Palladium-catalysed arylation of sulfonamide stabilised enolates

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Abstract—α-Arylation of methanesulfonamides using palladium catalysis is described. For example, treatment of N-benzyl-N-methylmethanesulfonamide with catalytic Pd(OAc)2 in the presence of sodium tert-butoxide, triphenylphosphine and toluene afforded N-benzyl-N-methylphenylmethanesulfonamide in 66% yield.

Since the early breakthroughs of 1997, palladium catalysed enolate arylation has become a reliable and widely applicable reaction. The methodology has been developed in research programmes pioneered by Hartwig and Buchwald (amongst others) and now accommodates a wide variety of stabilised carbanions with a degree of rational prediction as to the required base and ligand to facilitate the reaction.1

It has been demonstrated that sulfones also undergo the same type of arylation reaction. Intermolecular enolate arylation of substituted methylphenylsulfones (YCH2SO2Ph, Y = electron withdrawing group) with aryl iodides using Cul/NaH has been reported by Suzuki2 and Gorelik et al.3 while the use of a palladium catalyst in this transformation was published by Kondo and co-workers.4 Ciufolini has also reported one example of an intramolecular version of this type of reaction.5 In addition, Beletskaya and co-workers have recently published several examples of palladium catalysed intermolecular couplings of sulfone stabilised enolates with aryl bromides.6 N-Substituted methylphenylsulfoxides have also been demonstrated to proceed in intramolecular versions of this coupling reaction mediated by a palladium/BINAP catalyst.7

Only one example of an arylation reaction is found where the nucleophile is a sulfonamide.8 However, the success of this procedure required an enhancement of the acidity of the subject sulfonamide through the generation of a β-cyanosulfonamide. The relatively acidic 2-[N-(benzyloxymethyl)-N-methylaminosulfonyl]cyanoacetate (1) was coupled with aryl iodide 2a using tetrakis(triphenylphosphine)palladium(0) as catalyst and sodium hydride as base (Scheme 1) to afford 2b. Similar reactions have previously been performed by a SRN1 type reaction involving potassium and liquid ammonia chemistry.9

The preparation of compounds such as 1, containing both a sulfonamide and a cyano substituent to enhance the acidity of the protons between both functional groups, is relatively cumbersome. In cases where the α-aryl methanesulfonamide is required as in the target compound, such electron-withdrawing groups have to be removed after coupling with the aryl halide. The preparation of methanesulfonamides, on the other hand, is extremely simple through the reaction of methanesulfonyl chloride and the appropriate amine. It has,

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Scheme 1. Palladium catalysed arylation of a β-cyanosulfonamide.
However, previously been reported that highly nucleophilic carbanions (stabilised by only one electron-withdrawing group) such as those derived from methylenysulfone and methylenysulfoxide are unreactive in arylation chemistry.\textsuperscript{6,10,11} We found this fact surprising since the arylation of the closely related methylenysulfoximes has been demonstrated by Bolm et al.\textsuperscript{7} and other systems with high $pK_a$ values such as acetamides, acetonitrile and acetic acid esters ($pK_a \approx 31–35$)\textsuperscript{12} have been used successfully in enolate arylation reactions.\textsuperscript{13–17} Therefore, in this letter we wish to communicate the successful enol arylation reaction of methanesulfonamides with aryl halides using palladium catalysts.

Following the reported successful arylation of an $\alpha$-cyano methanesulfonamide,\textsuperscript{8} we prepared a similar substrate 3. It was found that 3 could be arylated with iodobenzene using a Pd(OAc)$_2$/PPh$_3$ catalyst in a toluene solution at 70 °C with NaO'Bu as base (Table 1, entry 1) to give the desired arylated product 4 in 63% yield. The same reaction with bromobenzene was performed at 110 °C and gave the product in 77% yield (entry 2). Incomplete conversion of both starting materials was observed, presumably due to the enhanced thermodynamic acidity of the product and the subsequent coordination of the resultant anion to the catalyst generating an intermediate with geometry unsuitable for further reaction.

Turning our attention to the use of alternative ligands and bases it was found that the use of the highly versatile P'Bu$_3$ ligand (entry 3)\textsuperscript{18} led to a higher yield in the conversion of 3 to 4 albeit in a more complex product matrix. It was also demonstrated that K$_3$PO$_4$ could be used as base in the presence of a small amount of N,N-dimethylacetamide as co-solvent (entry 4). Yields were, however, inferior to that obtained by using NaO'Bu as the base in the reaction.

Motivated by the successful arylation of 3, we reasoned that the arylation of the methanesulphonamide substrate, lacking the extra stabilising substituent, for example, 5a might be feasible. It was thought the higher $pK_a$ (between 32 and 35)\textsuperscript{12,13} of the mono-stabilised methanesulfonamide enolate would necessitate the use of a stronger base as has been observed for substrates like aliphatic amides and esters\textsuperscript{13,17,16} with similar $pK_a$ values. Initial attempts with the stronger NaHMDS base were, however, unsuccessful. Identical conditions used for the substrate 3, however, resulted in the formation of the desired arylated product 6a from 5a, albeit in low yield (~10% yield by GLC). Unlike the clean reaction observed for substrate 3, biphenyl was formed as a by-product (~20%). Under the same conditions a moderate yield (51%) of 6a was obtained with iodobenzene as the aromatic substrate in the reaction. The successful utilisation of bromobenzene as the aromatic partner in the same reaction, however, was realised by increasing the reaction temperature (entry 7). Contrary to the improved yield obtained with the P'Bu$_3$ ligand for the arylation reaction with 3, the yield of 6a was poor when attempted with the methanesulphonamide substrate 5a (entry 8). The use of K$_3$PO$_4$ as base was unsuccessful (entry 9) with substrate 5a (Scheme 2).

Following these investigations the nature of the sulfonamide was the subject of further studies. The N,N-diisopropyl methanesulphonamide 5b (Scheme 3, Table 2) was employed in our next study. Besides the formation of moderate yields (9–40% for bromobenzene) of the desired mono-arylated product 6b from 5b by utilising a number of phosphine ligands, diarylation to give 7b was observed in varying amounts (Table 2). BINAP was more selective towards mono-arylition than triphenylphosphine (see entries 1 and 3). The ligands PCY$_3$ and P'Bu$_3$ behaved very differently in this transformation with PCY$_3$ leading preferentially to the diarylated product 7b while P'Bu$_3$ was the most selective ligand for mono-arylition (entries 4 and 5). Cyclohexyl JohnPhos 8 gave moderate activity (similar to triphenylphosphine) with high mono-selectivity (entry 9). The use of a lower palladium loading (1 mol%) while maintaining a high

\begin{table}[h]
\centering
\caption{Yield determined by GC with 2-methoxynaphthalene as internal standard.}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|}
\hline
Entry & X & Yield & Biphenyl & Base 1.75 & Ligand & base & \% \hline
& & (mol) & (%) & equiv & & & 22 \% & \degree C \hline
1 & 3 & I & 63 & 0 & NaO'Bu & PPh$_3$ & 70 \hline
2 & 3 & Br & 77 & 0 & NaO'Bu & PPh$_3$ & 110 \hline
3 & 3 & Br & 81 & 0 & NaO'Bu & P'Bu$_3$ & 110 \hline
4 & 3 & I & 41 & 0 & K$_3$PO$_4$ & PPh$_3$ & 100 \hline
5 & 5a & Br & 10 & 20 & NaO'Bu & PPh$_3$ & 70 \hline
6 & 5a & I & 5 & 1 & NaO'Bu & PPh$_3$ & 75 \hline
7 & 5a & Br & 66 & 6 & NaO'Bu & PPh$_3$ & 110 \hline
8 & 5a & Br & 28 & <1–10 & NaO'Bu & P'Bu$_3$ & 110 \hline
9 & 5a & I & 0 & 10 & K$_3$PO$_4$ & PPh$_3$ & 110 \hline
\hline
\end{tabular}
\end{table}

\begin{scheme}
\caption{Arylation of N-benzyl-N-methyl sulfonamidoacetonitrile and N-benzyl-N-methyl methanesulphonamide (see Table 1 for conditions and yields).}
\end{scheme}

\begin{scheme}
\caption{Reagents and conditions: 2 mmol aryl bromide, 2.2 mmol sulfonamide, 3.5 mmol NaO'Bu, 5 mL toluene, 1–8% Pd(OAc)$_2$ ligand, 110 °C, 15 h (see Table 2 for ligand and yields).}
\end{scheme}
PPh₃ loading did not lead to lower arylation activity but instead led to the formation of similar amounts of the mono- and di-arylated products 6 and 7 and suppression of biphenyl formation (entry 6).

Using the more sterically hindered 2-bromotoluene instead of bromobenzene in the enolate arylation reaction with 5b also led to a marginal increase in selectivity of the product ratios of 6b and 7b, while the unhindered and electron-rich 4-bromoanisole led to almost exclusively the mono-arylated product (entries 8 and 9). These results indicate that not only steric factors, but also electronic factors are important in determining the selectivity and yield of this reaction.

The problems concerning diarylation of the N,N-diisopropyl substituted sulfonamide 5b proved to be less apparent on less sterically hindered sulfonamides. For example, treatment of substrates 5c–e under the same conditions used in entry 1 in Table 2 led to ratios of the monoarylated product 6c–e to the diarylated products 7c–e exceeding 10:1 where the major side product was biphenyl (entries 10–12).

In conclusion, we have shown the first examples of the α-arylation of methanesulfonamides under palladium, catalysis conditions using phosphine ligands and sodium t-butoxide as a base. The outcome of this reaction is apparently governed by a mixture of steric and electronic effects, with the major by-products being biphenyl and diarylation of the methanesulfonamide. Both aryl bromides and iodides are active participants in this coupling reaction.

References and notes

18. Fu's highly stable 'Bu₂P(HBF₄) salt was used (available from Strem Chemicals); Netherton, M. R.; Fu, G. C. Org. Lett. 2001, 3, 4295.
19. General experimental procedure: A screw-capped Pyrex tube (50 mL) was charged with sodium tert-butoxide (3.5 mmol), 10 mL dry toluene (distilled from sodium), methanesulfonamide 5 (2.2 mmol), and aryl bromide (2.0 mmol). A warmed (~60 °C for 1 min) suspension of Pd(OAc)₂ (36 mg, 0.16 mmol, 8 mol%), triphenylphosphine (120 mg, 0.46 mmol, 23 mol%), 2-methoxyanilathellene (an accurately weighed amount as internal standard) and toluene (3 mL) were added. The tube was flushed with nitrogen and heated to 100–110 °C in a Robosynteth multireactor for 15–20 h. The conversion of the methanesulfonamide and aryl bromide was determined by GLC analysis based on internal standard calculation. After a total reaction time of 15–20 h the reaction mixture was cooled and quenched by addition of water and dilute hydrochloric acid followed by extraction into ethyl acetate. After solvent removal, the residue was purified by column chromatography to afford the products.

Table 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Methanesulfonylamine 5</th>
<th>ArBr</th>
<th>Pd(OAc)₂ (mol %)</th>
<th>Ligand (mol %)</th>
<th>6 Yield (%)</th>
<th>7 Yield (%)</th>
<th>Biphenyl yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5b R¹ = R² = Pr</td>
<td>Bromobenzene</td>
<td>8</td>
<td>PPh₃ (23)</td>
<td>6b, 34</td>
<td>7b, 14</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>5b R¹ = R² = Pr</td>
<td>Bromobenzene</td>
<td>8</td>
<td>PoTo₃ (15)</td>
<td>6b, 9</td>
<td>7b, 0</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>5b R¹ = R² = Pr</td>
<td>Bromobenzene</td>
<td>5</td>
<td>BINAP (7.5)</td>
<td>6b, 45</td>
<td>7b, 9</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>5b R¹ = R² = Pr</td>
<td>Bromobenzene</td>
<td>4</td>
<td>P₃Bu₃ (8)</td>
<td>6b, 46</td>
<td>7b, 4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>5b R¹ = R² = Pr</td>
<td>Bromobenzene</td>
<td>5</td>
<td>PCys (10)</td>
<td>6b, 14</td>
<td>7b, 25</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>5b R¹ = R² = Pr</td>
<td>Bromobenzene</td>
<td>5</td>
<td>PCys (10)</td>
<td>6b, 34</td>
<td>7b, 29</td>
<td>&lt;1</td>
</tr>
<tr>
<td>7</td>
<td>5b R¹ = R² = Pr</td>
<td>Bromobenzene</td>
<td>2</td>
<td>PPh₃ (23)</td>
<td>6b, 30</td>
<td>7b, 10</td>
<td>Nd</td>
</tr>
<tr>
<td>8</td>
<td>5b R¹ = R² = Pr</td>
<td>Bromobenzene</td>
<td>6</td>
<td>PPh₃ (23)</td>
<td>6b, 52</td>
<td>7b, 2</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>5b R¹ = R² = Pr</td>
<td>4-Bromoanisole</td>
<td>5</td>
<td>PPh₃ (23)</td>
<td>6b, 34</td>
<td>7b, &lt;1</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>5e R¹-R²-(CH₂)₄-</td>
<td>Bromobenzene</td>
<td>8</td>
<td>PPh₃ (23)</td>
<td>6e, 35</td>
<td>7e, 6</td>
<td>9</td>
</tr>
<tr>
<td>11</td>
<td>5d R¹-R² = -(CH₂)₂O(CH₂)₂-</td>
<td>Bromobenzene</td>
<td>8</td>
<td>PPh₃ (23)</td>
<td>6d, 60</td>
<td>7d, 5</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>5e R¹ = Me, R² = Ph</td>
<td>Bromobenzene</td>
<td>8</td>
<td>PPh₃ (23)</td>
<td>6e, 34</td>
<td>7e, 4</td>
<td>14</td>
</tr>
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