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Copper-catalyzed *N*-arylation of sulfonamides with aryl bromides and iodides using microwave heating

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Abstract—The copper-catalyzed *N*-arylation of sulfonamides with a variety of aryl bromides and iodides using microwave heating is described. © 2003 Elsevier Science Ltd. All rights reserved.

N-Arylsulfonamides are important compounds, particularly in pharmaceutical research. A number of them have been reported to have significant biological activity, e.g. class III antiarrhythmic agents,[1] non-nucleotide reverse transcriptase inhibitors,[2] nonpeptidic vasopressin V1a receptor antagonists,[3] and HIV-1 protease inhibitors.[4] As such, significant efforts have gone into the development of efficient methods for their preparation.

The most straightforward routes to *N*-arylsulfonamides involve the direct formation of the aryl–nitrogen bond. The traditional protocols for *N*-arylation of sulfonamides prescribe simple copper salts or often copper metal as the catalyst and usually require drastic reaction conditions.[5] Due to this drawback which limits its scope, the copper-catalyzed *N*-arylation of sulfonamides with aryl halides has not been recognized as a powerful synthetic methodology in organic synthesis. Recently, Buchwald and co-workers[5,6] reported the palladium-catalyzed coupling of aryl halides with several sulfonamides. Lam and co-workers[7] also described the synthesis of *N*-arylsulfonamides through the copper-catalyzed *N*-arylation of sulfonamides with arylboronic acids. In a recent medicinal chemistry program, we found that microwave heating can be used to facilitate the *N*-arylation of sulfonamides.[8] Microwave irradiation has become increasingly popular in recent years to improve the yield and shorten reaction times in a variety of reactions[9] including the Goldberg reaction,[10] the copper-catalyzed amidation of aryl halides. However, to our knowledge, the microwave-mediated methodology on the *N*-arylation of sulfonamides with aryl halides has not yet been reported. This report describes our preliminary studies on the copper-catalyzed *N*-arylation of sulfonamides using microwave heating.

Treatment of iodobenzene with 2 equiv. benzenesulfonamide in the presence of copper(I) iodide (10 mol%) and potassium carbonate (2 equiv.) in *N*-methylpyrrolidinone at 195°C for 3 h under microwave irradiation provided *N*-phenylbenzenesulfonamide in 90% yield, after purification of the crude product using silica gel flash chromatography (Table 1, entry 1). As a control experiment, the same reaction mixture was heated at 195°C for 3 h in a sealed tube using an oil bath, and the product was obtained in 50% yield. This observation demonstrates the advantage of microwave radiation over conventional heating techniques. As shown in Table 1, these conditions worked well for a variety of aryl iodides (entries 2–4) and bromides (entries 5–9). It should be pointed out that the coupling reactions with aryl iodides (entries 1–4) generally provide better yields than those with the corresponding bromides (entries 5–8). To test the scope of this reaction, bromobenzene was treated with methanesulfonamide (entry 10), *p*-toluenesulfonamide (entry 11) and the secondary sulfonamide *N*-methylbenzenesulfonamide (entry 12) under the above conditions, and the yields were comparable to that obtained with benzenesulfonamide. Of special note is that the yield of the reaction was not greatly influenced by the presence of electron-donating or electron-withdrawing groups on the aryl halides. However, this type of *N*-arylation does not seem to work on aryl chlorides. For example, treatment of benzenesulfonamide with chlorobenzene in the presence of copper(I) iodide (10 mol%) and potassium carbonate (2 equiv.) provided very little product even after 20 h microwave heating.

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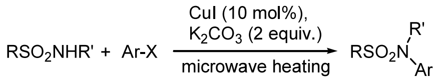
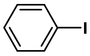
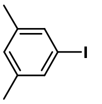
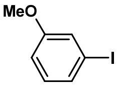
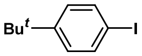
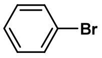
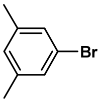
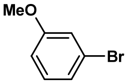
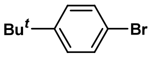
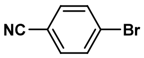
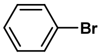
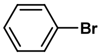
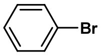
Table 1. *N*-Arylation of sulfonamides with aryl halides



$$RSO_2NHR' + Ar\text{-}X \xrightarrow[\text{microwave heating}]{\text{CuI (10 mol\%), } K_2CO_3 \text{ (2 equiv.)}} RSO_2N(R')Ar$$

Entry	RSO$_2$NHR’	Ar-X	Time	Yield[a]
1	PhSO$_2$NH$_2$		3 h	90%
2	PhSO$_2$NH$_2$		3 h	88%
3	PhSO$_2$NH$_2$		2 h	83%
4	PhSO$_2$NH$_2$		2 h	88%
5	PhSO$_2$NH$_2$		3 h	66%
6	PhSO$_2$NH$_2$		2 h	81%
7	PhSO$_2$NH$_2$		2 h	66%
8	PhSO$_2$NH$_2$		3 h	78%
9	PhSO$_2$NH$_2$		2 h	88%
10	MeSO$_2$NH$_2$		2 h	67%
11	*p*-TolSO$_2$NH$_2$		3 h	70%
12	PhSO$_2$NHMe		4 h	54%

[a] isolated yield.

In summary, we have developed an operationally simple and efficient method for the *N*-arylation of sulfonamides with a variety of aryl bromides and iodides.[11]

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8. The microwave unit used in our experiments is the Smith Creator® from Personal Chemistry. It continuously adjusts the applied wattage to maintain the desired temperature. Reactions were conducted in the Personal Chemistry proprietary 5 mL sealed vials.
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11. Representative procedure: To a solution of iodobenzene (102 mg, 0.5 mmol) and benzenesulfonamide (157 mg, 1 mmol) in *N*-methylpyrrolidinone (0.67 mL) in a vial were added potassium carbonate (138 mg, 1 mmol), and copper(I) iodide (9.5 mg, 0.05 mmol). The vial was sealed and heated by microwave at 195°C for 3 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was evaporated in vacuo, and the residue was purified by silica gel flash chromatography (20% acetone/80% hexanes) to give *N*-phenylbenzenesulfonamide (105 mg, 90%) as an oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.88 (1H, br. s), 7.07 (2H, d, $J=8.0$ Hz), 7.10 (1H, t, $J=8.0$ Hz), 7.23 (1H, t, $J=8.0$ Hz), 7.24 (1H, d, J=8.0 Hz), 7.42 (2H, t $J=8.0$ Hz), 7.52 (1H, t, $J=8.0$ Hz), 7.78 (2H, d, $J=8.0$ Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 121.8, 125.5, 127.2, 129.0, 129.4, 133.0, 136.4, and 139.0. The spectroscopic data is in full agreement with that obtained from an authentic sample purchased from Aldrich.