Applications of hypervalent iodine(III) reagents in constructing ortho-iodo aromatic ethers

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Abstract
A one-pot method for the synthesis of aromatic ethers using hypervalent iodine(III) reagents obtained from the corresponding iodoaryl compounds is developed. In this concise method, six diaryl ethers and three heterocyclic aromatic ethers are synthesized in good yields. Furthermore, possible mechanisms for the syntheses of the hypervalent iodine reagents and construction of the aromatic ethers are proposed.

Keywords
diaryl ethers, heterocyclic aromatic ethers, hypervalent iodine(III) compounds, mechanisms

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Introduction
Hypervalent iodine(III) reagents have been known for over a century, but these compounds have only recently been applied extensively in many important organic transformations.1–3 Diaryl ethers are common structural features in numerous biologically active compounds and natural products, some of which are potential drugs. Numerous methods have been developed to synthesize diaryl ethers, and new routes for a wide range of biologically active compounds have been devised.4–8 Heterocyclic aromatic ethers are likely to exhibit higher potent biological activity than the corresponding diphenyl ethers. However, many of the reported methods for the synthesis of heterocyclic aromatic ethers have limited efficiency.9 In this study, we report a concise and efficient method for the preparation of trivalent iodine compounds 4–6, and the application of these compounds for the construction of aromatic ethers.

Results and discussion
In our laboratory, we developed an efficient and inexpensive method for preparing diacetoxyiodoarenes10–12 in ideal yields from corresponding iodoarenes with sodium perborate tetrahydrate.13 The optimized method for the preparation of diacetoxyiodoarenes from iodoarenes is described in section “Experimental” (Scheme 1).

The ortho-iodo aromatic ethers can be synthesized smoothly from the corresponding phenols with the diacetoxyiodoarenes. In particular, the 4-pyridone also could be oxidized to ortho-iodo aromatic ethers via diacetoxyiodoarenes. The detail experiment of the preparation of aromatic ethers is described in section “Experimental” (Scheme 2).

A possible mechanism for the construction of diacetoxyiodoarenes has been proposed based on the experimental results (Scheme 3). The starting material is oxidized to an unstable intermediate iodosyl benzene a, which then reacts with acetic anhydride to form intermediate b. Intramolecular rearrangement then yields the diacetoxyiodoarenes. Infrared spectroscopy and UV-Vis light spectroscopy data showed that all of the diacetoxyiodoarenes existed in virtually ionic form.13

Based on the experiment results and previous reports,14 a possible mechanism for the formation of heterocyclic aromatic ethers is shown in Scheme 4.

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Initially, the lone pair of the hydroxy group attacks the iodine of the diacetoxyiodoarene, which loses an acetic acid to form intermediate c. Intramolecular electrophilic aromatic substitution with loss of an acetate anion then yields cation d. Next, aromatization forms the relatively stable intermediate e, and a subsequent shift of the phenyl group from iodine to oxygen then yields the heterocyclic aromatic ether.
Conclusion

In this work, we report an efficient method for synthesis of diacetoxyiodoarenes via intramolecular rearrangement, and three diacetoxyiodoarenes were prepared smoothly via this method. Then, the front freshly prepared compounds are used to oxidize some phenols, and the corresponding six diaryl ethers and three heterocyclic aromatic ethers are synthesized in good yields. Both of the possible mechanisms of preparing diacetoxyiodoarenes and constructing diaryl ethers are proposed.

Experimental

All chemical reagents were obtained from commercial suppliers (Aldrich, Tokyo Chemical Industry (TCI), Aladdin, Macklin, and Bidepharm Pure Chemical Industries) and were used without further purification. Anhydrous solvents were obtained via standard protocols. All non-aqueous reactions were carried out under an Ar atmosphere. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 glass plates precoated with a 0.25-mm thickness of silica gel (Yantai Jiangyou). Column chromatography was carried out on Cica Silica Gel 60N (spherical, neutral, 40–50 μm or 63–210 μm). $^1$H and $^{13}$C NMR spectra were obtained on a Varian UNITY plus 300 (300 MHz for $^1$H and 75 MHz for $^{13}$C) instrument, with CDCl3 as the solvent and d internal reference. IR spectra were measured on a JNM FTIR-460 Plus spectrometer. Mass spectra were recorded on JEOL D-200, JEOL JMS-GCmate II, SHIMAZU GC-MS-QP 500, or JEOL AX 505 spectrometers. Melting points were recorded with a Yanagimoto micro melting point apparatus and are uncorrected.
Optimized method for the preparation of diacetoxyiodoarenes from iodoarenes

NaBO₃·4H₂O (10 mmol) was slowly added portionwise over 30 min to a stirred solution of iodoarene I (1 mmol) in Ac₂O (1.5 mL) and AcOH (99.5%, 1.5 mL) under Ar at 55 °C. The mixture was stirred at 55 °C until the starting material had disappeared completely (as confirmed by TLC analysis). Water (20 mL) was added and the reaction mixture was stirred at room temperature for 30 min. A considerable amount of solid precipitates was observed. The solid was separated by filtration, washed with water (2.5 mL), and dried under air at room atmosphere. The filtrate was extracted with EtOAc (3 10 mL). And the combined extracts were dried over anhydrous MgSO₄ and filtered. The solvent was evaporated under reduced pressure. The combined crude products were purified by recrystallization from a mixture of AcOH/H₂O (1:1).

General procedure for the preparation of aromatic ethers

A mixture of 4-pyridone or substrate 10-12 (100 mg) and freshly prepared diacetoxyiodoarene (5 equiv.) in MeOH (5 mL) was refluxed for 4-8 h. The reaction mixture was quenched with saturated NaCl (10 mL) and extracted with ethyl acetate (3 10 mL). The organic layers were combined, dried over MgSO₄, and concentrated under vacuum. The residue was purified by column chromatography on silica gel to afford the desired product.

Diacetoxyiodobenzene (4). Yield: 91%; white solid; m.p. 161–163 °C (lit. 161.2–162.2 °C). ¹H NMR (300 MHz, CDCl₃): δ 1.98 (6 H, s), 7.46 (2 H, d, J = 7.6 Hz), 7.58 (1 H, td, J = 7.6 Hz, J = 1.1 Hz), 6.07 (2 H, d, J = 7.6 Hz, J = 1.1 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 20.18 (q), 20.18 (q), 121.38 (s), 130.77 (d), 131.59 (d), 134.73 (s), 176.26 (s). IR (KBr, cm⁻¹): 3048, 2923, 1562, 1464, 1397, 1270, 1199, 882; MS-ES: m/z = 297 (M⁺); HRMS-ES: m/z [M⁺] calecd for C₁₀H₉INO: 296.9651; found: 296.9652.

3-Iodo-4-(p-tolyloxy)pyridine (8). Yield: 91%; colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 2.37 (3 H, s), 6.53 (1 H, d, J = 5.77 Hz), 6.97 (2 H, d, J = 9.52 Hz), 7.20 (2 H, d, J = 9.52 Hz), 8.25 (1 H, d, J = 5.77 Hz), 8.33 (1 H, s); ¹³C NMR (75 MHz, CDCl₃): δ 20.92 (q), 85.15 (s), 110.69 (d), 120.46 (d), 130.44 (d), 135.44 (s), 150.25 (d), 151.28 (s), 158.25 (d), 163.93 (s); IR (neat, cm⁻¹): 3034, 1567, 1504, 1462, 1271, 1201, 1016, 885; MS-ES: m/z = 311 (M⁺); HRMS-ES: m/z [M⁺] calecd for C₁₂H₁₀INO: 310.9807; found: 310.9799.

3-Iodo-4-(α-tolyloxy)pyridine (9). Yield: 95%; colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 2.16 (3 H, s), 6.04 (1 H, d, J = 5.49 Hz), 7.03 (1 H, d, J = 7.69 Hz), 7.19-7.32 (4 H, m), 8.28 (1 H, d, J = 7.77 Hz), 8.86 (1 H, s); ¹³C NMR (75 MHz, CDCl₃): δ 16.07 (q), 84.64 (s), 109.89 (d), 121.14 (d), 126.19 (d), 127.55 (d), 130.26 (s), 131.87 (d), 150.12 (d), 151.54 (s), 157.96 (d), 163.42 (s); IR (neat, cm⁻¹): 3035, 2360, 1563, 1464, 1271, 1181, 888; MS-ES: m/z = 311 (M⁺); HRMS-ES: m/z [M⁺] calecd for C₁₂H₁₀INO: 310.9807; found: 310.9791.

Methyl 3-iodo-4-(p-tolyloxy)benzoate (13). Yield: 85%; colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 2.36 (3 H, s), 3.90 (3 H, s), 7.62 (1 H, d, J = 8.52 Hz), 6.95 (2 H, d, J = 7.97 Hz), 7.19 (2 H, d, J = 7.97 Hz), 7.89 (1 H, dd, J = 8.52, 1.92 Hz), 8.52 (1 H, d, J = 1.92 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 20.91 (q), 52.26 (q), 86.48 (s), 115.82 (d), 119.80 (d), 128.85 (s), 130.47 (d), 134.49 (s), 141.25 (d), 152.91 (s), 161.12 (s), 165.13 (s); IR (neat, cm⁻¹): 2863, 1720, 1588, 1505, 1477, 1433, 1253; MS-ES: m/z = 368 (M⁺); HRMS-ES: m/z [M⁺] calecd for C₁₅H₁₃IO₄: 367.9909; found: 367.9909.

Methyl 5-iodo-2-methoxy-4-(p-tolyloxy)benzoate (14). Yield: 91%; white solid; m.p. 77-99 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.36 (3 H, s), 3.69 (3 H, s), 3.87 (3 H, s), 6.35 (1 H, s), 6.94 (2 H, d, J = 8.52 Hz), 7.19 (2 H, d, J = 8.52 Hz), 8.30 (1 H, s); ¹³C NMR (75 MHz, CDCl₃): δ 20.91 (q), 52.08 (q), 56.18 (q), 75.09 (s), 101.54 (d), 116.12 (s), 119.36 (d), 130.46 (d), 134.28 (s), 142.43 (d), 152.98 (s), 161.10 (s), 165.31 (s), 165.50 (s); IR (neat, cm⁻¹): 2948, 1687, 1588, 1505, 1438, 1276, 1103, 834; MS-ES: m/z = 398 (M⁺); HRMS-ES: m/z [M⁺] calecd for C₁₅H₁₃IO₄: 398.00015; found: 398.00010.

2-Iodo-4-nitro-1-(p-tolyloxy)benzene (15). Yield: 79%; colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 2.39 (3 H, s), 6.67 (1 H, d, J = 9.07 Hz), 6.98 (2 H, d, J = 8.52 Hz), 7.24 (2 H, d, J = 8.52 Hz), 8.10 (1 H, dd, J = 9.07, 2.75 Hz), 8.73 (1 H, d, J = 2.75 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 20.97 (q), 85.66 (s), 114.63 (d), 120.22 (d), 125.13 (d), 130.77 (d), 135.33 (d), 135.51 (s), 142.66 (s), 152.17 (s), 162.78 (s); IR (neat, cm⁻¹): 3093, 2923, 1576, 1518, 1465, 1324, 1260893; MS-ES: m/z = 355 (M⁺); HRMS-ES: m/z [M⁺] calecd for C₁₅H₁₃INO₂: 354.9706; found: 354.9713. 821

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Methyl 3-iodo-4-(o-tolyloxy)benzoate (16). Yield: 89%; colorless oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.19 (3 H, s), 3.90 (3 H, s), 6.54 (1H, d, $J=8.79$ Hz), 6.97 (1 H, d, $J=7.69$ Hz), 7.14-7.31 (3 H, m), 7.87 (1 H, d, $J=8.79$, 1.92 Hz), 8.54 (1 H, d, $J=1.92$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 16.25 (q), 52.25 (q), 85.67 (s), 114.38 (d), 120.56 (d), 125.38 (d), 125.54 (s), 127.38 (d), 130.10 (s), 131.15 (d), 131.74 (d), 141.30 (d), 152.90 (s), 160.57 (s); IR (neat, cm$^{-1}$): 2950, 2360, 1720, 1581, 1478, 1433, 1283, 1252, 1111; MS-ES: $m/z$ = 368 (M$^+$); HRMS-ES: $m/z$ [M]$^+$ calcd for C$_{15}$H$_{13}$IO$_3$: 367.9909; found: 367.9910.

Methyl 5-iodo-2-methoxy-4-(o-tolyloxy)benzoate (17). Yield: 86%; colorless oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.21 (3 H, s), 3.65 (3 H, s), 3.87 (3 H, s), 6.18 (1 H, s), 6.94 (1 H, d, $J=7.97$ Hz), 7.12-7.31 (3 H, m), 8.32 (1 H, s); 13C NMR (75 MHz, CDCl$_3$): $\delta$ 16.28 (q), 52.05 (q), 56.11 (q), 74.27 (s), 100.07 (d), 115.65 (s), 119.99 (d), 125.23 (d), 127.32 (d), 129.86 (s), 131.72 (d), 142.50 (d), 152.87 (s), 160.91 (s), 161.25 (s), 164.48 (s); IR (neat, cm$^{-1}$): 2949, 2360, 1731, 1592, 1488, 1244, 1093, 781; MS-ES: $m/z$ = 398 (M$^+$); HRMS-ES: $m/z$ [M]$^+$ calcd for C$_{16}$H$_{15}$IO$_4$: 398.0015; found: 398.0010.

2-iodo-4-nitro-1-(o-tolyloxy)benzene (18). Yield: 85%; colorless oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.17 (3 H, s), 6.54 (1 H, d, $J=9.07$ Hz), 7.01 (1 H, d, $J=7.69$ Hz), 7.19-7.34 (3 H, m), 8.09 (1 H, d, $J=9.07$, 2.75 Hz), 8.75 (1 H, d, $J=2.75$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 16.13 (q), 85.03 (s), 113.45 (d), 120.90 (d), 125.25 (d), 126.15 (d), 127.67 (d), 130.13 (s), 131.98 (d), 135.39 (d), 142.56 (s), 152.32 (s), 162.06 (s); IR (neat, cm$^{-1}$): 3093, 2359, 1574, 1518, 1462, 1341, 1258, 745; MS-ES: $m/z$ = 355 (M$^+$); HRMS-ES: $m/z$ [M]$^+$ calcd for C$_{13}$H$_9$IN$_2$O$_3$: 354.9705; found: 354.9713.

Declaration of conflicting interests
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