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A mild and efficient copper-catalyzed N-arylation of unprotected sulfonimidamides using boronic acids

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ABSTRACT

An efficient and low cost copper catalyzed system for N-arylation of sulfonimidamides has been developed. The reaction proceeds at room temperature under base free conditions. Various *N*-aryl, *N*-heteroaryl, and *N*-cyclopropyl sulfonimidamides were obtained in good to excellent yields.

The chemistry of sulfonamide has been widely explored due to their application in the synthesis of biologically active molecules in drug discovery.[1] Surprisingly, the analogous sulfonimidamides have been explored to a lesser extent. Sulfonimidamides, which has a nitrogen atom in place of oxygen, were shown as bioisostere of sulfonamide in medicinal chemistry.[2] Sulfonimidamides are explored in the synthesis of biologically active compounds, such as oncolytic sulfonylureas[3] and for the preparation of tetrahedral transition state analogues of aspartic acid and metallo protease.[4] Sulfonimidamides containing compounds are reported as pesticidal agents[5] and also as sodium channel antagonists.[6]

Sulfonimidamides were first reported in 1960 by Levechenko. This found some application in organic synthesis, such as aziridation of olefins,[7] imination of sulfides,[8] and C–H amination of hydrocarbons.[9] Bolm and coworkers explored the use of sulfonimidamides in organocatalytic asymmetric aldol reactions[10] and as a chiral ligand in enantioselective Henry reaction.[11] Recent studies were reported in asymmetric hydrogenation of cyclic enamides by using rhodium and iridium complexes of sulfonimidamido-based phosphoramidites (SIAPhos).[12]

Unprotected sulfonimidamides (Fig. 1, $R^3 = H$, R^1, $R^2 \neq H$) were initially reported by Johnson et al. [13]and later Arvidsson et al.[14] developed an efficient synthetic route based on the approachreported by Bolm et al.[15] In subsequent investigations, they have developed an efficient catalyst system for N-arylation of unprotected sulfonimidamides with aryl bromides using 3 mol % of palladium catalyst (Ru–Phos precatalyst). An efficient copper catalyzed N-arylation of N-protected sulfonimidamides was reported by Bolm[16] and Malacria[17] using aryl halide. Later Arvidsson explored the synthesis of aryl and heteroaryl acyl sulfonimidamides by palladium catalyzed carbonylation.[18] Though these methods are very useful and efficient it would be desirable to utilize an environmentally benign catalyst system for this transformation. In addition to this an alternate substrate in place of aryl halides that could facilitate a chemo selective reaction in the presence of reactive functional groups would be advantageous. Our intention was to explore the utility of the well documented Chan–Lam coupling reaction in the synthesis of N-arylated sulfonimidamides. Herein we wish to report the results of copper catalyzed coupling of unprotected sulfonimidamides with arylboronic acids as an alternative to Pd catalyst and aryl halides.

Highly efficient methodology for the synthesis of Boc protected sulfinamide **1** was established by Bolm and coworkers[19] Arvidsson and coworkers, later stabilized the synthesis of Boc protected sulfonimidamides **2** by oxidative chlorination of protected sulfinamide **1** using NCS (3.0 equiv) in acetonitrile, followed by amination of the resulting sulfinimidoyl chloride with morpholine in situ.[14] The reported yield for this reaction over two steps was 61% after 43 h. We were able to improve the yield and time with a slight modification of this procedure (Scheme 1).

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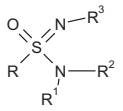


Unprotected sulfonimidamides (R^3 = H, R^1,R^2= Alkyl)
N-protected sulfonimidamides (R^1,R^2= H, R^3= PG)

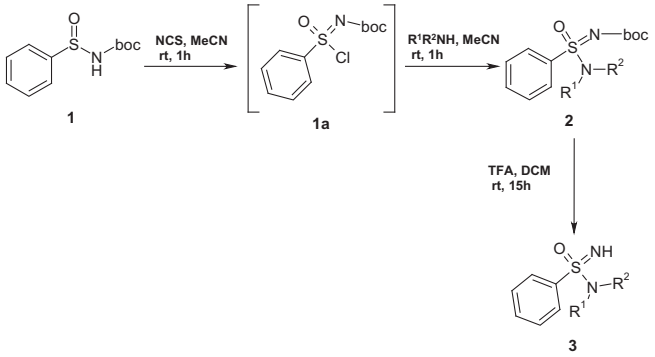
Figure 1. Structure of sulfonimidamides.

The previous reaction was reported without isolating intermediate **1a**. In our modified procedure, compound **1a** was isolated by an aqueous workup after the oxidative chlorination and morpholine was added to a solution of crude product in acetonitrile. The yields for Boc-protected sulfonimidamides **2a** were improved up to 89% and the reaction time was reduced to 2 h (Table 1, entry 1).[20] The substrate scope was tested with various secondary amines and the results of this reaction are summarized in Table 1. Good yields were obtained for piperidine (Table 1, entry 2), pyrrolidine (Table 1, entry 3), and diethyl amine (Table 1, entry 4). Finally unprotected sulfonimidamides **3a**–**d**[21] were obtained by deprotection of Boc using TFA in DCM as reported earlier.

The next goal was to perform the N-arylation of the above prepared sulfonimidamides using Cham–Lam coupling reaction. Our investigation started with the coupling of 4-(phenylsulfonimidoyl)morpholine **3a** and phenyl boronic acid **4** in dichloromethane solvent using different copper salts.

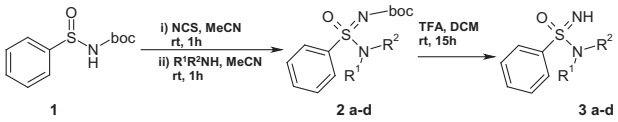
Based on the initial results as depicted in Table 2 anhydrous copper acetate was found to be the optimum catalyst for this transformation and showed best results under base-free conditions but the reaction took 48 h to complete in DCM (Table 2, entry 4). Other copper salts such as CuCl and $CuSO_4$ (anhydrous) also worked but the purification of the product took longer time due to some close impurities formed in the reaction (Table 2, entry 1 and 2) and did not work when CU-TMEDA was used as the catalyst (Table 2, entry 3). The reaction worked well when MeOH was used as solvent at room temperature with $Cu(OAc)_2$ (Table 2, entry 5) and $CuSO_4$ (Table 2, entry 10) gave moderate yields. CuCl (Table 2, entry 11) was inactive under the same conditions. We next studied the effect of catalyst loading and the arylboronic acids. Best results were obtained with 10 mol % of copper acetate and 2.3 equiv of boronic acid under base free conditions (Table 2, entry 3). Having optimized the reaction conditions[22] we next explored the scope of the reaction with various arylboronic acids. The results of this are summarized in Table 3.

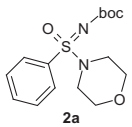
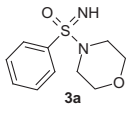
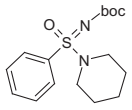
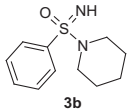
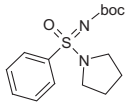
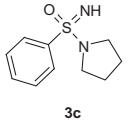
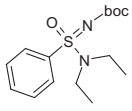
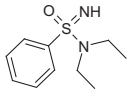
As can be seen from Table 3 good results were obtained with arylboronic acids with para substitution despite the electronic



Scheme 1. Synthesis of unprotected sulfonimidamides **3**.

Table 1
Synthesis of unprotected sulfonimidamides



Entry	Product	Yield[a] (%)	Product*	Yield[b] (%)
1	 2a	90	 3a	89
2	 2b	89	 3b	88
3	 2c	89	 3c	88
4	 2d	86	 3d	81

Reaction conditions:
[a] (i) NCS (3.0 equiv), MeCN, rt, 1 h. (ii) R^1R^2NH (2.5 equiv), MeCN, rt, 1 h:
[b] TFA, DCM, rt, 15 h. All the reactions were started with 2 g scale.
* Product after deprotection of Boc group.

nature of the substitution (Table 3, **5b**–**f**). Moderate yields of the products were obtained with *ortho* substituted arylboronic acid (Table 3, **5h**) but it was poor with a bulkier *ortho* substituent (Table 3, **5g**). It is noteworthy that many reactive functional groups such as bromo, ester, cyano, and methanesulfonyl (Table 3, **5c**–**f**) were tolerated in the above mentioned reaction conditions. The resultant products could be further derivatized using standard transformations known for these functional groups.

Heterocyclic boronic acids reacted well under these conditions. Good yields were obtained for 3-pyridyl, pyrimidin-5-yl, and 3-thiophene boronic acids (Table 3, **5i**–**k**). Cyclopropylboronic acid did not react under the optimized reaction conditions. It worked well in the presence of a ligand and base under heating conditions ($Cu(OAc)_2$ (1.0 equiv), bipyridyl (0.8 equiv), Na_2CO_3, DCE, 90 °C, 3 h, sealed tube) (Table 3, **5l**).

The optimized reaction conditions[21] were also applied to alternatively substituted unprotected sulfonimidamides (Fig 1, R^3 = H) such as *N*-(phenylsulfonimidoyl)piperidine **3b**, *N*-(phenylsulfonimidoyl)pyrrolidine **3c** and *N*-(phenylsulfo-nimidoyl)diethyl **3d**. N-arylation of these three sulfonimidamides showed good results with phenyl, 4-bromophenyl, and 4-methanesulfonylphenylboronic acids (Table 4, **6a**–**i**).

In conclusion, we have improved the yield of sulfonimidamides by modifying the existing procedure with a reduced reaction time. We have enabled a low-cost catalyst system as an alternative to the palladium catalyst for N-arylation of unprotected sulfonimidamides. Boronic acids were used in place of aryl halides which were useful especially in the case of substrates containing reactive functional groups. Excellent yields were obtained with aryl, heteroaryl, and cyclopropyl boronic acids. This method would compare well and complement existing methods.