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Synthesis of Quaternary Aryl Phosphonium Salts: Photoredox-Mediated Phosphine Arylation

A. F. Fearnley, J. An, M. Jackson, P. Lindovska and R.M. Denton*

We report a synthesis method for the construction of quaternary aryl phosphonium salts at ambient temperature. The regiospecific reaction involves the coupling of phosphines with aryl radicals derived from diaryliodonium salts under photoredox conditions.

Quaternary phosphonium salts are a fundamentally important class of organophosphorus compounds, which have been applied as synthesis reagents\(^i\) phase-transfer catalysts,\(^ii\) ionic liquids,\(^iii\) anti-cancer agents\(^iv\) as well as in drug delivery.\(^v\) More recently, phosphonium salts have begun to be explored as Lewis acids\(^vi\) as a result of their low-lying \(\sigma^*\) orbitals, opening up an exciting new class of organocatalysts.

Despite this diverse range of applications methods for the construction of aryl-substituted phosphonium salts are limited. Transition metal-mediated couplings of phosphines\(^vii\) and aryl halides, such as the palladium-catalysed reactions reported by Charette and co-workers (Scheme 1A),\(^viii\)\(^ix\)\(^x\) known but typically take place at high temperatures. An important alternative method was recently reported by Juge and co-workers (Scheme 1B) and involves the interception of \textit{in situ}-generated arynes with phosphines at room temperature.\(^xi\) This method is limited somewhat by the availability of 2-(trimethylsilyl)aryl triflates and poor the regioselectivities obtained during the coupling of unsymmetrical arynes with phosphines.

With these limitations in mind we sought a method that could be conducted at ambient temperature and was regiospecific with respect to carbon-phosphorus bond formation. We reasoned that the arylation of tervalent organophosphorus compounds with iodonium salts,\(^xii\) first reported by Reutov and co-workers in 1965\(^xiii\) and subsequently revisited by Kampmeier,\(^xiv\) could meet the above criteria. The latter non-preparative mechanistic study corroborated a redox radical chain process involving aryl and phosphoryl radicals\(^xv\) and, despite being overlooked since,\(^xvi\) suggested that a synthetically useful phosphine arylation reaction could be developed. Herein we report a photoredox-initiated arylation reaction between aryliodonium salts and phosphines under ambient reaction conditions (Scheme 1C).

(A) Transition metal-catalysed coupling

\[
\begin{align*}
\text{Ar} - X & \quad \xrightarrow{\text{Pd} \text{(dba)}_3 \text{ (1 mol\%)}} \quad \text{Ar} - \Theta \cdot \text{X} \\
R_1^1 \cdot P \cdot R_2^2 \cdot R_3^3 & \quad \xrightarrow{\text{xylenes, 125 } ^\circ \text{C}} \\
& \quad R_1^1 \cdot R_2^2 \cdot R_3^3
\end{align*}
\]

(B) Arylation via aryne intermediates

\[
\begin{align*}
\text{Ar} - \Theta & \quad \xrightarrow{\text{MeCN, room temp.}} \quad \text{Ar} - \Theta \\
R_1^1 \cdot P \cdot R_2^2 \cdot R_3^3 & \quad \xrightarrow{\text{TMS, OTf}} \\
& \quad R_1^1 \cdot R_2^2 \cdot R_3^3 \cdot \text{OTf}
\end{align*}
\]

(C) THIS WORK: radical arylation

\[
\begin{align*}
\text{Ar} - \Theta & \quad \xrightarrow{\text{visible light}} \quad \text{Ar} - \Theta \\
R_1^1 \cdot P \cdot R_2^2 \cdot R_3^3 & \quad \xrightarrow{\text{Ru(bpy)}_3 \text{Cl}_2 \cdot \text{H}_2\text{O}} \\
& \quad \text{MeCN, room temp.}
\end{align*}
\]

Scheme 1.

We began by establishing a new method for the initiation of the putative radical chain at ambient temperature under photoredox conditions.\(^xvii\) To this end the combination of visible light with \(\text{Ru(bpy)}_3 \text{Cl}_2\) was explored (Table 1). Gratifyingly, the photo-redox initiated arylation of triphenylphosphine with diphenyliodonium triflate (entry 1) gave the corresponding phosphonium salt in good conversion. Next, the analogous reaction without the 10W lamp was investigated (entry 2) and gave a much-reduced 23% conversion. The arylation reaction did proceed in the presence of visible light without \(\text{Ru(bpy)}_3 \text{Cl}_2\), albeit more slowly (12% conversion after 20 mins, entry 3).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Initiator</th>
<th>Time (min)</th>
<th>Conversion a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 W lamp Ru(bpy)Cl₂, 2 mol%</td>
<td>20</td>
<td>19 10 73</td>
</tr>
<tr>
<td>2</td>
<td>Ru(bpy)Cl₂, 2 mol%</td>
<td>20</td>
<td>71 6 23</td>
</tr>
<tr>
<td>3</td>
<td>10 W lamp</td>
<td>20</td>
<td>84 6 12</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>120</td>
<td>100 0 0</td>
</tr>
<tr>
<td>5</td>
<td>AIBN (80 °C), 10 mol%</td>
<td>240</td>
<td>0 50 50</td>
</tr>
</tbody>
</table>

\[ ^{a}\text{Determined via } ^{31} \text{P NMR analysis of the crude reaction mixture.}\]

Finally, in the absence of both ruthenium and visible light (entry 4) no conversion to phosphonium salt was obtained after 120 minutes. These experiments demonstrate that Ru(bpy)₃Cl₂ in combination with visible light from a 10 W lamp serve as an effective radical initiator in this system at ambient temperature. For comparison initiation using AIBN proved to be less efficient (entry 5) giving 23% conversion at 80 °C after two hours. Having established that the combination of Ru(bpy)₃Cl₂ and visible light was effective for initiating a radical-based coupling reaction we proceeded to examine the scope of this room temperature arylation protocol.

We began by arylating a range of triarylphosphines with diphenyliodonium triflate (Table 2, entries 1,3,4,5 and 6) to afford the corresponding phosphonium salts 2 in moderate to excellent isolated yield following flash chromatography and recrystallization. The arylation of methyldiphenylphosphine (entry 2) was also efficient.

Next we sought to prepare further phosphonium salts bearing functional groups that would facilitate further transformations after arylation. To this end we prepared two chlorophenyl(mesityl)iodonium triflates and carried out arylation reactions with a range of phosphines (entries 7-11). The phosphonium salt products were obtained in good to moderate yields and are suitable for further functionalization via cross coupling. In each case selective transfer of the chlorophenyl group over the mesityl group was observed.

In summary the arylation protocol provides access to a range of functionalised aryl phosphonium salts under ambient conditions.
Table 2. Scope of the arylation reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>2h</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>2i</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>2j</td>
<td>57</td>
</tr>
<tr>
<td>11</td>
<td>2k</td>
<td>46</td>
</tr>
</tbody>
</table>

\[ \text{Ru(bipy)}_2\text{Cl}_2\cdot6\text{H}_2\text{O} 2 \text{ mol\%} \rightarrow \text{Ar} \begin{array}{c} \text{P} \\ \text{OTf} \end{array} \]

\[ \begin{array}{c} \text{R}_1 \\ \text{R}_2 \\ \text{R}_3 \end{array} \begin{array}{c} 10 \text{ W lamp, MeCN, room temp.} \\ \text{2 mol\%} \end{array} \]

Typical procedure: iodonium salt (1.0 equiv, 0.7-0.8 mmol), phosphine (1.5 equiv) and Ru(bipy)_2Cl_2·6H_2O [10 mol%]. Yields are for isolated phosphonium salts following normal phase flash chromatography and recrystallisation.
We speculate that this arylation proceeds through a charge transfer complex (Scheme 1B) than the radical chain process (Scheme 1C). 3 minutes resulted in 26% conversion. This suggests that the arylation process is weighted more towards and triethylamine.

diphenylityoxidative quenching of excited ruthenium(II) by the iodonium salt. In a third experiment (Scheme 2C) from the reaction of the intermediate phosphoniumyl radical cation with water. trapping of phenyl radicals, as is the production of increased amounts of triphenylphosphine oxide (16% compared to 73% under standard conditions, entry 1 Table 1). This is consistent with the pathways depicted in Scheme 1A. Finally, an arylation reaction in which irradiation was stopped after 3 minutes resulted in 26% conversion. This suggests that the arylation process is weighted more towards Scheme 1B than the radical chain process (Scheme 1C).

The reaction also proceeds in the presence of visible light but absence of Ru(bipy)$_3$ (Table 1, entry 3). We speculate that this arylation proceeds through a charge transfer complex (Scheme 1D) from which...
electron transfer from phosphine to iodonium salt may occur in the presence of visible light to provide the phosphoniumyl radical cation and phenyl radical.

In conclusion we have developed synthesis method for the construction of aryl-substituted phosphonium salts under mild conditions. This protocol opens up a valuable new route to functionalised aryl phosphonium salts and demonstrates the utility of photoredox-mediated arylation reactions in the area of organophosphorus chemistry.

Notes and references

We are grateful to Dr. Mick Cooper, Graham Coxhill, Shazad Aslam and Kevin Butler for analytical support.


12 This mechanistic study involved two substrates, namely, triphenylphosphine and trimethylphosphite. The reactions were non-preparative and conducted in NMR tubes.


Given the proximity of the lamp to the reaction vessel the internal temperature was monitored and found to
be 32 °C. A further 1 h control experiment between Ph₃P and Ph₃OTf at 32 °C resulted in the formation of Ph₃PO
(6 %) and Ph₂POTf (3%) with 92% of Ph₃P remaining.

The selective transfer of electron deficient aryl groups over the relatively electron rich mesityl group has been
observed previously non-catalysed nucleophilic arylation reactions, see (a) J. Malmgren, S, Santoro, N, Jalalian, F.
2015, 80, 6456. We observed no arylation between triphenylphosphine and 4-methoxyphenyl(mesityl)iodonium triflate
under the reaction conditions depicted in Table 2.


For recent work involving phoshonium radical cations, see K.D. Reichl, D.H. Ess, and A.T. Radosевич, J. Am.

For electrochemical generation of the trimesityl phosphoniumyl radical and subsequent reaction with water to
afford the corresponding phosphine oxide, see: B. Merzougui, Y. Berchadsky and P. Tordo, G. Gronchi,

We are grateful to a reviewer for suggesting this experiment.

There are several other methods for the generation of aryl radicals under photoredox conditions, for example
from diazonium salts, see (a) H. Cano-yelo and A. Deronzier, J. Chem. Soc., Perkin Trans. 2, 1984, 16, 1093; (b) H.
Cano-yelo and A. Deronzier, Tetrahedron Lett. 1984, 25, 5517; (c) D. Kalyani, K.B. McMurtrey, S.R. Neufeldt and
M.S. Sanford, J. Am. Chem. Soc., 2011, 133, 18566. It is likely that further arylation reactions of tervalent
phosphorus compounds will be developed along these lines.