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

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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).¹ Aryl and heteroaryl sulfonamides are prominent amongst these molecules and are usually prepared from the combination of an aryl (or heteroaryl) sulfonyl chloride and an amine.² This is an effective and reliable process, although it does have limitations. For example, certain heteroaryl sulfonyl chlorides are unstable, and ready access to the desired sulfonyl chloride is also needed.

Sulfonyl chlorides are most often prepared from the electrophilic sulfonylation of an arene, using either [HSO₃]⁺ or [ClSO₂]⁺ synthons as the electrophile.³ 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.⁴ This approach avoids the limitations imposed by aromatic electrophilic substitution reactivity, but instead involves the preparation of a potentially odoriferous thiol and the use of strong oxidizing conditions, which can often limit functional-group compatibility. A conceptually different approach involves transforming a pre-activated, nucleophilic arene into a sulfonyl chloride and an amine.² This is an effective and reliable process, although it does have limitations. For example, certain heteroaryl sulfonyl chlorides are unstable, and ready access to the desired sulfonyl chloride is also needed.

Received: 10.09.2015
Accepted: 25.09.2015
Published online: 13.10.2015

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Figure 1 Bioactive sulfonamides

Celbrex (COX-2 inhibitor) a component of Bactrim (antibiotic) Penoxsulam (herbicide)
ammonium sulfinates from the combination of aryl iodides have shown that it is possible to access a wide range of aryl preformed organometallic reagent and the sulfur dioxide nates can be readily obtained from the combination of a for reaction with SO$_2$-surrogates. In this context, we lytically generating reactive organometallic intermediates from benign substrates such as aryl halides and then cata-

...and DABSO using palladium(0) catalysis (Scheme 1, b). We were able to demonstrate that the ammonium sulfinate intermediates could be converted into a range of derivatives, mostly sulfone based, but including a single sulfonamide example. The sulfonamide was obtained by treatment of the ammonium sulfinate with sulfonyl chloride, followed by addition of an amine. The need to employ sulfonyl chloride, a notoriously sensitive reagent that requires frequent purification, represents a significant limitation to this method. Shavnya and Mascitti have described related chemistry, in which catalytically generated sodium sulfinites are converted into sulfonamides by treatment with NBS and an amine. In these cases the sulfonamides were obtained in only moderate (37–65%) yields. Given our convenient and high-yielding sulfonamide synthesis starting from preformed organometallics, and our success in producing ammonium sulfinites from aryl iodides using palladium catalysis, we were attracted to the merger of the two methods, to deliver a general sulfonamide synthesis that uses aryl halides as substrates (Scheme 1, c). This Letter documents the successful realization of this goal.

The main issue in merging the two DABSO-based methods was reconciling the different solvents used in the two transformations; the palladium-catalyzed ammonium sulfinate formation was performed in isopropanol, while the Grignard addition to DABSO had employed THF as solvent, before addition of an aqueous amine/hypochlorite solution. Using the coupling of 4-iodotoluene, DABSO and morpholine as a test reaction we evaluated different solvent combinations (Scheme 2). Pleasingly, the simplest experimental conditions proved effective, as performing the initial catalytic sulfinate formation in isopropanol and then adding an aqueous solution of morpholine and sodium hypochlorite directly to this allowed the target sulfonamide to be isolated in 90% yield. Experiments that removed the isopropanol 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 CH$_2$Cl$_2$ 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>1,2-Dimethoxybenzene</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>1-Naphthylbenzene</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>Benzene</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>2-Methoxybenzene</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>2-Methylthiophene</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>1-Hydroxybenzene</td>
<td>57</td>
</tr>
<tr>
<td>7</td>
<td>4-Chlorobenzene</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>4-Bromobenzene</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>2-Fluorobenzene</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>4-Methoxybenzene</td>
<td>82</td>
</tr>
<tr>
<td>11</td>
<td>2-Nitrobenzene</td>
<td>75</td>
</tr>
</tbody>
</table>

Table 1 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arene</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>4-Methylthiophene</td>
<td>60&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>Naphthalene</td>
<td>77</td>
</tr>
<tr>
<td>14</td>
<td>1-Naphthylbenzene</td>
<td>79</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: Pd(OAc)<sub>2</sub> (5 mol%), Pd<sub>2</sub>BU (7.5 mol%), DABSO (0.6 equiv), Et<sub>3</sub>N (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.

A <i>para</i>-hydroxy-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 SO<sub>2</sub> 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](image)

**Scheme 3** Scope of the amine component in one-pot sulfonamide formation. Reagents and conditions: Pd(OAc)$_2$ (5 mol%), Et$_3$N (3.0 equiv), PrOH (0.2 M), 75 °C, 16 h, then amine (3.0 equiv), NaOCl (2.0 equiv) added after 2 h. 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%.

**General Procedure for the Formation of Sulfonamides 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)$_2$ (3.0 mg, 20.0 μmol, 5 mol%), and CataCium A (110 mg, 31.6 μmol, 7.5 mol%), sealed with a rubber septum and flushed with nitrogen. Under positive pressure of nitrogen, Et$_3$N (3.0 equiv), Pd(OAc)$_2$ (5 mg, 20.0 μmol, 2 equiv), and DABSO (4 equiv), Et$_3$N (3.0 equiv), PrOH, 75 °C, 16 h, then amine (3.0 equiv), NaOCl (2.0 equiv) added after 2 h. 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%.

**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**


(4) For example, see: Wright, S. W.; Hallstrom, K. N. J. Org. Chem. 2006, 71, 1080.


(14) For a Au(I)-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.