One-Pot Sulfonamide Synthesis Exploiting the Palladium-Catalyzed Sulfination of Aryl Iodides

Emmanuel Ferrer Flegeau
Jack M. Harrison
Michael C. Willis*

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK
michael.willis@chem.ox.ac.uk

Dedicated, with best wishes, to Professor Steven Ley on the occasion of his 70th birthday

Abstract Aryl ammonium sulfinates, conveniently prepared from aryl iodides and the sulfur dioxide surrogate DABSO, under the action of a palladium(0) catalyst, are transformed in a one-pot process to a variety of functionalized sulfonamides. The sulfinate to sulfonamide transformation is achieved by simple treatment with an aqueous solution of the relevant amine and sodium hypochlorite (bleach). A broad range of amines, including anilines, and amino acid derivatives, are combined efficiently with a variety of aryl iodides, leading to sulfonamides in high yields.

Key words sulfonamides, palladium catalysis, sulfinates, amines, aryl halides

Some of the features that contribute to sulfonamide groups finding wide application in pharmaceuticals and agrochemicals include their chemical and metabolic stability, three-dimensional structure, polarity, and connectivity. These properties have resulted in sulfonamide-containing molecules being developed as treatments for a broad range of indications (Figure 1).

Sulfonyl chlorides are most often prepared from the electrophilic sulfonylation of an arene, using either [HSO3]+ or [ClSO2]+ synthons as the electrophile. Again, these are well-established reactions, but the products accessible can be limited by the inherent characteristics of aromatic electrophilic substitution reactions, in that only certain substrates are sufficiently reactive to undergo the reactions, and only certain substitution patterns are straightforward to achieve. An alternative approach relies on the preparation of an aryl thiol, followed by exhaustive oxidation of the thiol to the corresponding sulfonyl chloride

Figure 1 Bioactive sulfonamides

Received: 10.09.2015
Accepted: 25.09.2015
Published online: 13.10.2015

License terms: © Georg Thieme Verlag Stuttgart · New York — Synlett 2016, 27, 101–105
have shown that it is possible to access a wide range of aryl surrogates (DABCO)(SO2)2,7 DABSO (Scheme 1, a).8 Organo-preformed organometallic reagent and the sulfur dioxide nates can be readily obtained from the combination of a lytically generating reactive organometallic intermediates from benign substrates such as aryl halides and then catalytic sulfinate formation in isopropanol and then adding an aqueous solution of morpholine and sodium hypochlorite directly to this allowed the target sulfonamide 3a to be isolated in 90% yield. Experiments that removed the isopropyl alcohol after the first step, and then added a second solvent with the amine, were uniformly less successful. For example, using only water for the second step resulted in <5% of the sulfonamide, while employing CH2Cl2 delivered the sulfonamide in 73% yield.

We next explored the variation that was possible for the aryl iodide substrate, using morpholine as the constant amine component (Table 1). A variety of neutral and electron-donating substituents performed well, with ortho, meta, and para substitution all possible (entries 1–5). The successful inclusion of the para-SMe derivative is notable (en-
try 5), as the preparation of products featuring S functionality at differing oxidation levels can be challenging using traditional methods.

**Table 1** Scope of the Aryl Iodide Component in One-Pot Sulfonamide Formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arene</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeI</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>MeI</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>MeI</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>MeO</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>MeS</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>HOI</td>
<td>57</td>
</tr>
<tr>
<td>7</td>
<td>ClI</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>BrI</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>FCI</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>MeO</td>
<td>82</td>
</tr>
<tr>
<td>11</td>
<td>NC</td>
<td>75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arene</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Me</td>
<td>60</td>
</tr>
<tr>
<td>13</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

* Reaction conditions: Pd(OAc)₂ (5 mol%), PAd₂Bu (7.5 mol%), DABSO (0.6 equiv), Et₃N (3.0 equiv), i-PrOH (0.2 M), 75 °C, 16 h, then morpholine (3 equiv), NaOCl (10.3% aq solution, 2 equiv), r.t., 90 min.
* NCS (2 equiv) used in place of NaOCl.

A para-hydroxyl substituent was successfully incorporated into the sulfonamide product, providing a good illustration of a substrate that would likely be incompatible with the Grignard-based method (entry 6). Electron-withdrawing substituents, including halides, were also efficient substrates, providing sulfonamides in good yields (entries 7–12). Amongst these examples are several substrates that are potentially susceptible to nucleophilic addition from preformed organometallics (ester, nitrile, ketone; entries 10–12). It should be noted that NCS was employed as the oxidant with the ketone example, as hypochlorite delivered only a poor yielding reaction. A simple heterocycle (entry 13) and a 1-naphthyl (entry 14) example are also shown to work well.

Variation of the amine component is shown in Scheme 3. Primary amines generally performed well (4a–d); notable amongst this group are several that feature potentially sensitive functionality, including an acetal (4b), a trisubstituted alkene (4c), and a pyridyl group (4d). Cyclopropane and cyclobutane-substituted amines delivered the targeted sulfonamides, although in slightly reduced yields (4e,f). Aniline derivatives could also be successfully employed as substrates (4g,h). Finally, amino acid derivatives could be employed, allowing the corresponding sulfonamides to be isolated in reasonable yields (4i,j). The reactions to prepare sulfonamides 4d and 4j were both performed on a 4.23 mmol scale (1.0 g of aryl iodide), demonstrating that synthetically useful scales are not problematic.

In conclusion, we have shown that a variety of aryl sulfonamides can be prepared from aryl iodides, the SO₂ surrogate DABSO, and amines. The aryl iodide substrates first undergo conversion to an ammonium sulfinate intermediate using a palladium(0)-catalyzed sulfination. Addition of an aqueous solution of the amine and sodium hypochlorite then provides the desired sulfonamides. The reactions are straightforward to perform, tolerate a variety of acidic and
electrophilic functional groups on the arene, as well as encompassing the use of both primary and secondary amines, anilines, and amino acid derivatives.

![Scheme 3: Scope of the amine component in one-pot sulfonylamide formation. Reagents and conditions: Pd(OAc)₂ (5 mol%), Pd$_2$Bu (7.5 mol%), DABSO (0.6 equiv), Et₃N (3.0 equiv), i-PrOH (0.2 M), 75 °C, 16 h, then amine (3 equiv), NaOCl (10.3% aq solution, 2 equiv), 2 °C to r.t., 45 min to 3.5 h. Additional amine (3.0 equiv) and NaOCl (2.0 equiv) added after 2 h. The reaction was performed on 4.23 mmol scale (1.0 g) of starting aryl iodide. Additional amine (3.0 equiv) and NaOCl (2.0 equiv) added after 2 h. The solvent from first step was removed and replaced by water. The ee of the methyl ester derivative was confirmed by chiral HPLC to be >99%.](image)

**General Procedure for the Formation of Sulfonylamides Using Morpholine, Exemplified by the Preparation of 4-Tosylmorpholine 3a**

An oven-dried glass reaction tube was charged with the relevant aryl iodide (4-iodotoluene) (87 mg, 0.40 mmol, 1 equiv), DABSO (58 mg, 0.24 mmol), Pd(OAc)$_2$ (5.0 mg, 20.0 μmol, 5 mol%), and CataCXium A (11.0 mg, 31.6 μmol, 7.5 mol%), sealed with a rubber septum and flushed with nitrogen. Under positive pressure of nitrogen, Et$_3$N (168 μL, 1.20 mmol, 3 equiv) and anhydrous 2-i-PrOH (1.5 mL) were added sequentially through the septum. The reaction mixture was then immersed in a preheated oil bath at 75 °C for 16 h. The formation of the ammonium sulfinate and the disappearance of the aryl iodide are easily followed by HPLC. After cooling to r.t., the relevant amine (morpholine) (104 μL, 1.20 mmol, 3 equiv) and previously titrated 10.31% w/w aq NaOCl (0.47 mL, 0.80 mmol, 2 equiv) were added sequentially through the septum and stirred at r.t. for 90 min until consumption of the sulfinate was observed by HPLC. Upon completion, the reaction mixture was filtered through Celite and the filter washed with acetone until disappearance of the brown color. The organic solution was then concentrated and the residue purified by flash chromatography with silica gel under standard eluent mixtures [typically EtOAc in PE (40–60 °C bp PE)]. The products were dried under high vacuum and analyzed by NMR and IR spectroscopy and MS.

**Acknowledgment**

This work was supported by the EPSRC.

**Supporting Information**

Supporting information for this article is freely available online at http://dx.doi.org/10.1055/s-0035-1560578 and includes experimental procedures and associated characterization data.

**References**


(14) For a Au(1)-catalyzed sulfinate synthesis, including examples of conversion to sulfonamides, see: Johnson, M. W.; Bagley, S. W.; Mankad, N. P.; Bergman, R. G.; Mascitti, V.; Toste, F. D. *Angew. Chem. Int. Ed.* **2014**, 53, 4404.