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Matsuoka, Keitaro; Komami, Narumi; Kojima, Masahiro; Yoshino, Tatsuhiko; Matsunaga, Shigeki

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Synthesis of Heteroaryl Iodanes(III) via ipso-Substitution Reactions Using Iodine Triacetate Assisted by HFIP


[a] K. Matsuoka, N. Komami, Dr. M. Kojima, Dr. T. Yoshino, Prof. Dr. S. Matsunaga
Faculty of Pharmaceutical Sciences
Hokkaido University
Kita-ku, Sapporo 060-0812 (Japan)
E-mail: tyoshino@pharm.hokudai.ac.jp
smatsuna@pharm.hokudai.ac.jp

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Abstract: The synthesis of monoaryl-I$_3$-iodanes generally requires the oxidation of iodoarenes, but the functional group compatibility is often problematic when using oxidizable substrates such as heteroaromatic compounds. Although electrophilic aromatic substitution or ipso-substitution reactions using iodine tricarboxylates have been studied as an alternative synthetic route to dicarboxyldiiodanes, several common heteroaromatic substrates such as indoles, quinolines, (benzo)furans, and (benzo)thiophenes have not been investigated to date. Here, we report that ipso-substitution reactions of heteroaromatic stannanes using I(OAc)$_3$ in the presence of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) effectively provide diacetoxydiiodoarenes, which can be converted into the corresponding iodonium ylides or be directly used in an one-pot iodoarylation reaction.

Monoaryl-I$_3$-iodanes, i.e., hypervalent iodine(III) species bearing one aromatic substituent (ArI$_3$), have found widespread applications in organic synthesis. These compounds can serve as safe and less toxic oxidants and/or terminal co-oxidants in most reported transformations, in which the aryl group is not involved in the products. However, an investigation into monoaryl-I$_3$-iodanes as electrophilic aryl group donors has disclosed a unique sigmatropic rearrangement reaction pathway leading to the introduction of a 2-idoaryl group in nucleophiles without cleavage of the carbon–iodine bond. In addition, monoaryl iodonium ylides with a Meldrum’s acid backbone, which are readily obtained from monoaryl-I$_3$-iodanes, are efficient precursors for $^{18}$F positron emission tomography (PET) probes. In order to further extend their applications as arylating agents, the development of broadly applicable synthetic routes to monoaryl-I$_3$-iodanes is of great importance.

The oxidation of aryl iodides is the most straightforward and thus well-documented protocol providing access to monoaryl-I$_3$-iodanes (Scheme 1a).[7-13] The functional group compatibility is, however, of great concern when applied to oxidizable substrates. To avoid an additional oxidation step, the direct introduction of a trivalent iodine moiety (-I$_3$) in aromatic rings using [I(OOCOCF$_3$)$_3$]$_2$(OCCOF$_3$)(NO) (ITT) or I(OAc)$_2$ has been investigated (Scheme 1b).[14-16] Electrophilic aromatic substitution reactions using ITT were reported by Maletina in 1974[14] and by Kurosawa in 1987.[15] A recent report by Wirth demonstrated the potential of such electrophilic substitution reactions with iodine tricarboxylates as an alternative route to monoaryl-I$_3$-iodanes, thus circumventing said additional oxidation step.[16]

We have reported that arylermanes, arylstannanes, and arylsilanes undergo selective ipso-substitution reactions with ITT to afford bis(trifluoroacetoxy)iodoarenes under mild reaction conditions (Scheme 1c).[17] Such ipso-substitution reactions with stable organometallic precursors enable reactions at low temperatures, thus improving the functional-group compatibility. Although several oxidizable functional groups were tolerated in our previous protocol, we encountered difficulties in expanding the scope to some common heteroaromatic compounds such as indoles and quinolines. We speculated that such limitations may be due to the high electrophilicity of ITT and the instability of the resulting bis(trifluoroacetoxy)iodoarenes. This assumption prompted us to investigate similar ipso-substitution reactions using the less electrophilic I(OAc)$_3$, which should afford more stable diacetoxyiodoarenes. Herein, we report selective ipso-substitution reactions of heteroarylstannanes using I(OAc)$_3$ to afford diacetoxyiodoarenes, which can be converted into the corresponding iodonium ylides or be directly used for an one-pot iodoarylation reaction.

(a) Oxidation of aryl iodides

(b) Electrophilic aromatic substitution using iodine tricarboxylates

(c) Our previous work: ipso-substitution using ITT

(d) This work: ipso-substitution using I(OAc)$_3$

Scheme 1. Synthetic routes to monoaryl-I$_3$-iodanes.
Prior to investigating the aforementioned challenging heteroaromatic substrates, we optimized the reaction conditions using tributy[4-chlorophenyl]stannane (1a) as a model substrate (Table 1). We decided to use arylstannanes expecting that their high reactivity in ipso-substitution reactions\[^{20}\] would compensate for the attenuated electrophilicity of I(OAc)\(_3\) compared to that of ITT. We initially treated 1a with I(OAc)\(_3\) in CH\(_2\)Cl\(_2\) at 0 °C, followed by a treatment with a basic aqueous solution of Meldrum’s acid derivative 2 to convert the product into 3a for analysis. However, 3a was obtained only in 19% yield together with large amounts of unreacted/recovered 1a (entry 1). To improve the reactivity, we subsequently screened several acidic additives to activate I(OAc)\(_3\) (entries 2–8). Although the addition of strong acids such as Tf\(_2\)O, TMSOTf, BF\(_3\)OEt\(_2\), and B(C\(_\ell\)F\(_3\))\(_3\) resulted in complete consumption of 1a, 3a was not obtained (entries 2–5). In these cases, an ESI-MS analysis of the crude mixtures indicated the formation of the corresponding diaryliodonium salt, probably due to a further ipso-substitution reaction of 1a with the resulting diacetoxiyodoarene promoted by such strong acids.\[^{19–21}\] On the other hand, mild acidic additives were effective to selectively promote a single ipso-substitution to afford 3a in moderate to good yield (entries 6–8). Accordingly, we selected 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)\[^{22}\] as the optimal additive (entry 8) for further examination upon considering both the reactivity and the functional group compatibility. The ipso-substitution reaction proceeded in moderate yield even at –20 °C in the presence of HFIP (entry 9). Increasing the amount of HFIP improved the yield (entries 10 and 11) and 1a was fully converted in the presence of a large excess of HFIP (entry 11). Under these optimized conditions, iodonium ylide 3a was readily isolated in 73% yield by a single recrystallization of the crude material without chromatographic purification.

Subsequently, we investigated the ipso-substitution of indolylstannane 1b (Scheme 2). Treatment of 1b with I(OAc)\(_3\) and HFIP at –40 °C successfully provided the corresponding diacetoxiyodoindole intermediate, which was then converted into iodonium ylide 3b in 88% yield. In addition, the in-situ-generated diacetoxiyodoindole was subjected to a cyanomethylation reaction using 4, following the report by Wang and Peng.\[^{29}\] Even though the use of TMSOTf, which was used in the original report, led to a complex mixture, we found that the use of TFAA as the activator facilitated the desired reaction, providing an isomeric mixture of 5b and 5b’ in moderate yield and selectivity.

We also examined ipso-substitution reactions of indole derivatives 1b and 6b using ITT instead of I(OAc)\(_3\) (Table 2). Under most reaction conditions, only complex mixtures were obtained, which we tentatively attributed to undesired electrophilic aromatic substitution or oxidation reactions at the C2 or C3 position of the indole (entries 1–6). When we used indolylstannane 1b as the substrate and EtCN as the solvent, 3b was obtained in moderate yield, but many unidentified byproducts were also formed. These results demonstrate the limitations of using ITT in combination with oxidizable heteroaromatic substrates.

![Scheme 2](image-url)

**Table 1.** Optimization of the ipso-Substitution of Arylstannane 1a Using I(OAc)\(_3\)^\(\text{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (equiv)</th>
<th>Temp. [°C]</th>
<th>Yield(^\text{[c]}) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>Tf(_2)O (1.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>TMSOTf (1.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>BF(_3)OEt(_2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>B(C(_\ell)F(_3))(_3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>TFA (1.3)</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>TFAA (1.3)</td>
<td>0</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>HFIP (1.3)</td>
<td>–20</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>HFIP (3.0)</td>
<td>–20</td>
<td>77</td>
</tr>
<tr>
<td>10</td>
<td>HFIP (10)</td>
<td>–20</td>
<td>97 (73)^(\text{[b]})</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1) 1a (0.050 mmol), I(OAc)\(_3\) (0.060 mmol), and the corresponding additive in CH\(_2\)Cl\(_2\) (0.50 mL) for 2 h at the indicated temperature; 2) 2 (0.10 mmol), aq. Na\(_2\)CO\(_3\) (0.30 mL; 10% w/v) for 1 h at room temperature. [b] Determined by \(^1\)H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as the internal standard. [c] Isolated yield after recrystallization from CH\(_2\)Cl\(_2\)/hexane on a 0.30 mmol scale. TFA = trifluoroacetic acid. TFAA = trifluoroacetic anhydride.
Applying the optimized reaction conditions using I(OAc)₃ to a variety of (hetero)arylstananes (1) provided the corresponding (hetero)aryl iodonium ylides (3) in moderate to excellent yield (Scheme 3). It is noteworthy that iodonium ylides 3, which are efficient precursors for [18F] PET probes,[5] were in most cases readily isolated by a direct recrystallization of the crude reaction mixtures. In addition to electron-rich nitrogen-containing heterocyclic substrates (1b,d,e), electron-deficient quinolinylstananes (1f,g) also underwent this ipso-substitution in good yield upon increasing the reaction temperature to 0 °C (3f,g). We also investigated furan-, thiophene-, benzofuran-, and benzothiophene-derived stannanes, all of which efficiently provided the corresponding iodonium ylides (3h–n) at −20 or −40 °C.

In summary, ipso-substitution reactions of various electron-rich and electron-deficient heteroaromatic arylstananes using I(OAc)₃ in the presence of HFIP effectively generates the corresponding diacetoxyiodoarenes in moderate to excellent yield. The present method enables the otherwise difficult synthesis of hypervalent iodine(III) compounds, thus facilitating the investigation of the fundamental properties, reactivity, and synthetic applications of such species.

**Table 2. Control Experiments: ipso-Substitution of Indole Derivatives Using ITT.[a]**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (M)</th>
<th>Solvent</th>
<th>Temp. [°C]</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6b (GeMe₃)</td>
<td>CH₂Cl₂</td>
<td>−20</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>6b (GeMe₃)</td>
<td>EtCN</td>
<td>−20</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>6b (GeMe₃)</td>
<td>CH₂Cl₂</td>
<td>−40</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>6b (GeMe₃)</td>
<td>EtCN</td>
<td>−40</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>1b (SnBu₃)</td>
<td>CH₂Cl₂</td>
<td>−40</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>1b (SnBu₃)</td>
<td>EtCN</td>
<td>−40</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1) 1b or 6b (0.050 mmol), I(OOCF₂),[OCOCF₃](NO) (0.030 mmol), and the corresponding additive in the indicated solvent (0.50 mL) for 2 h at the indicated temperature; 2) 2 (0.05 mmol), aq. Na₂CO₃ (0.15 mL; 10% w/v) for 1 h at room temperature. [b] Determined by ¹H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as the internal standard.

![Scheme 3. Substrate scope of the ipso-substitution reactions of (hetero)arylstananes 1 using I(OAc)₃. Reaction conditions: 1) 1 (0.30 mmol), I(OAc)₃ (0.36 mmol), and HFIP (3.0 mmol) in CH₂Cl₂ (3.0 mL) for 2 h at the indicated temperature; 2) 2 (0.60 mmol), aq. Na₂CO₃ (10% w/v, 1.8 mL) for 1 h at room temperature. The isolated yield after a recrystallization is shown unless otherwise stated. [a] Isolated yield after column chromatography on silica gel. [b] The reaction was carried out using I(OAc)₃ (0.30 mmol, 1.0 equiv).](image)

**Acknowledgements**

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**Keywords:** hypervalent iodine • iodonium ylide • ipso-substitution • iodine triacetate • stannane

**References:**


For oxidation reactions with Oxone, see: A. A. Zagulyaeva, M. S. Yusubov, V. V. Zhakhvin, J. Org. Chem. 2010, 75, 2119-2122.


Heteroaryl iodonanes(III) were prepared via ipso-substitution reactions of heteroarylstannanes using $\text{I(OAc)}_3$ in the presence of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). Both electron-rich and electron-deficient heteroarylstannanes were applicable substrates, and the corresponding iodonium ylides were synthesized in a one-pot fashion. The present method thus enables the otherwise difficult synthesis of hypervalent iodine(III) compounds.