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High-Yielding One-Pot Synthesis of Diaryliodonium Triflates from Arenes and Iodine or Aryl Iodides†

Marcin Bielawski and Berit Olofsson*

Unsymmetric and symmetric diaryliodonium triflates are synthesized from both electron-deficient and electron-rich substrates in a fast, high yielding, and operationally simple protocol employing arenes and aryl iodides or iodine.

Hypervalent iodine compounds have recently received considerable attention as mild, non-toxic and selective reagents in organic synthesis.1, 2 Iodine(III) reagents with two heteroatom ligands, e.g. (diacetoxyiodo)benzene and iodosylbenzene, are successfully employed in oxidations of alcohols, akenes and α-oxidations of carbonyl compounds.3 The properties of iodine(III) reagents with two carbon ligands resemble those of metals such as Hg, Pb and Pd, allowing for reaction pathways similar to metal-catalyzed reactions while avoiding the drawbacks of cost, toxicity and threshold values in pharmaceutical products.4 Diaryliodonium salts are the most studied compounds in this class; they are versatile electrophiles in α-arylation of carbonyl compounds4, 5 and metal-catalyzed cross-couplings,6 and are frequently employed as photo initiators in polymerizations.7 Synthetic routes to diaryliodonium salts typically involve 2-3 steps, with initial oxidation of an aryl iodide to iodine(III) followed by ligand exchange with an arene to the diaryliodonium salt.8 Preformed inorganic iodine(III) reagents, such as iodosyl fluorosulfate, have been employed to shorten the route.9 These reagents are, however, unstable and not commercially available. Reported reactions with oxidation and ligand exchange in the same pot suffer from narrow substrate scope10, 11 or long reaction times,11 need excess reagents12 or employ toxic chromium reagents.13 In many cases a subsequent anion exchange step is necessary, as the anion influences both the solubility and reactivity of the iodonium salt. Non-nucleophilic anions, such as triflate or tetrafluoroborate, have proven superior to halide anions in many applications.6, 14

The lack of general and efficient methods for the synthesis of diaryliodonium salts is cumbersome, and clearly limits their scope as environmentally benign reagents in organic chemistry.15 The development of an operationally simple protocol with broad substrate scope would greatly facilitate the application of these efficient, non-toxic arylation agents. Herein we present our preliminary results on a fast, high-yielding, one-pot synthesis of the title compounds.

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† Electronic Supplementary Information (ESI) available: [Synthetic procedures, analytical data and NMR spectra for salts 3]. See http://dx.doi.org/10.1039/b000000x/
To determine the generality of this novel one-pot reaction, it was applied to the synthesis of various diaryliodonium salts 3 from aryl iodides 1 and arenes 2 (Table 2). Most previous protocols have been restricted to the synthesis of either electron-rich or electron-deficient iodonium salts, as the reactivity of the arenes varies dramatically with the electronic properties.10 Aryl iodides 1 and arenes 2 were thus selected to investigate the formation of both electron-rich and electron-deficient salts, including heteroaryl salts. The use of iodobenzene both as aryl iodide (1a) and arene (2b) yielded 4-iodophenyl(phenyl)iodonium trflate (3b) as a single regiosomer (entry 2). Likewise, the reaction of 1a with toluene (2e) was smooth, and unsymmetrical salt 3e could be isolated in good yield (entry 3). The electron-rich arenes anisole (2d) and thiophene (2e) were, as expected, very reactive under the standard conditions. By decreasing the temperature to -78 °C, salts 3d and 3e could be obtained in excellent yields (entries 4, 5). Heteroaryl salt 3e has previously been synthesized in several steps via the corresponding stannane,18 which further illuminates the efficiency and environmental friendliness of our procedure.

Unsymmetrical salt 3c could also be formed by the reaction of 4-iodotoluene (1b) with benzene, as shown in entry 6. Aryl iodide 1b was also employed to form the symmetrically substituted bis(4-methylphenyl)iodonium salt 3f (entry 7). The reason for the moderate yield of 3f is unclear, as 2-iodotoluene (1e) delivered salts 3g and 3h in high yields upon reaction with benzene and toluene, respectively (entries 8, 9).

Generally, the synthesis of electron-rich salts was easier from iodobenzene and a substituted arene than from the “reverse” reaction of a substituted aryl iodide with benzene (compare entries 3 and 6). 4-idoanisole and 2-iodothiophene both participated in the reaction with benzene, but salts 3d,e were contaminated with unidentified byproducts.

### Table 2 Synthesis of substituted diaryliodonium salts 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar1-I + Ar2-H</th>
<th>mCPBA, TfOH, CH2Cl2</th>
<th>Ar1-I+Ar2-OtF</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a (PhI)</td>
<td>2a (PhH)</td>
<td>3a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>2a (PhH)</td>
<td>1a (PhI)</td>
<td>3a</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>1a (PhI)</td>
<td>2c (PhMe)</td>
<td>3c</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>1a (PhI)</td>
<td>2d (PhOMe)</td>
<td>3d</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>1a (PhI)</td>
<td>2e (thiophene)</td>
<td>3e</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>1b (4-MePhI)</td>
<td>2a (PhH)</td>
<td>3c</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>1b (4-MePhI)</td>
<td>2c (PhMe)</td>
<td>3h</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>1c (2-MePhI)</td>
<td>2a (PhH)</td>
<td>3g</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>1c (2-MePhI)</td>
<td>2c (PhMe)</td>
<td>3h</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>1d (4-NO2PhI)</td>
<td>2a (PhH)</td>
<td>3i</td>
<td>85</td>
</tr>
<tr>
<td>11</td>
<td>1e (2-chloro-5-iodopyridine)</td>
<td>2a (PhH)</td>
<td>3j</td>
<td>60</td>
</tr>
<tr>
<td>12</td>
<td>1e (2-chloro-5-iodopyridine)</td>
<td>2d (PhOMe)</td>
<td>3k</td>
<td>53</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 (1.0 equiv), 2 (1.0 equiv), mCPBA (1.1 equiv) and TfOH (2.0 equiv) in CH2Cl2, see Table 1 and ESI for details. Formed with complete regioselectivity. Isolated yield. 3.0 equiv of TfOH was used.

### Table 3 Direct synthesis of salts 3 from arenes and iodine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar-H + I2</th>
<th>mCPBA, TfOH, CH2Cl2</th>
<th>Ar-I+Ar-OtF</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a (PhH)</td>
<td>1a (PhI)</td>
<td>3a</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>2a (PhH)</td>
<td>1a (PhI)</td>
<td>3a</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>2e (PhMe)</td>
<td>2c (PhMe)</td>
<td>3f ratio 3:1</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>2e (PhMe)</td>
<td>2c (PhMe)</td>
<td>3h</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>2f (PhCl)</td>
<td>80</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2g (4-nitro-m-xylene)</td>
<td>19 h</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 (1.0 equiv), 2 (4-10 equiv), mCPBA (4 equiv) and TfOH (4 equiv) in CH2Cl2, see ESI for details. Formed with complete regioselectivity apart from entry 3. Isolated yield.

Electron-deficient iodonium salts were, on the other hand, best made from the corresponding electron-deficient aryl iodide with benzene as the arene. This is exemplified by the reaction of iodo-4-nitrobenzene (1d) with benzene, which delivered salt 3i in 85% yield (entry 10). The reverse reaction with iodobenzene and nitrobenzene was sluggish and gave salt 3b as a byproduct, the result of competing reaction pathways of 1a between oxidation and reaction with the formed iodonium(III) intermediate.

The generality of the developed protocol is especially evident from the successful reaction of 2-chloro-5-iodopyridine (1e) with benzene or anisole to give salts 3j and 3k, respectively (entries 11, 12). Iodonium salts containing this aryl moiety have recently been used in an efficient total synthesis of (-)-Epibatidine.4 Pyridyl iodonium salts have previously been inaccessible by acidic routes, and salt 3j was formerly obtained by a basic, atom-inefficient two-step procedure 19 in moderate yield, which was still inadequate for the preparation of salt 3k. The formation of iodonium salts 3 from substituted arenes 2 was in all cases highly regioselective, yielding salts 3b-d,f,h,k with complete para-selectivity. Likewise, the reaction of 1a with thiophene (2e) afforded only 2-substituted 3e.

Having succeeded in the direct synthesis of diaryliodonium salts from aryl iodides, we looked into possible extensions of this reaction. As aryl iodides are readily available but often expensive, we argued that it might be possible to form the aryl iodide in situ.21 Hence, the reaction of benzene (2a) and iodine with mCPBA and TfOH was studied, and indeed delivered iodonium salt 3a in high...
yield in only 10 min at 80 °C or 22 hours at room temperature (Table 3, entries 1, 2).

This efficient synthesis of diaryliodonium salts was subsequently applied to other arenes. Toluene (2c) yielded a mixture of salts 3h and 3f with 3:1 regioselectivity favouring ortho-iodination (entry 3). The regioselectivity was higher at lower conversions, and pure 3h was obtained after one hour at 0 °C (entry 4). Chlorobenzene (2f) gave symmetric salt 3i with complete para-selectivity (entry 5). Even highly functionalized, deactivated arene 2g participated in the reaction to give salt 3m (entry 6). As this one-pot reaction involves several consecutive steps and many possible sources of byproducts, it is surprising that salts 3 are easily isolated in moderate to good yields.

In conclusion, a facile, direct synthesis of diaryliodonium triflates from the corresponding aryl iodide and arene has been realized. The method is fast, high yielding, operationally simple and has a large substrate scope. Electron-rich salts are conveniently synthesized from iodobenzene and the corresponding arene, and electron-deficient salts are formed by the reaction of a substituted aryl iodide with benzene. The protocol can be extended to the synthesis of iodonium salts directly from iodine and arenes, conveniently circumventing the need for aryl iodides. A thorough investigation of the scope and limitations of this reaction is underway, and will be reported separately.

This work was financially supported by the Department of Organic Chemistry at Stockholm University.

Notes and references

15. E.g. Sanford and coworkers needed four different methods to produce the iodonium salts used in their novel arylation protocol, see ref. 6.
17. Commercial mCPBA was used without drying. The exact amount of oxidant was determined by titration, see ESL.
20. For the synthesis and use of 3-j, see B. Olofsson and V. K. Aggarwal, Proc. 2nd Int. Conf. on Hypervalent Iodine, 2006, 47-50. The attempts to synthesize salt 3k are unpublished.
21. The oxidation of iodine and arenes to aryl iodides or (diacetoxyiodo)benzene is known; see M. D. Hossain and T. Kitamura, Tetrahedron Lett., 2006, 47, 7889-7891 and references therein. After the completion of this work Kitamura reported a procedure for the direct synthesis of diaryliodonium salts from iodine, requiring heating at 40 °C for 72 h and a sequential anion exchange step (12 h), see reference 11.
Unsymmetric and symmetric diaryliodonium triflates are synthesized from both electron-deficient and electron-rich substrates in a fast, high yielding, and operationally simple protocol employing arenes and aryl iodides or iodine.