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Synthetic Communications

Copper catalyzed N-arylation of sulfonamides with aryl bromides under ligand-free conditions

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Abstract: A practical strategy for the C-N cross-coupling of both aliphatic and aromatic sulfonamides with a variety of substituted aryl bromides is reported. Under the optimized conditions, a good representative of N-arylated products were obtained in good to excellent yields (up to 78 %) under the ligand-free conditions.

Keywords: sulfonamides, copper (I) iodide, aryl bromides, ligand-free, N-arylation

INTRODUCTION

The classical methods of generating C-N bonds have been fuelled mainly by the copper-mediated Ullmann[1] reaction. The traditional Ullmann-type reaction has some limitations which include high-temperature conditions as well as the use of stiochiometric amounts of copper. Previously, significant modifications have been made on the Ullmann-type C-N cross coupling reactions which involved the use of a mono or bidentate chelators to speed up the rate of reaction at a lower temperature and render the system to be catalytic.[2] Despite the progress, most of the strategies remain confined due to the air or moisture sensitivity, unavailability or due to the high cost from the preparation of specially modified ligands. As a result, it is still necessary to discover a simpler and more viable catalytic system for cross coupling. Considering the industrial and practical aspect, the catalytic system should ideally be economical and experimentally straightforward in terms of the steps involved. Lastly, the reaction should be ligand-free as far as possible.

N-arylated sulfonamides consist of a sulfonamide functional group which is an important moeity in many drug designs and pharmaceutical research. These substrates are important building blocks that can be found in various marketed drugs and potential drug candidates. However, the number of protocols for the generation of *N*-arylated aliphatic sulfonamides via cross coupling reactions remain limited. In particular, N-arylated methane sulfonamides have been demonstrated to possess biological activities associated with TRPV1 antagonists,[3] reverse transcriptase inhibitor,[4] and class III antiarrhythmic agents.[5]

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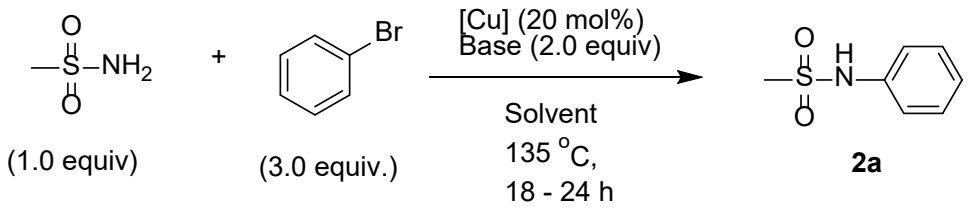
In the preparation of N-arylated aliphatic sulfonamides, Liu and Guo demonstrated the coupling reactions between sulfonamides and aromatic iodides using a N-methyl glycine/CuI catalytic system under inert conditions.[6] The substrate scope for alkyl sulfonamides was limited only to methane sulfonamide and the protocol required additional steps to modify the amino acid to its suitable form. Ruble described a Pd system for the preparation of *N*-arylated alkyl sulfonamide. The protocol exhibited a wide substrate scope including differently substituted aliphatic sulfonamides to give a series of adducts in excellent yields. However, the protocol comprised the use of designated t-BuXPhos phosphine ligands in combination with the more expensive and toxic Pd catalyst.[7] In both cases, the required use of the ligands was essential for the success of these protocols.

In the case of aromatic sulfonamides, Touré and co-workers reported a CuI/*N,N*-dimethylcyclohexane catalytic system for the *N*-arylation of sulfonamide cross-coupling reaction with heteroaryl halide.[8] Wang reported the *N*-arylation of sulfonamides with aromatic bromides through the use of dmeda ligands in the presence of CuI. The need for stringent inert conditions and ligands were vital for the success of these coupling reaction.[9] Wu and co-workers reported the copper-catalyzed N-arylation of sulfonamides with a variety of aryl bromides and iodides which necessitated the use of microwave heating.[10] To overcome some of these limitations, our research group has reported practical protocols for the N-arylation reactions of nitrogen nucleophiles with aryl iodides using copper catalysis under ligand-free conditions.[11] These reactions are simple to carry out and practical since it precluded the need for stringent inert conditions. However, the use of the more toxic and reactive aryl iodide was vital for the protocols to be successful compared to the bromides counterparts as the electrophilic partners. The application of aryl bromides as coupling partners remained limited mainly due to its lower reactivities despite its added advantages of being less toxic and cheaper to use. As a result, reports on the use of aryl bromides under ligand free coupling reactions is scarce. To date, the N-arylation of sulfonamides with substituted aryl bromides under ligand-free conditions has not been demonstrated. Recently, we have published our findings on the cross coupling of indazoles with aryl bromides via copper catalysis using ligand-free systems.[12] As part of our continuing endeavours to develop environmentally friendly and sustainable ligand-free protocols for C-N cross-couplings using aryl bromides as coupling reagents, herein we report a practical and highly efficient ligand-free copper-catalyzed coupling protocol between aliphatic and aromatic sulfonamides with substituted aryl bromides under ligand-free condition.

RESULTS AND DISCUSSION

In our preliminary study, a systematic approach was carried out to optimize the reaction conditions for the copper catalyzed cross coupling reaction using methanesulfonamide and bromobenzene as model substrates.

Table 1: Optimisation cross-coupling reactions between methane sulfonamide and bromobenzene.[a]



Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	CuI	K_3PO_4	DMF	67
2	CuBr	K_3PO_4	DMF	65
3	CuCl	K_3PO_4	DMF	48
4	Cu_2O	K_3PO_4	DMF	66
5	$CuCl_2$	K_3PO_4	DMF	66
6	CuI	Cs_2CO_3	DMF	76
7	CuI	K_2CO_3	DMF	61
8	CuI	Cs_2CO_3	DMSO	64
9	CuI	Cs_2CO_3	*t*-Butanol	Trace
10	CuI	Cs_2CO_3	Toluene	Trace

[a] Unless otherwise stated, the reactions were carried out with 1 equivalent of methanesulfonamide, 3.0 equivalents of bromobenzene, 0.2 equivalents of Cu(I) salt, 2.0 equivalents of base and 750 μL of solvent at 135°C for 18-24 hours. [b] Isolated yield of product after flash column chromatography.

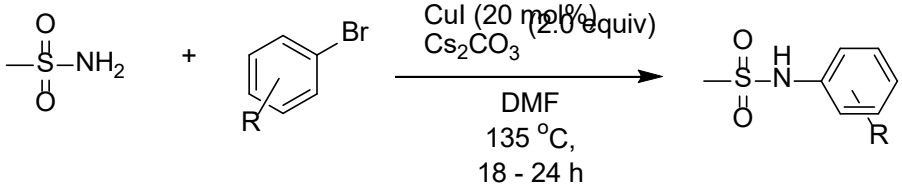
The initial reaction using CuI, K_3PO_4 in DMF at 135 ºC afforded the best result whereby the desired arylated adduct was obtained in 67% yield (Table 1, entry 1) amongst the other Cu salts used in the screening stage. The study also showed that both CuBr and Cu_2O were suitable metal salts for the transformation, providing the adducts in 65% and 66% yields, respectively (Table 1, entries 2 and 4). However, reaction carried out using CuCl gave the lowest yield of 48%. Moreover, the reaction using a representative Cu(II) halide source such as $CuCl_2$ also gave the *N*-arylated derivative in 66 % (entry 5).

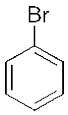
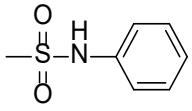
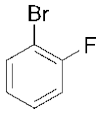
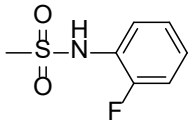
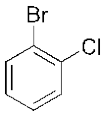
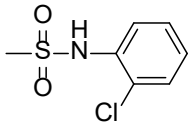
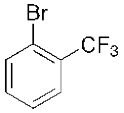
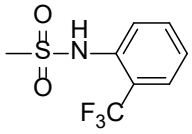
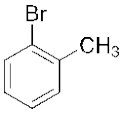
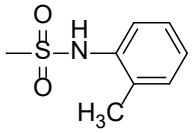
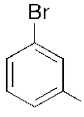
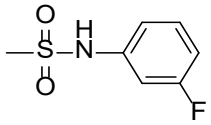
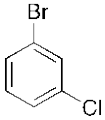
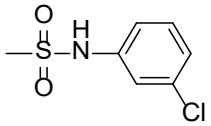
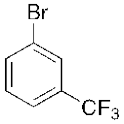
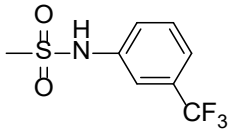
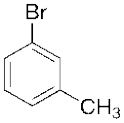
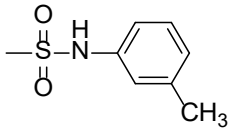
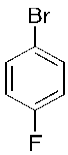
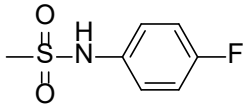
Next, we investigated the effect of different bases, such as Cs_2CO_3 and K_2CO_3 on the arylation process (entries 6 and 7). A suitable base will facilitate the removal of the HBr in the catalytic cycle to enable it to form a highly reactive Cu(III) and set the stage for the final reductive elimination step. Therefore, it is essential to evaluate the different bases and the consequent experimental yield that each base can produce. In this study, Cs_2CO_3 was shown to be the best base affording the product in 76% yield while K_2CO_3 also proved to be a suitable base for the reaction.

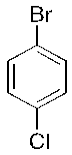
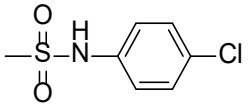
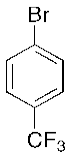
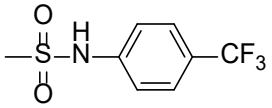
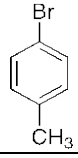
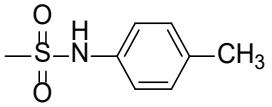
In the solvent screening experiments, polar aprotic solvent such as DMF has a high polarity constant which enables it to act as an effective solvent to dissolve the polar reactants and facilitate the coupling reaction. This might account for the stronger ability of the solvent to stabilize the catalytic intermediates thus affording a higher yield compared to DMSO. On the contrary, both *t*-butanol and toluene and were shown to be unsuitable for the reaction as trace amount of the products were detected in both cases. In summary, the N-arylation of methane sulfonamide was achieved by using a combination of CuI (20 mol-%) and Cs_2CO_3 (2 equiv), stirring the mixture at 135 ºC in DMF.

With the optimized reaction conditions, we carried out the coupling reactions of differently substituted bromobenzenes with methanesulfonamide to investigate the generality of the system.

Table 2. CuI catalyzed *N*-arylation of *p*-toluenesulfonamide with aryl bromides.[a]



Entry	ArX	Product		Yield (%)[b]
1			**2a**	76
2			**2b**	51
3			**2c**	64
4			**2d**	38
5			**2e**	36
6			**2f**	58
7			**2g**	68
8			**2h**	59
9			**2i**	51
10			**2j**	63

11			**2k**	72
12			**2l**	60
13			**2m**	60

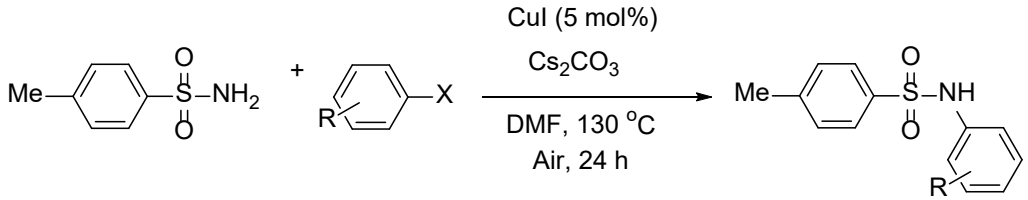
[a] Unless otherwise stated, the reactions were carried out with 1 equivalent of methanesulfonamide, 3.0 equivalents of bromobenzene, 0.2 equivalents of CuI, 2.0 equivalents of Cs_2CO_3 and 750 µL of DMF at 135°C for 18-24 hours. [b] Isolated yield of product after flash column chromatography.

The aim of the substrate studies is to determine the electronic effect and the position of the substituted groups of the various aryl bromides on the product yield. As shown in Table 2, it was evident that ortho-substituted aryl bromo generally gave rise to poor yields regardless of the electronic properties of the substituents. This could be due to the steric hindrance of the substituents on the ortho-position which hamper the oxidative addition step in the catalytic cycle. The steric effect was most evident in the case of -CH_3 substituted aryl bromides (Table 2, entry 5) which afforded the lowest yield as compared with the other ortho-substituents of the aryl bromides. This is to be anticipated since the CH_3 is the bulkiest group and thus the steric effect will be the most pronounced as compared to the other ortho-substituents. The same effect was also observed for the CF_3 substituent (entry 6) in the ortho position.

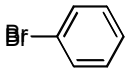
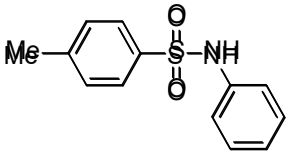
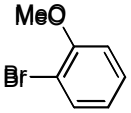
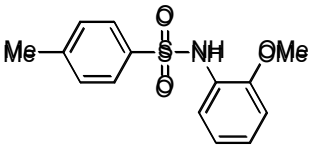
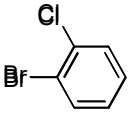
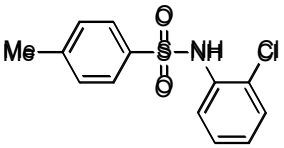
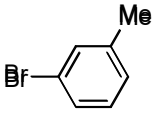
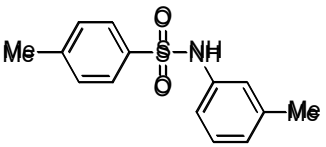
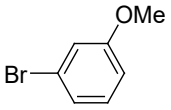
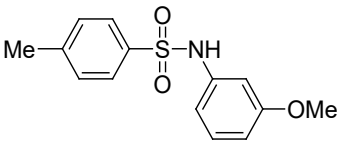
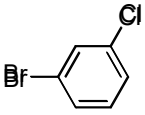
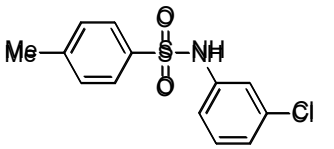
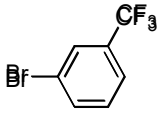
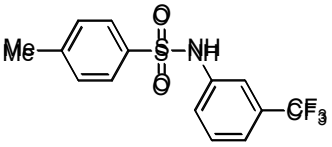
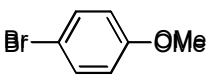
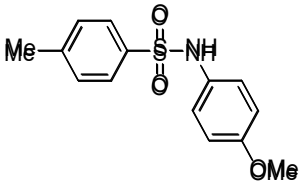
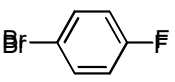
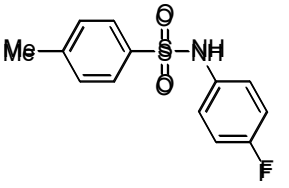
The effect on the yields obtained with the halide substituents in the meta- and para-positions were investigated. The reactions afforded comparable yields, implying that electronic effect of a second halide substituent on the aryl halides does not have any pronounced impact on the overall outcome. It noteworthy that this cross-coupling is highly chemoselective as cross coupling takes place preferentially at the carbon with the Br atom despite the existence of either F or Cl atom on the same electrophilic partner. The cross-coupling reactions using meta- and para- substituted -OCH_3 aryl bromides were futile as trace amount of the products were detected on TLC during the monitoring stage. Henceforth, the trace products were not isolated and reported in Table 2. This is due to the lower reactivity imparted by the electron-donating nature of the -OCH_3 substituent. Subsequently, this electronic effect deactivates the aryl bromide from undergoing the oxidative step and thus greatly hinders the progress of the reaction, resulting in trace products. This also accounted for the results obtained whereby aryl bromides with electron donating group (EDG) substituents in the meta- and para- position leads to reduce yields as compared to the electron withdrawing group (EWG) substituents.

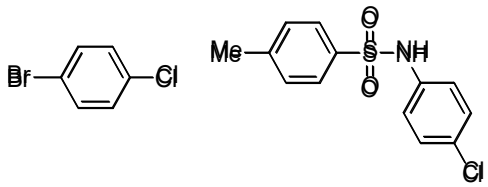
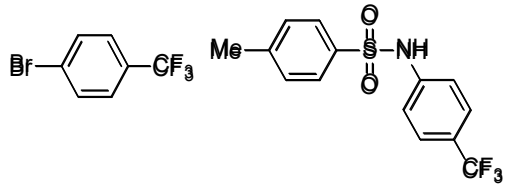
Next, we broaden the scope of this catalytic system to aromatic sulfonamides by reacting *p*-methanesulfonamides with selected aryl bromides under the optimized conditions. The results are shown in Table 3.

Table 3. CuI catalyzed *N*-arylation of *p*-toluenesulfonamide with aryl bromides.[a]



1 **2**

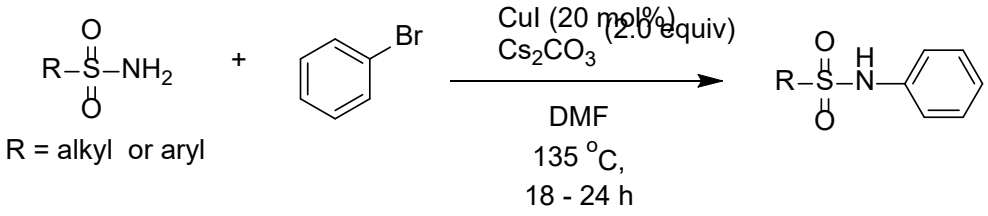
Entry	ArX	Product		Yield[b] (%)
1			**3a**	78
2			**3b**	48
3			**3c**	44
4			**3d**	59
5			**3e**	61
6			**3f**	70
7			**3g**	70
8			**3h**	60
9			**3i**	59

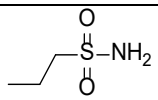
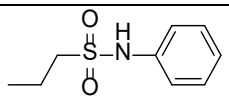
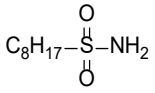
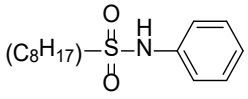
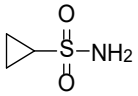
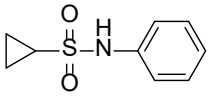
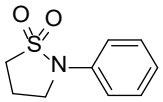
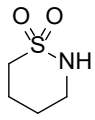
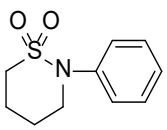
10		**3j**	56
11		**3k**	76

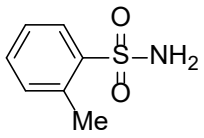
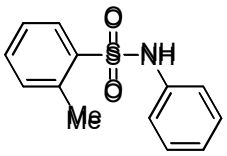
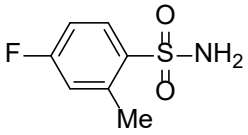
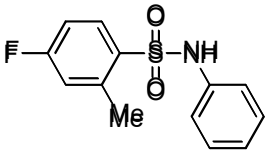
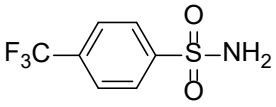
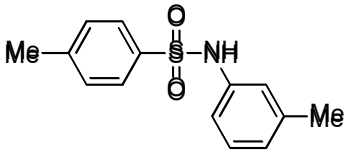
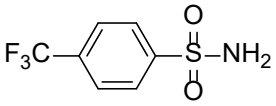
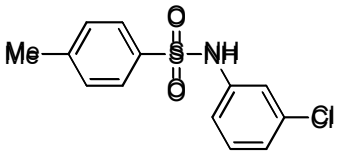
[a] Unless otherwise stated, the reactions were carried out with 1 equivalent of *p*-toluene sulfonamide, 3.0 equivalents of bromobenzene, 0.2 equivalents of CuI, 2.0 equivalents of Cs_2CO_3 and 750 µL of DMF at 135°C for 18-24 hours. [b] Isolated yield of product after flash column chromatography.

In general, the corresponding N-arylated sulfonamides were obtained in good and excellent yields using 20 mol% of catalyst loading (Table 3, entries 1-14). Similar trends were observed for these coupling reactions in comparison to those employing aliphatic sulfonamides. Ortho-substituted aryl bromides hamper the cross-coupling reaction, affording the expected products in lower yields compared to the meta- and para- substituted counterparts. There were no significant electronic effects observed for meta- (entries 4–6) and para- (entries 7–11) substituted aryl iodides.

Table 4: CuI catalyzed *N*-arylation of sulfonamides with bromobenzene.[a]



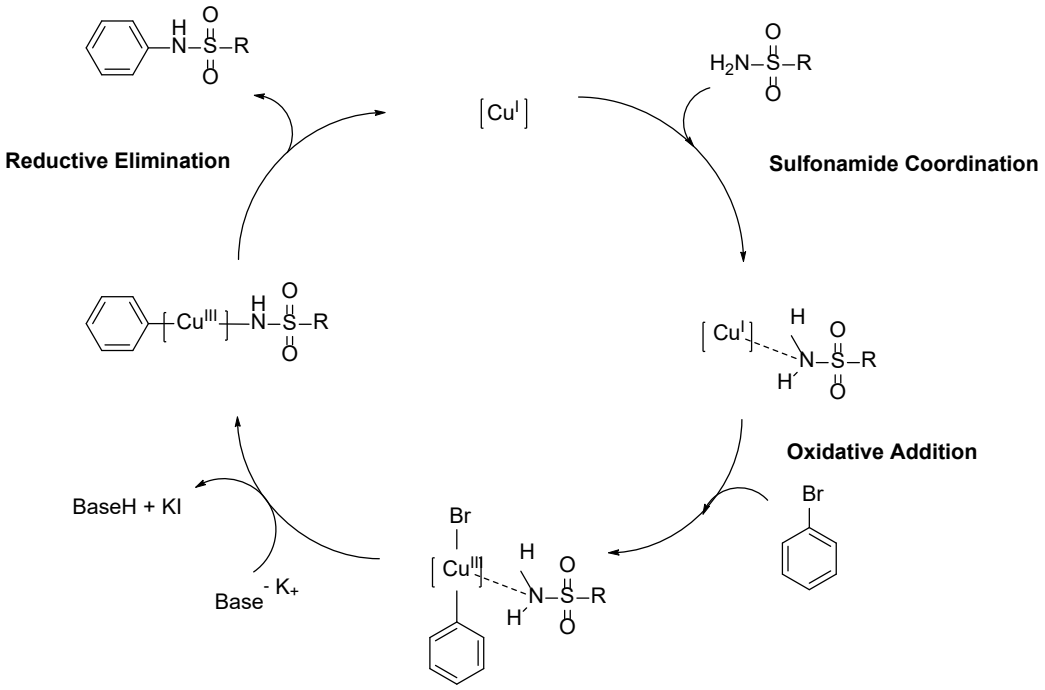
Entry	ArX	Product	Yield (%)[b]
1		**4a** 	54
2		**4b** 	48
3		**4c** 	80
4		**4d** 	75
5		**4e** 	50

6			**4f**	62
7			**4g**	69
8			**4h**	62
9			**4i**	68

[a] Unless otherwise stated, the reactions were carried out with 1 equivalent of sulfonamide, 3.0 equivalents of bromobenzene, 0.2 equivalents of CuI, 2.0 equivalents of Cs_2CO_3 and 750 µL of DMF at 135°C for 18-24 hours. [b] Isolated yield of product after flash column chromatography.

Finally, we proceed with the cross coupling of various alkyl and aryl sulfonamides with selected aryl bromides to further test the practicality of the protocol. The results are shown in Table 4. In the study using alkyl sufonamides, it was shown that the catalytic system was effective for all the investigated sulfonamides with the intended N-arylated adducts obtained ranging from moderate to good yields. With reference to the straight chained aliphatic sulfonamides, it was noted that the product yields decreased with increasing carbon chain length of the alkyl group possibly due to a decrease in substrates solubilities in the polar aprotic solvent (Table 4, entries 1 and 2). The reaction using a representative cyclopropyl substituent was successful whereby a good yield of 80% was obtained (entry 3). The N-arylation of cyclic sulfonamides using cyclopentyl and cyclohexyl groups were also promising, affording the derivatives in 75% and 50% yields, respectively (entries 4 and 5). As for the aromatic sulfonamides derivatives, the yields obtained were comparable with no significant electronic effects from either the sulfonamides and representative aryl bromides (entries 6 – 10).

A tentative mechanistic pathway for the Cu catalysed reaction is illustrated in Scheme 1 based on reported literature. In the reaction between methanesulfonamide and bromobenzene, the methanesulfonamide nucleophile coordinates with the active copper(I) species via its lone pair of electrons preceded by the oxidative addition of the bromobenzene species leading to the generation of a copper(III) complex. Subsequently, an acid base reaction takes place whereby HBr was eliminated from the catalyst intermediate by the base Cs_2CO_3 to form the highly reactive copper(III) complex. The final step involves reductive elimination to release the intended *N*-arylated product while the catalyst is regenerated and retains its original oxidation state of +1.



Scheme 1. Proposed mechanism for the *N*-arylation of methanesulfonamide

EXPERIMENTAL

General Procedure for N-arylation of sulfonamides

To an 8 mL reaction vial, the following reagents were added sequentially: sulfonamide (1.5 mmol), Cu salt (0.30 mmol), K_3PO_4 (2.0 equivalent), dimethylformamide (750 μl) and aryl bromide (4.5 mmol, 3.0 equiv.). The vial was tightly sealed with parafilm followed by adhesive tape. The sealed vial was then placed in a silicon oil bath set at 135 °C. The reaction mixture was subsequently stirred under reflux in the closed system at the pre-set temperature overnight. At the end of the reaction, the reaction mixture was filtered through a 10 mL sintered funnel packed with Celite under vacuum. The remaining residue was washed with 3 x 10 mL of methanol and the filtrate was quantitatively collected. The combined organic fraction was dried with anhydrous $MgSO_4$ and the crude product was obtained under reduced pressure with the aid of a rotary evaporator. The crude product was then purified by column chromatography on silica. The structure of the final *N*-arylated derivative was confirmed by 1D-NMR analysis.

N-Phenylmethanesulfonamide (2a)

Following the general procedure, the coupled product was obtained as a light brown solid after purification by flash chromatography.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.41 (m, 2 H), 7.19 – 7.28 (m, 3 H), 6.76(bs, 1H), 3.03 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 129.7, 125.4, 120.8, 39.2.

HRMS Calcd [M^-]: 171.0354. Found: 171.0392.

All spectral data correspond to those given in the literature.[13]

CONCLUSION

In summary, we have demonstrated the coupling of both aliphatic and aromatic sulfonamides with a wide selection of substituted aryl bromides using CuI as the catalyst under ligand free condition. A good representative of *N*-arylated aromatic and aliphatic a sulfonamides were successfully synthesized in moderate to excellent yields. The ligand-free conditions coupled with a low catalyst loading presented a more practical and economical approach compared to other reported methods. Moreover, the protocol is simple to perform and the reagents for the catalytic system are commercially available which thus make it economical and sustainable for industrial applications.

ACKNOWLEDGEMENT

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Supporting Information: Full experimental detail, ^{1}H and ^{13}C NMR spectra and elemental analysis. This material can be found via the "Supplementary Content" section of this article's webpage.'

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Copper catalyzed N-arylation of sulfonamides with aryl bromides under ligand-free conditions

Yong-Chua Teo*, Yun-Ru Tan, Kyra Saanvi M., Chu-Ken Loh, Swee-Ngin Tan

A practical strategy for the C-N cross-coupling of both aliphatic and aromatic sulfonamides with a variety of substituted aryl bromides is reported. Under the optimized conditions, a good representative of N-arylated products were obtained in good to excellent yields (up to 78 %) under the ligand-free conditions.