Efficient Preparation of *ortho*-Aminobenzenesulfonamides using Ligand-Free Copper(I)-Catalyzed Amination

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Abstract: A general and efficient method of copper-catalyzed amination of 2-iodobenzenesulfonamide has been developed under very mild conditions, with good to excellent yields. This method uses inexpensive copper(I) iodide as catalyst, readily available 2-iodobenzenesulfonamides and aliphatic amines as the starting materials, and does not require the use of any ligand system or any expensive supplementary additives.

Key words: 2-iodobenzenesulfonamide, copper(I) catalyst, N-arylation, ligand-free, 2-aminobenzenesulfonamides

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] non-peptidic vasopressin, VIa receptor antagonists,[3] and HIV-1 protease inhibitors,[4] and the results of many studies on chemotherapy for experimental streptococcal infections indicate that compounds such as sulphanilamide which have a nitrogen and a sulfur attached to a benzene nucleus are very effective.[5] Significant effort has therefore been focused on the development of efficient methods for their preparation.

Copper-catalyzed Ullmann–Goldberg coupling, a well-known reaction for the introduction of amine functionality using aromatic halides, has been used for this purpose.[6] Great progress has been made in the last few years in the copper-catalyzed N-arylation of amines,[7] but a simple and general procedure for the copper-catalyzed coupling of aliphatic amines with aryl halides under mild conditions still remains to be found.[8] Despite progress, these reactions still require high reaction temperatures (60–120 °C), which may cause problems for substrates with thermally sensitive moieties or in situations such as combinatorial chemistry applications, where it is inappropriate to heat reactions. It is therefore highly desirable to develop milder copper-catalyzed coupling methods. Several ligands have been introduced to promote copper-catalyzed N-arylation of aliphatic amines since 2003, in particular *N*,*N*-diethylsalicylamide,[8b] amino acids,[9] amino alcohols,[10] phosphoramidite[11] and oxime-phosphine oxide.[12] Buchwald[13] recently successfully utilized copper(I) iodide complexes as the catalyst to achieve an N-arylation reaction of aliphatic amines at room temperature, and Zhao[14] described the amination of 2-halobenzoic acids using *rac*-BINOL as the ligand to synthesize *N*-alkylanthranilic acids. Cu-catalyzed amination of *ortho*-substituted aryl halides usually requires the use of a slightly higher reaction temperature (100 °C),[8b] and affords the desired compounds in low yields.[8a]

Several advancements have been made in the field of external ligand-free copper catalysis amination,[15] but to the best of our knowledge, only one example of direct CuI catalyst amination of 2-iodobenzenesulfonamide derivatives has previously been reported,[16] and the synthesis of 2-aminobenzenesulfonamides was achieved using microwave irradiation at 100 °C in the presence of a ligand. This very recent report prompts us to report our observations in this field. In continuation of our work to develop copper-catalyzed cross-couplings,[17] we report herein a mild and simple convenient method of copper-catalyzed direct amination of 2-iodobenzenesulfonamide derivatives using air-stable CuI as the ligand-free catalytic system, for which we then investigated the scope and limitations of the reaction. *N*-Benzyl-2-iodobenzenesulfonamide and benzylamine were chosen as the model substrates to explore the reaction conditions including the catalysts, bases and solvents. Several copper salts such as CuCl, CuBr, CuI, CuCN and CuO were tested using DMF as the solvent and K_2CO_3 as the base, and the results showed that CuI was the most effective catalyst, while no target product was observed in the absence of a copper catalyst. Testing different amounts of reactive copper showed that the use of 0.1 molar equivalent relative to the 2-iodobenzenesulfonamide was sufficient to achieve a satisfactory conversion rate. Very poor conversion rates and yields (<10%) were obtained when copper(II) salts such as copper oxide (CuO) were used as catalyst instead of copper(I) salts for the coupling of 2-iodobenzenesulfonamide with aliphatic amines. The nature of the base was also investigated, and we found that Cs_2CO_3 and K_2CO_3 were the most effective in providing the best results, while $NaHCO_3$, Na_2CO_3, K_3PO_4 and Et_3N were ineffective. In addition, when the reaction was performed in the absence of a base, the starting material was recovered. We also investigated the effects of solvent and we concluded that

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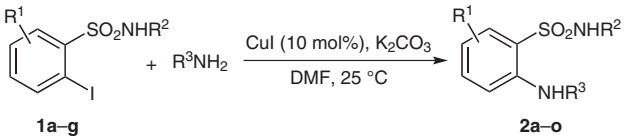
solvents with Lewis basicity properties were necessary. DMSO was slightly inferior to DMF, and THF, MeCN and toluene were much less effective. The reaction medium is homogeneous during the whole transformation.

After the optimization process for catalysts, bases and solvents, amination of the *ortho*-iodobenzenesulfonamides was performed with 10 mol% of CuI as the catalyst, and one equivalent of potassium carbonate or cesium carbonate in DMF at room temperature for four hours (Scheme 1).

The starting 2-iodobenzenesulfonamides **1** were synthesized from benzenesulfonic acid or 2-aminobenzenesulfonic acid by a standard method.[18,19]



1a–g 2a–o

Scheme 1 Synthesis of *ortho*-aminobenzenesulfonamides

The optimized amination procedure was then applied to a variety of commercially available aliphatic amines and 2-iodobenzenesulfonamide derivatives to evaluate the synthetic potential of this method. The results are summarized in Table 1.

Table 1 CuI-Catalyzed Coupling of 2-Iodobenzenesulfonamides with Aliphatic Amines

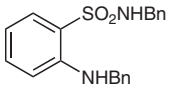
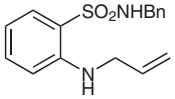
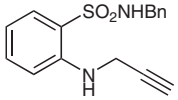
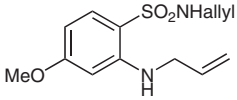
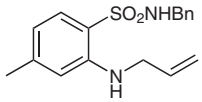
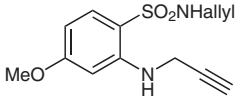
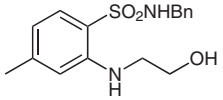
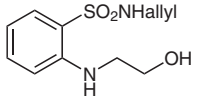
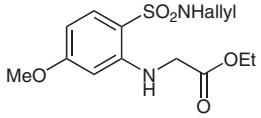
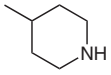
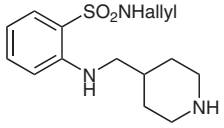
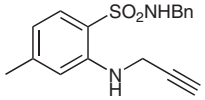
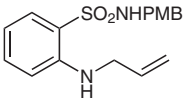
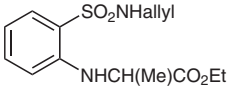
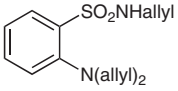
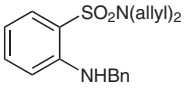
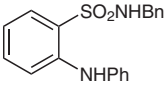
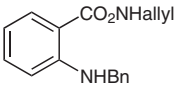
Entry	R^1	R^2	**1**	R^3	Product	**2**	Yield (%)
1	H	Bn	**1a**	Bn		**2a**	80
2	H	Bn	**1a**	allyl		**2b**	85
3	H	Bn	**1a**	propargyl		**2c**	79
4	*p*-MeO	allyl	**1b**	allyl		**2d**	75
5	*p*-Me	Bn	**1c**	allyl		**2e**	70
6	*p*-MeO	allyl	**1b**	propargyl		**2f**	78
7	*p*-Me	Bn	**1c**	$(CH_2)_2OH$		**2g**	69
8	H	allyl	**1d**	$(CH_2)_2OH$		**2h**	64
9	*p*-MeO	allyl	**1b**	CH_2CO_2Et		**2i**	59
10	H	allyl	**1d**			**2j**	66
11	*p*-Me	Bn	**1c**	propargyl		**2k**	68

Table 1 CuI-Catalyzed Coupling of 2-Iodobenzenesulfonamides with Aliphatic Amines (continued)

Entry	R^1	R^2	**1**	R^3	Product	**2**	Yield (%)
12	H	PMB	**1e**	allyl		**2l**	61
13	H	allyl	**1d**	$CH(Me)CO_2Et$		**2m**	65
14	H	allyl	**1d**	$(allyl)_2$		**2n**	20
15	H	$(allyl)_2$	**1f**	Bn		**2o**	0
16	H	Bn	**1a**	Ph		**2p**	0
17[a]	H	allyl	**1g**	Bn		**2q**	20

[a] *N*-Allyl-2-iodobenzamide was used in this case; PMB = *p*-methoxybenzyl.

The reaction described is extremely versatile and provides convenient access to various 2-(*N*-alkylamino)benzenesulfonamides **2** from readily available 2-iodobenzenesulfonamides **1** and aliphatic amines. A number of 2-iodobenzenesulfonamides and amines were used and it was found that each primary aliphatic amine provided good yields of the corresponding coupling product (entries 1–13, Table 1). However, aromatic amines showed no reactivity in amination (entry 16, Table 1). These results demonstrated that the nucleophilicity of the amine was a crucial parameter in this coupling reaction. Interestingly, reactions performed with secondary amines provided poor results (entry 14, Table 1) and this finding was used to achieve selective N-arylation starting from polyamine for which only the reactivity of the primary amine function of the 4-aminomethylpiperidine was observed (entry 10, Table 1). It is also interesting to note that the unprotected β-aminoalcohol provided only the N-arylation reaction with good yields (entries 7 and 8, Table l). It should be noted that neither biaryl nor dehalogenated products were observed in any case.

In contrast to secondary sulfonamides, tertiary 2-iodobenzenesulfonamides were found to be non-reactive (entry 15, Table 1) in spite of heating at a higher temperature (100 °C). On the other hand, when *N*-benzyl-2-iodobenzamide **1g** was used as the substrate instead of 2-iodobenzensulfonamide, a very poor yield of the desired amination product was obtained (entry 17, Table 1). The results showed that the presence of NH of the sulfonamide group seems to be crucial. As the NH-sulphonamide substituent is not particularly a strong electron-withdrawing group able to promote the reaction, we thought that the nitrogen atom after a deprotonation reaction by potassium carbonate could chelate the copper(I) species and due to the proximity of the carbon–iodine bond, oxidative addition would be favored. Interestingly, from the available optically active L-alanine, the *N*-aryl amino ester **2m** was obtained as the optically pure amino ester (entry 13, Table 1) in good yields and without racemization. In comparison, using conditions described by Hanson[16] (MW, 100 °C, ligand), amination of **1d** using the L-alanine led to a mixture of the expected product **2m** and by-products, reflecting an overall decrease in yield. Separation of this mixture by column chromatography on silica gel proved to be difficult. As shown in Table 1, the amination reactions tolerate various functional groups, including alkoxy, hydroxyl, ester and olefin groups. This advantage would allow this method to assemble anilines of considerable structural diversity.

In summary, we have developed an efficient, simple and inexpensive method of copper-catalyzed amination of 2-iodobenzenesulfonamide using aliphatic amines in DMF at room temperature.[20] This procedure provides the easy formation of a variety of 2-(*N*-alkylamino)benzenesulfonamides in good to high yields, and a variety of functional groups are compatible with the reaction conditions. This reaction does not involve the use of an expensive, air-sensitive palladium(0) catalyst or any additive ligand. Extension of this ligand-free copper(I)-catalyzed amination to other classes of functionalized 2-iodobenzenesulfonamide derivatives and aliphatic amines is currently being studied in our laboratory.

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(20) **Typical Experimental Procedure for the Synthesis of *N*-Benzyl-2-(propargylamino)benzenesulfonamide (2c)**: 2-Iodobenzenesulfonamide (300 mg, 1 mmol), K_2CO_3 (138 mg, 1 mmol) and anhyd DMF (10 mL) were introduced into a dry Schlenk flask under argon. The mixture was cooled to 0 °C and degassed under agitation (10 min). Then amine (1.1 mmol) and CuI (19 mg, 0.1 mmol) were introduced successively under argon flux. The mixture was brought to r.t. and left under stirring for 12 h. The reaction mixture was diluted with Et_2O, washed with aq NH_4Cl and H_2O, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by chromatography on silica gel (petroleum ether–Et_2O, 50:50) or by crystallization (petroleum ether–CH_2Cl_2, 80:20); yield: 79%; white solid; mp 64–66 °C. IR (KBr): 1599, 2114, 2963, 3252, 3389 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.79 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.47 (td, *J* = 7.9, 1.3 Hz, 1 H), 7.13–7.26 (m, 5 H), 6.79–6.91 (m, 2 H), 6.06 (t, *J* = 5.4 Hz, 1 H), 5.25 (t, *J* = 6.2 Hz, 1 H), 3.94–4.06 (m, 4 H), 2.24 (t, *J* = 2.4 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.2, 139.4, 135.7, 134.0, 129.8, 128.2 (2 × C), 127.4 (2 × C), 121.4, 116.9, 112.6, 79.5, 71.4, 46.8, 32.4. MS (EI): *m/z* = 300 [M] (8), 130 (51), 129 (59), 108, 106 (100), 102 (22), 91 (63). Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.83; H, 5.41; N, 9.35.