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A mild and efficient new synthesis of aryl sulfones from boronic acids and sulfinic acid salts

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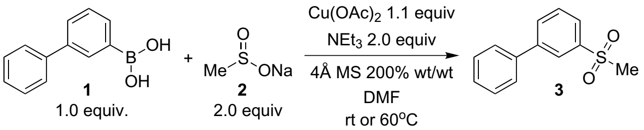
Abstract—A new efficient and mild preparation of sulfones from boronic acids and sulfinic acid salts is reported. The cross-coupling reaction mediated by cupric acetate gives access to a variety of sulfones in excellent yield.

Sulfones are an important class of functional group in organic chemistry and medicinal chemistry as well. Aryl sulfones are widely used in medicinal chemistry and found on several drugs, including the recently developed selective COX-2 inhibitor Vioxx.[1] Many methodologies exist for the preparation of aryl sulfones. Among these methods figure the oxidation of corresponding sulfides,[2] the reaction of organolithium or Grignard reagents with sulfonate esters[3] and the sulfonylation of arenes,[4] which are attractive methods because of their simplicity. However, the incompatibility of various functional groups with these methods reduces their scope of application. More recently, the metal-mediated cross coupling reactions of sulfinic acid salts with aryl halides and triflates were reported as mild alternatives to these previous methods.[5–8] Under these milder conditions, more functional groups are tolerated, but these reactions are limited to aryl bromides, aryl iodides, and aryl triflates, and use air or moisture sensitive reagents.

Taking into account the wide variety of boronic acids and boronate esters commercially available or easily accessible and the compatibility of these compounds with numerous functional groups, we considered using these boron derivatives as precursors in the preparation of sulfones. Work published by Evans et al.,[9] Lam et al.,[10] and more recently by Guy et al.[11] demonstrated the potential of cross coupling reactions mediated by copper to promote the formation of aryl ether, C–N bond, and thioether from boronic acids under mild conditions and in good yields. Based on these reports, we sought to apply this methodology for the preparation of aryl sulfones using sulfinic acid salts as reagents. Herein, we wish to report the results from our investigation that led to the development of this new mild and efficient methodology.

To validate the proposed transformation and optimize the reaction conditions, we used 3-biphenylboronic acid and sodium methanesulfinate as testing substrates (Scheme 1). For our first attempt, we applied the conditions developed by Evans et al. for the formation of biarylether,[9] but replacing CH_2Cl_2 by DMF due to solubility problems (Scheme 1). The result from this first reaction was encouraging, since the desired sulfone was obtained in a 70% yield. The reaction was only 50% complete after 12 h at rt, but heating the reaction mixture at 60 °C for an additional 2 h led to complete conversion of the starting material. Two side products were isolated and identified as biphenyl coming from the reduction of the boronic acid and as 3-hydroxy biphenyl, which is probably related to water presence as described by Evans et al.[9] for the preparation of biaryl ether.



Scheme 1. Cross-coupling reaction between aryl boronic acid and sodium methanesulfinate.

Keywords: Aryl sulfone; Cross-coupling reaction; Boronic acid.

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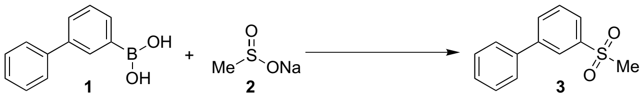
In order to improve the yield of the reaction, we first investigated temperature and solvent effects (Table 1). To increase the rate, the reaction was repeated in DMF at 60 °C and surprisingly the yield went down between 10% and 60% (Table 1, entry 1). Under the same conditions, use of DMSO as solvent increased the yield to 86% (Table 1, entry 2). However, yields were very modest with other solvents such as THF, isopropanol, and 1-methyl-2-pyrrolidinone (Table 1, entries 3–5). In these cases, the reaction was not as clean as for the reaction done with DMF or DMSO and more reduction of the boronic acid was observed. Then, we looked at the reaction temperature, and it appeared that the reaction was cleaner at rt than at 60 °C. In fact, more reduction of the boronic acid was observed at higher temperature. On the other hand, the cross coupling reaction did not go to completion at room temperature with NEt_3 as base whether we used DMF or DMSO as solvent. The presence of a base was found to be necessary to the reaction, since only trace amount of sulfone was isolated without it. Different bases were then evaluated to improve the rate and the yield of the reaction. Organic and inorganic bases were screened, such as DBU, cesium carbonate, cesium fluoride, pyridine, and potassium carbonate. Potassium carbonate was the only one that resulted in significant yield improvement over NEt_3. Moreover, the reaction was completed after 16 h at rt using potassium carbonate when carried in DMSO. Under these conditions, the desired sulfone was isolated in 97% yield (Table 1, entry 6). As observed with NEt_3, lower yield (78%) was obtained at higher temperature (Table 1, entry 7) despite a faster reaction rate. The presence of O_2 was found to be favorable to the reaction, as observed for biaryl ether formation,[9] and only a trace amount of sulfone was formed when the reaction was carried out under N_2 atmosphere. Many copper salts were tested [CuI, $CuBr_2$, $Cu(NO_3)_2$, $Cu(acac)_2$, $Cu(TFA)_2$] as reaction promoter, but they were all inferior to $Cu(OAc)_2$ and stoichiometric quantity of copper reagent was necessary. From our optimization work, the best conditions for the reaction were defined as follows: 1 equiv of boronic acid, 1.5 equiv of sulfinic acid salt, 1.1 equiv of $Cu(OAc)_2$, 2 equiv (wt/wt) of 4 Å molecular sieves in DMSO at rt in a flask equipped with an air drying tube.[12]

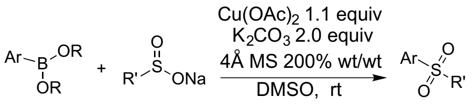
Table 1. Optimization of reaction conditions



Entry	Solvent	Temperature (°C)	Base	Yield (%)
1	DMF	60	NEt_3	60
2	DMSO	60	NEt_3	86
3	THF	60	NEt_3	15
4	*i*PrOH	rt	NEt_3	30
5	NMP	60	NEt_3	30
6	DMSO	rt	K_2CO_3	97
7	DMSO	60	K_2CO_3	78

Since many therapeutic agents bear a methyl sulfone group, we mainly focused our efforts on cross coupling reactions using sodium methanesulfinate. Following the procedure described above, many methyl sulfones were prepared in good to excellent yield as listed in Table 2. As reported with our model substrate 3-biphenylboronic acid (entry 1), the cross coupling reaction was highly effective with a wide range of boronic acids[13] with various functional groups. Electron rich and electron deficient substrates reacted quite similarly to afford methyl sulfones in comparable yield. The substitution pattern of the aromatic ring did not greatly affect the reaction, and *ortho*, *para*, and *meta* substitution were well tolerated.

Table 2. Synthesis of sulfones from boronic acid



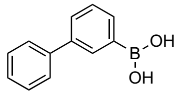
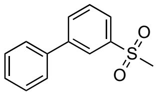
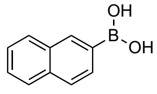
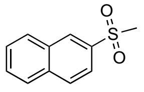
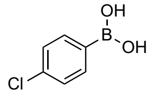
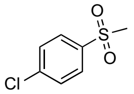
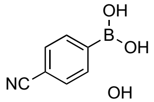
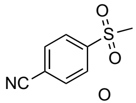
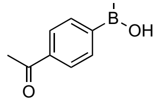
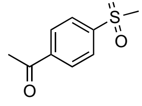
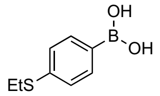
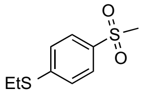
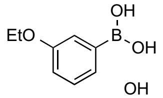
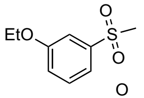
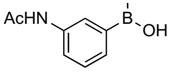
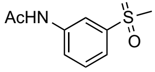
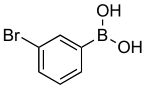
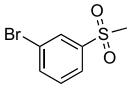
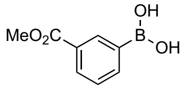
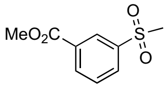
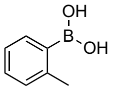
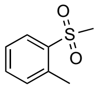
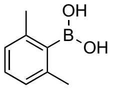
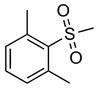
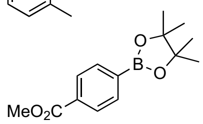
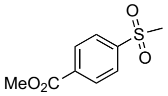
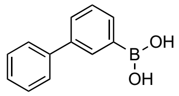
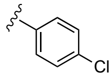
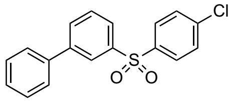
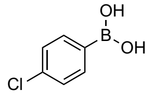
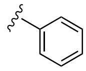
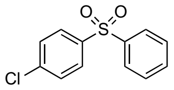
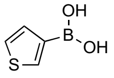
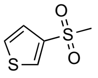
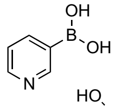
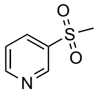
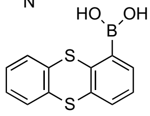
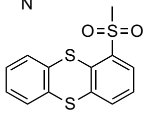
Entry	Starting material	R′	Product	Yield (%)[a]
1		Me		97
2		Me		83
3		Me		66
4		Me		76
5		Me		71[b]

Table 2 (*continued*)

Entry	Starting material	R′	Product	Yield (%)[a]
6		Me		83
7		Me		89
8		Me		69
9		Me		70
10		Me		78
11		Me		70
12		Me		63[b]
13		Me		80[b]
14				61
15				60
16		Me		54
17		Me		19
18		Me		42

[a] Isolated yield.

[b] Reaction heated to 60 °C.

Of particular note is the sterically hindered 2,6-dimethylbenzene boronic acid, which reacted to give the corresponding sulfone (entry 12) in good yield. In this case, the reaction needed to be heated to 60 °C to go to completion. Bromine and chlorine atom (entries 3 and 9) were also well tolerated as substituents on the aryl boronic acid and could be used for further functionalization on the aryl ring. Of particular interest is the reaction with 3-acetamidobenzene boronic acid (entry 8), which afforded the methyl sulfone in good yield compared to the corresponding reaction with aryl halide substrates, which afford lower yield for similar cross coupling reaction using copper salts.[6] The reaction also proceeded with a pinacol boronate ester in excellent yield (entry 13), thus expanding the scope of the reaction. In addition, this methodology can be extended to the preparation of diaryl sulfones, which are also compound of interest. Thus, following the same procedure, diaryl sulfones were prepared in good yield (entries 14 and 15) from commercially available aryl sulfinic acid salts. The cross coupling reaction also proceeded with certain heterocyclic substrates such as thiophene-3-boronic acid, pyridine-3-boronic acid, and thianthren-1-boronic acid (entries 16–18) but totally failed to give the expected sulfone when applied to 2-thiopheneboronic acid. Yields obtained with these heterocyclic substrates were generally lower than those from cross coupling reactions with nonheterocyclic boronic acids. However, the reaction conditions were not optimized for heterocyclic substrates and further optimization work will be needed to improve the yield with these substrates.

These preliminary results illustrate the scope and efficiency of this methodology for the synthesis of methyl and aryl sulfones under extremely mild conditions. Catalytic version of this process is also of interest and further investigations are ongoing. The possibility of extending this methodology to the preparation of vinyl sulfones is also currently under evaluation.

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12. Typical experimental procedure: To a round bottom flask equipped with an air drying tube (filled with drierite) was added aryl boronic acid (1 equiv) to DMSO (0.25 M). To the mixture was added 1.1 equiv of $Cu(OAc)_2$, 1.5 equiv of sodium sulfinate, 2 equiv of K_2CO_3, and 4 Å MS (200% wt/wt). The mixture was stirred for 16 h at rt and then filtered on a Celite pad eluted with EtOAc. The filtrate was diluted with EtOAc and aqueous saturated ammonium chloride and the aqueous layers were extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography to afford the desired product.
13. All boronic acids were from commercial source and used as such for the reaction.