adding MeOH and were collected by filtration to recover the tetraiodide 2 or 4. A series of recycle processes was finally completed by reoxidation of the recovered tetraiodide 2 or 4 to the initial reagents 1a, b or 3b using m-chloroperbenzoic acid (mCPBA). In this way, the reagents could be reproduced with almost the same purity and have been repeatedly used without any loss of activities.11 Indeed, the reuse of the reagent 1b in the same reaction gave a comparable result (3 h, 70% yield of coupling product 6a), and the tetraiodide 2 was also recovered in over 95% yield.

With the reagent 1b (0.5×1/4 eq, 50 mol% of iodine(III) atom relative to the substrates 5), the reactions of the thiophenes 5 smoothly proceeded under the homogeneous conditions in the HFIP solvent in the presence of TMSBr (Table 1). This facile and clean method could mainly give the head to tail (H-T) linked dimers 6 from various 3-substituted thiophenes 5 under mild conditions. Typically, the high reactivity of 1b allowed no requirement for excess amounts of the reagent in the reactions. In each case, the recovery of the reagent 1b was over 95% by the above mentioned recycling procedure, and thus the crude products 6 could be obtained from the MeOH filtrates and purified by short column chromatography on silica gel. Similar to the substrate 5a, the 3-substituted thiophenes 5b–d having the shorter or longer alkyl substituents gave the desired products 6b–d in comparable yields with a high degree of regioselectivities (entries 2–4). The bulkier substituents did not affect the yield of the products 6e and 6f (entries 5, 6). In our metal-free method, the bromo group in the substrate 5g was tolerable during the reaction (entry 7). The thiophene 5h having the alkoxy group was subjected to the reaction to give the corresponding coupling dimer 6h in an excellent yield without any reoptimization of the reaction conditions (entry 8). The synthesis of electron-rich alkoxy substituted bithiophenes is known to be especially challenging in other oxidation strategies due to their low oxidation potentials for facilitating additional in situ undesired oligomerizations of the formed dimers.18

We next tried to extend the coupling method to more reactive N–H pyroles, but the acid-sensitive N–H pyrole 8a gave a number of insoluble identified byproducts in acidic HFIP. Therefore, we screened other non-acidic solvents, and CH2Cl2 gave a better result for N–H pyrole 8a (Chart 2). The reaction of 3-alkylpyrrole 8b was, unfortunately, not as selective as thiophenes 5, but the two regioisomers 9b and 10b could be separated by column chromatography techniques.19 The N-substituted pyrrole 8c, on the other hand, reacted at both α- and β-positions to give the α,β′-bipyrrrole 11c rather than the α,α′-bipyrrrole albeit in low yield. In summary, we have established the first facile and clean method for the oxidative biaryl coupling reaction of heteroaromatic compounds using recyclable hypervalent iodine reagents. The present protocol is quite simple, and cleanly gave no requirement for excess amounts of the acid-sensitive N–H pyrole 8a.

Experimental

General: The 1H- and 13C-NMR spectra were recorded by a JEOL JMN-300 spectrometer operating at 300 MHz in CDCl3, at 25 °C with tetramethylsilane as the internal standard. The data are reported as follows: chemical shift in ppm (δ), integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad singlet, m=multiplet), and coupling constant (Hz). The infrared spectra (IR) were obtained using a Hitachi 270-50 spectromete-

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Table 1. Oxidative Biaryl Coupling Reaction of 3-Substituted Thiophenes Using 1b (Eq. 2)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 5</th>
<th>Product</th>
<th>Total yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hex (5a)</td>
<td>6a: 7a= &gt;99:1</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>Me (5b)</td>
<td>6b: 7b= 93:7</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>Butyl (5c)</td>
<td>6c: 7e= 98:2</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>Octyl (5d)</td>
<td>6d: 7d= &gt;99:1</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>i-Butyl (5e)</td>
<td>6e: 7e= 98:2</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>n-Hex (5f)</td>
<td>6f: 7f= &gt;99:1</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>(CH3)3Br (5g)</td>
<td>6g: 7g= &gt;99:1</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>OMe (5h)</td>
<td>6h: 7h= &gt;99:1</td>
<td>67</td>
</tr>
</tbody>
</table>

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The molar ratio of thiophenes 5, 1b, TMSBr is 1:0.5×1/4:1. In each case, 10–20% of the starting materials 5 were recovered. a) Isolated yield after purification.

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Chart 2

The molar ratio of pyroles 8, 1b, TMSBr is 1:0.5×1/4:1. The percentages indicate the isolated yields of 9–11 after purification.
ter; absorptions are reported in reciprocal centimeters with the following relative intensities: s (strong), m (medium), or w (weak). The mass spectra were obtained using a Shimadzu GCMS-QP 5000 instrument with ionization voltages of 70 eV. The high resolution mass spectra and elemental analysis were performed by the Elemental Analysis Section of Osaka University. The column chromatography and TLC were carried out on Merck Silica gel 60 (230—400 mesh) and Merck Silica gel F254 plates (0.25 mm, respectively). The spots and bands were detected by UV irradiation (254, 365 nm).

All commercially available reagents and solvents were used as received without further purification.

**Preparation of 1b** To a stirred solution of 1,3,5,7-tetraakis(4-iodophenyl)adamantane 2 (1.42 g, 1.5 mmol) in CHCl3 (150 ml) AcOH (150 ml) was added m-chloroperoxybenzoic acid (mCPBA) (ca 69% purity, 3.12 g, 18 mmol) at room temperature. The mixture was stirred for 12 h under the same reaction conditions until the cloudy solution became clear. The resultant mixture was filtered, and CHCl3 was removed using a rotary evaporator. Hexane was added to the residue to precipitate 1,3,5,7-tetraakis(4-diacetoxyiodo)phenyladamantane. After filtration, the crude product was obtained in nearly quantitative yield.

1,3,5,7-Tetraakis(4-diacetoxyiodo)phenyladamantane (1b) Tinanium(iv) chloride (40.3 mmol) and triethylamine (58.4 mmol) were added to a solution of mixture of CH3CN and hexane, and then dried in vacuo to give 1b (1.05 g, 94%) as a slightly yellow oil.

1,3,5,7-Tetraakis(4-hydroxy(tosyloxy)iodo)phenyladamantane (1b) Tinanium(iv) chloride (40.3 mmol) and triethylamine (58.4 mmol) were added to a solution of mixture of CH3CN and hexane, and then dried in vacuo to give 1b (1.05 g, 94%) as a slightly yellow oil.

**Typical Procedure for Direct Oxidative Biaryl Coupling Reaction Using 1b** To a stirred solution of 3-hexylthiophene 5a (101 mg, 0.6 mmol) in (CF3)2CHOH (6 ml) was added 1b (127.8 mg, 0.3×1/4 mmol) and then TMSB (0.08 ml, 0.6 mmol) at room temperature when the color of the solution immediately changed to brown. For stirring 3 h, CH2Cl2 saturated NaHCO3aq and solid Na2SO4·7H2O were successively added to the reaction mixture with stirring. The organic layer was then separated and evaporated to dryness. MeOH (10 ml) was added to the reaction mixture, and it was filtered to give the tetraiodide 2 (confirmed by H-NMR analysis and TLC), which was washed several times with small portions of MeOH for purification. The filtrate was evaporated and subjected to column chromatography (SiO2, hexane) to give 3,4-dideoxy-2,2-biithiophene 6a (75 mg, 75%) as a slightly yellow oil. The reaction chemistry of the product 6a was determined by comparing it to the authentic sample.

3,4-Dideoxy-2,2-biithiophene (6a) Slightly yellow oil; 1H-NMR (CDCl3): δ: 0.83—0.92 (9H, m), 1.20—1.35 (12H, m), 1.52—1.70 (4H, m), 2.63 (2H, t, J = 8.4 Hz), 2.74 (2H, t, J = 8.4 Hz), 6.89—6.92 (2H, m), 7.03 (1H, s), 7.12 (1H, d, J = 5.5 Hz) ppm. 13C-NMR (75 MHz, CDCl3): δ: 14.1, 22.6, 29.0, 29.1, 29.2, 29.7, 30.4, 30.5, 30.7, 31.6, 31.7, 119.9, 123.4, 127.3, 129.9, 130.9, 135.8, 139.3, 143.5 ppm. HR-FAB-MS: m/z 334.1784 [M]+ (Calcd for C17H14O2S2: 334.1789).

3,4-Dideoxy-2,2-biithiophene (6b) Slightly yellow oil; 1H-NMR (CDCl3): δ: 2.28 (3H, s), 2.38 (3H, s), 6.86—6.87 (2H, m), 6.94 (1H, s), 7.11 (1H, d, J = 5.1 Hz) ppm. 13C-NMR (75 MHz, CDCl3): δ: 15.3, 15.7, 120.4, 123.0, 127.8, 131.3, 133.7, 136.3, 140.8 ppm. 1H-NMR (CDCl3): δ: 0.83—0.96 (6H, m), 1.29—1.42 (4H, m), 1.58—1.67 (4H, m), 2.61 (2H, t, J = 7.5 Hz), 2.75 (2H, t, J = 7.5 Hz), 6.87—6.96 (3H, m), 7.13 (1H, d, J = 5.1 Hz) ppm. 13C-NMR (75 MHz, CDCl3): δ: 13.9, 22.4, 22.6, 28.9, 30.2 (×2), 32.6, 32.9, 119.9, 123.4, 127.3, 129.9, 130.9, 131.4, 139.3, 143.5 ppm. IR (KBr) cm⁻¹: 3501 w, 2930 w, 2858 s, 1723 w, 1456 m, 1377 s, 1263 s, 1088 w, 831 m, 748 s, 652 m. Anal. Calc. for C17H12O2S2: C, 69.01; H, 7.96; S, 23.03. Found: C, 69.01; H, 7.93; S, 22.74.

3,4-Didecarboxylic acid 2,2-biithiophene (6c) Slightly yellow oil; 1H-NMR (CDCl3): δ: 0.86—0.88 (6H, m), 1.20—1.30 (20H, m), 1.56—1.63 (4H, m), 2.52 (2H, t, J = 7.5 Hz), 2.74 (2H, t, J = 7.5 Hz), 6.80—6.89 (3H, m), 7.05 (1H, d, J = 5.1 Hz) ppm. 13C-NMR (75 MHz, CDCl3): δ: 14.1, 15.3, 22.7, 29.1, 29.3, 29.4 (×2), 30.5, 30.7, 31.8, 319.9, 123.4, 127.3, 129.9, 131.0, 135.8, 139.4, 143.5 ppm. IR (KBr) cm⁻¹: 3923 w, 2935 s, 1464 m, 1377 w, 1200 w, 1086 w, 831 m, 721 m, 652 w. Anal. Calc. for C17H12O2S2: C, 73.78; H, 9.80; S, 16.15.

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**References and Notes**


19) The coupling reaction of other 3-substituted pyroles 8 proceeded in good yields, but the selectivity of H-T and H-H dimers is not so high as that of thiophenes 5 under the present conditions. Further optimization for control of the regioselectivity in the bipyrrole synthesis will be described in due course.