Copper-Catalyzed N-Arylation of Sulfonimidamides

Stéphane Azzaro, Marine Desage-El Murr, Louis Fensterbank,* Emmanuel Lacôte,* Max Malacria*

UPMC Université Paris 6, Institut Parisien de Chimie Moléculaire (UMR CNRS 7201),
C. 229, 4 place Jussieu, 75252 Paris Cedex 05, France
Fax +33(1)44277360; E-mail: louis.fensterbank@upmc.fr; E-mail: emmanuel.lacote@upmc.fr; E-mail: max.malacria@upmc.fr

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Abstract: An efficient copper-catalyzed method for introducing aryl substituents on the amino end of sulfonimidamides has been developed. Microwave irradiation allows for short reaction times and good yields, and a variety of aromatics can be coupled.

Key words: sulfonimidamides, copper catalysis, microwave, amino ligands, N-coupling

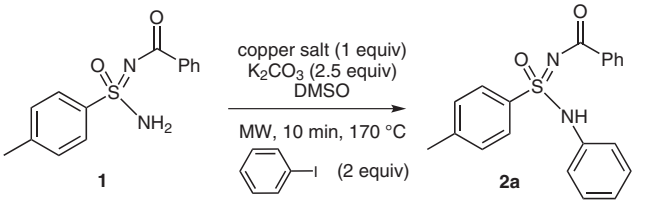
Sulfonimidamides are chiral analogues of sulfonamides with a stereogenic sulfur atom.[1] These compounds have been studied for potential biological applications as analogues of the aspartic acid transition state in metalloproteases,[2a] HNO (nitroxyl) donors,[2b] and analogues of oncolytic sulfonylureas[2c] and recently in organocatalysis.[3] While the first report on sulfonimidamides from the Levchenko group[4] dates back to the early 1960s, the chemistry[5] of these hexavalent sulfur derivatives has long been overshadowed by that of their popular cousins sulfonamides and sulfones.[6] Sulfonimidamides have been shown to act as efficient nitrene precursors in the presence of hypervalent iodine reagents under both copper- and rhodium-catalyzed conditions to give aziridination,[7] imination[7a,8] as well as C–H insertion[9] products. All these methods make use of sulfonimidamides with a free amino group as the reactive end of the molecule. As part of a program devoted to the chemistry of oxidized sulfur moieties,[10] we thought it would be useful to develop a straightforward access to amino-functionalized sulfonimidamides.

Metal-mediated coupling reactions provide an efficient and flexible pathway to form carbon–heteroatom bonds. Moreover, the use of ligands in these systems provides an option to introduce asymmetric versions and generate enantiopure products. Notably, following the pioneering work of Ullmann,[11] copper-mediated couplings have been an ever-growing area in the last decades and have been extensively used in many fields of synthesis.[12]

Regarding C–N bond formation using sulfonylated derivatives, Bolm recently reported a stoichiometric copper-mediated coupling reaction[13] between sulfonimidamides and halogenated aryl derivatives, yielding derivatives substituted on the secondary amino group. Several copper(I) salts were tested in this study and electron-poor as well as electron-rich aryl moieties could be coupled.

Our first attempts to obtain N-substituted sulfonimidamides using Bolm's protocol suggested that the use of microwave activation could allow for shorter reaction times and higher yields. A generic coupling between a sulfonimidamide and phenyl iodide was first tested (Table 1) and a variety of copper(I) and copper(II) salts gave satisfactory overall results, with yields ranging from 72–87%.

Table 1 Stoichiometric Copper-Mediated Coupling



Entry	Copper catalyst	Yield (%)
1	CuCl[a]	87
2	CuBr	80
3	CuI	80
4	$Cu(EH)_2$[b]	80
5	$Cu(OAc)_2$	72

[a] Similar reaction performed under thermal conditions (100 °C, 20 h) gave 65% yield.
[b] $Cu(EH)_2$: copper(II) ethyl hexanoate.

We next tried to use catalytic amounts of the copper salt with a classic DMEDA ligand (*N*,*N*′-dimethylethylenediamine) and were pleased to see that this reaction could perform under such catalytic conditions (Table 2). Copper sulfate gave an initial yield of 80% (entry 4) and, while decreasing the catalyst loading from 15–10 mol% led to significant lowering of yield under microwave conditions (entry 5), switching to thermal conditions gave the expected product in 93% yield (entry 6).

Subsequent screening of the ligand (Table 3) led us to investigate copper ligands such as ethylenediamine derivatives, phenanthrolines, vicinal diamines, and the previously mentioned 4-hydroxyproline, following Ma's results.[12c]

While DMEDA itself gave the expected aryl-substituted sulfonimidamide in 80% yield, switching to less hindered

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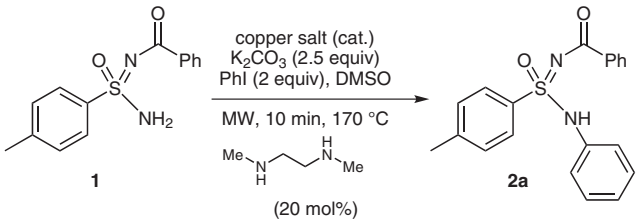
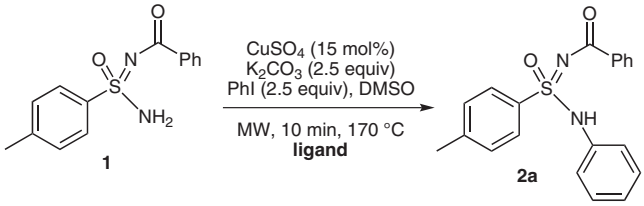
Table 2 Catalytic Conditions for the Copper-Catalyzed Coupling

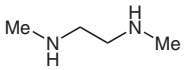
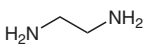
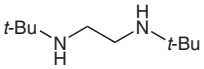
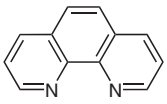
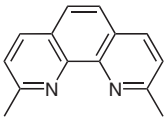
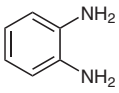
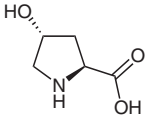


Entry	Copper Catalyst (mol%)	mol%	Yield (%)
1	CuCl	15	50
2	Cu_2O	15	30
3	$Cu(OAc)_2$	15	74
4	$CuSO_4$	15	80
5	$CuSO_4$	10	60
6[a]	CuCl	15	93

[a] Thermal conditions: 80 °C, 16 h.

Table 3 Influence of the Ligand

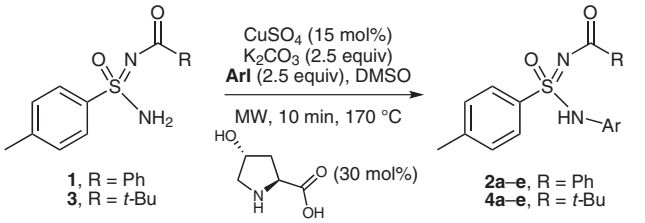


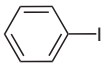
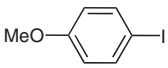
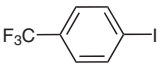
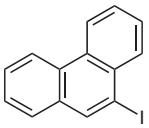
Entry	Ligand	mol%	Yield (%)
1		20	80
2		20	61
3		20	63
4		20	37
5		20	19
6		20	50
7		20 30 40	82 91 77

unsubstituted ethylenediamine (entry 2) or more sterically congested *N*,*N*′-*tert*-butylethylenediamine (entry 3) only led to lesser yields. Phenanthroline derivatives (entries 4 and 5) gave even more disappointing results with yields below 50% whereas the vicinal diamine (*ortho*-aminoaniline, entry 6) gave average yields, albeit slightly higher. However, 4-hydroxyproline (entry 7) gave very satisfactory results, with an optimum loading of 30 mol% that provided the final product in 91% yield.

Having determined the best catalytic system, we then investigated the scope of the reaction in terms of tolerated iodide structures along with a modification of the amide group from phenyl to *tert*-butyl (Table 4). A variety of aromatics was efficiently coupled with yields ranging from 50–93%. Although heteroaromatics (entries 3 and 4), electron-donating (entries 5 and 6), electron-withdrawing (entries 7 and 8) groups and bulky rings (entries 9 and 10) seem well tolerated, the best results remained for the coupling of simple phenyl (entries 1 and 2). However, although a chiral ligand had been used, no resolution could be observed and only racemic mixtures of products were obtained.[14]

Table 4 Substrate Scope and Influence of Amide Group

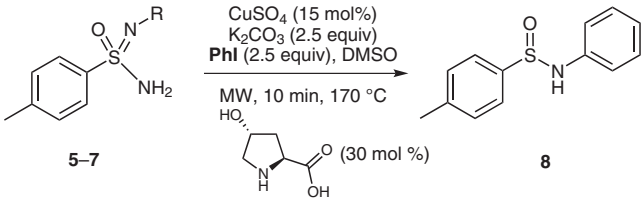


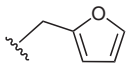
Entry	ArI	R	Product	Yield (%)
1		Ph	**2a**	91
2		*t*-Bu	**4a**	93
3		Ph	**2b**	54
4		*t*-Bu	**4b**	75
5		Ph	**2c**	88
6		*t*-Bu	**4c**	71
7		Ph	**2d**	70
8		*t*-Bu	**4d**	60
9		Ph	**2e**	50
10		*t*-Bu	**4e**	77

This method was also applied to the N-arylation of sulfonimidamides bearing a carbonyl-free side chain (Table 5). Interestingly, in this series, the expected arylated sulfonimidamides were not isolated. Instead, N-arylated sulfinamide products were observed.[15]

In conclusion, we have developed an efficient copper-catalyzed method for introducing aryl substituents on the amino end of sulfonimidamides. This system works on a variety of structures but does not allow enantiomeric excesses to be obtained. This is probably due to the high flexibility of the system and a more constrained and rigid substrate might be better suited for that matter. A new

Table 5 Sulfonimidamides Bearing a Carbonyl-Free Side Chain



Entry	Compound	R	Yield (%)
1	**5**	Bu	65
2	**6**	cyclohexyl	99
3	**7**		75

reactivity on nonelectron-deficient sulfonimidamides was also unveiled.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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