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A simple and efficient method for sulfonylation of amines, alcohols and phenols with cupric oxide under mild conditions

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ABSTRACT

Cupric Oxide efficiently catalyzed the synthesis of sulfonamides and sulfonic esters. This method has been applied to a variety of substrates including nucleophilic and sterically-hindered amines, alcohols and phenols with excellent yields of sulfonamides and sulfonic esters. The remarkable selectivity under mild and neutral conditions of this commercially available inexpensive catalyst is an attractive feature of this method.

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1. Introduction

The development of simple, efficient, environmentally-benign and economically viable chemical processes or methodologies for widely used organic compounds is in great demand. Sulfonamides are extremely useful pharmaceutical compounds because they exhibit a wide range of biological activities such as anticancer, anti-inflammatory and antiviral functions.[1] Furthermore, sulfonamides have been used as protecting groups of OH or NH functionalities for easy removal under mild conditions.[2] Even though many synthetic methods have been reported,[3] the sulfonylation of amines with sulfonyl chlorides in the presence of a base is still being used as the method of choice because of high efficiency and simplicity of the reaction.[4] However, this approach is limited by the formation of undesired disulfonamides with primary amines and by the need of harsh reaction conditions for less nucleophilic amines such as anilines.[5] Additionally, side reactions take place in the presence of a base. Indium metal has been used for the catalytic sulfonylation of amines and alcohols; however, it requires a longer reaction time and stringent reaction conditions.[6] Therefore, developing a general, mild and novel method in order to synthesize sulfonamides and sulfonic esters in the absence of a strong base is necessary. In this Letter, we report a simple and efficient method for the sulfonylation of amines, alcohols and phenols.

2. Results and discussion

The catalytic activity of cupric oxide for the sulfonylation of *p*-anisidine (2 mmol) with *p*-toluene sulfonyl chloride (2 mmol) under room temperature was studied and it was found that the application of less than 0.1 mmol of cupric oxide in acetonitrile (5 ml) gave a moderate yield of the corresponding sulfonamide (Table 1, entries 1–3), whereas the use of more than 0.1 mmol gave an excellent yield (Table 1, entries 4–6).

In order to find out the most effective sulfonylation, *p*-anisidine was chosen as a model substrate. It was treated with 2 mmol of *p*-toluene sulfonyl chloride in the presence of 0.1 mmol of CuO in various solvents at room temperature (Table 2). The reaction in THF, CH_2Cl_2, $CHCl_3$, Et_2O, EtOAc, DMF (Table 2, entries 1–6) were found less effective. Since then, we have carried out the reaction in the presence of the CH_3CN solvent to get an excellent yield (92%, entries 7 and 8).

In order to find out the most effective catalyst for sulfonation, we employed various metal oxides during the sulfonation of *p*-anisidine with *p*-toluene sulfonyl chloride (1:1 equimolar) at room temperature (Table 3). According to the results obtained, cupric oxide was found to be the most efficient catalyst. However, other metal oxides such as ZnO, MgO, Cu_2O_3, SiO_2 and CaO exhibit less significant catalytic properties in the sulfonylation of *p*-anisidine with *p*-toluene sulfonyl chloride.

We used a wide variety of compounds to which were applied optimal reaction conditions to prepare a wide range of sulfonamides. The results are summarized in Table 4.[9] Aromatic amines were sulfonylated under the CH_3CN solvent at room temperature

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Table 1
Catalytic effect of CuO in the sulfonylation of *p*-anisidine with *p*-toluene sulfonyl chloride in the presence of cupric oxide in acetonitrile at room temperature

Entry	CuO mmol (mg)	Time (h)	Yield[a] (%)
1.	0.005 (0.4)	6	55
2.	0.01 (0.8)	4	60
3.	0.05 (4)	4	70
4.	0.10 (8)	1	92
5.	0.15 (12)	1	92
6.	0.20 (16)	1	92

[a] Isolated yield of the corresponding sulfonylated product.

Table 2
Sulfonylation of *p*-anisidine with *p*-toluene sulfonyl chloride in the presence of copper oxide with different solvents

Entry	CuO mmol	Solvent	Time (h)	Yield[a] (%)
1	1.0	THF	4	65
2	1.0	CH_2Cl_2	2	85
3	1.0	$CHCl_3$	1.5	74
4	1.0	Et_2O	4	80
5	1.0	EtOAc	4	75
6	1.0	DMF	5	82
7	1.0	CH_3CN	1	92[b]
8	0.1	CH_3CN	1	92[b]

[a] Isolated yield.
[b] CH_3CN solvent is more effective.

Table 3
Sulfonylation of *p*-anisidine with *p*-toluene sulfonyl chloride in the presence of different metal oxides with CH_3CN solvent

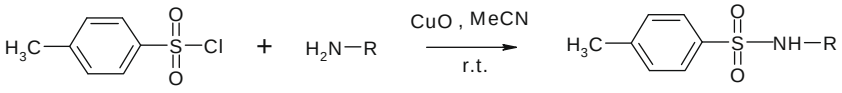
Entry	Metal oxide	mmol (mg)	Time (h)	Yield[a] (%)
1	CuO	0.1 (8)	1	92
2	ZnO	0.1 (8.1)	2	85
3	MgO	0.2 (8)	3	50
4	Cu_2O_3	0.1 (17.6)	7	40
5	SiO_2	0.1 (6.0)	8	30
6	CaO	0.1 (5.6)	4	50

[a] Isolated yield.

with excellent yields (Table 4, entries 1–13). Aromatic amines with an electron-donating group showed similar reactivity, whereas those with an electron-withdrawing group showed somewhat lower reactivity (Table 4, entries 8–11). The primary and secondary amines which were also sulfonylated under similar conditions gave excellent yields (Table 4, entries 14–18). Sulfonamide was obtained with a sterically-hindered amine (*t*-$BuNH_2$) at room temperature with considerable yields (Table 4, entry 19). However, the reaction refluxing with MeCN reached completion in 30 min (0.5 h) with an excellent yield of sulfonamide (Table 4, entries 2 and 15) (Scheme 1).

Sulfonic esters are valuable intermediates in organic synthesis and various sulfonic esters have important pharmacological properties.[7] Sulfonic esters can be prepared from the reaction of sulfonyl chloride with alcohols in the presence of a base.[8] However, the

Table 4
CuO-catalyzed sulfonylation of amines



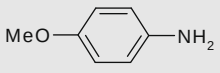
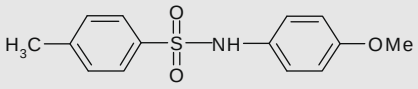
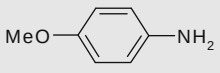
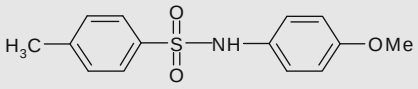
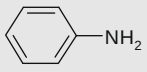
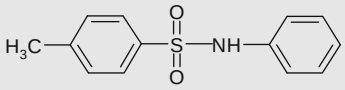
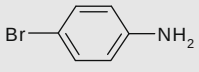
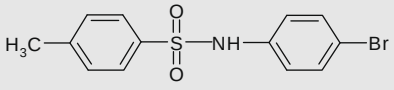
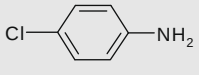
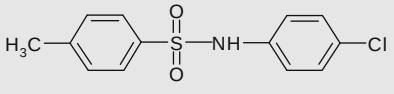
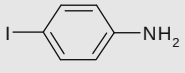
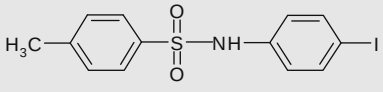
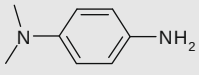
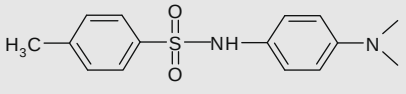
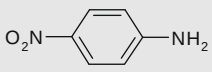
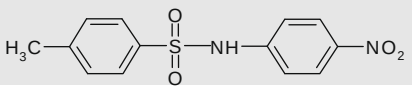
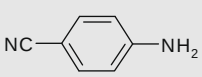
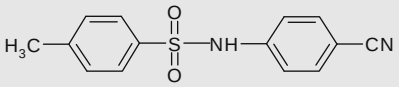
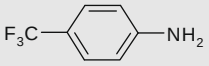
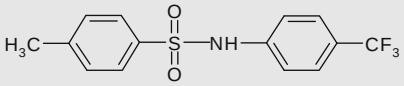
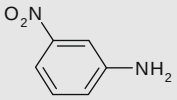
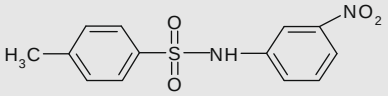
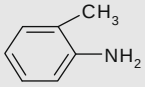
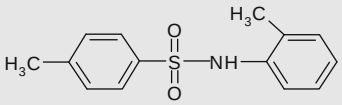
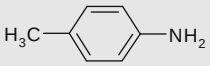
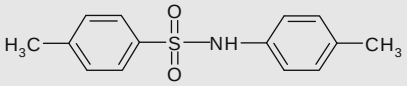
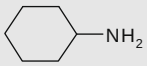
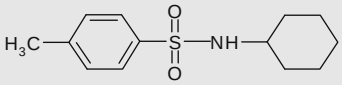
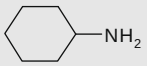
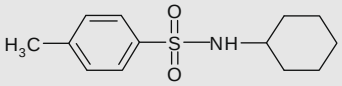
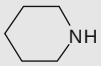
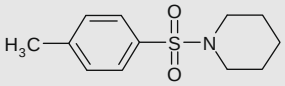
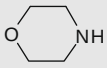
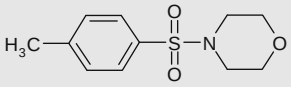
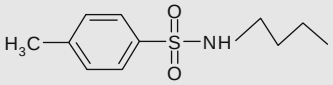
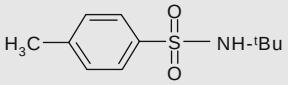
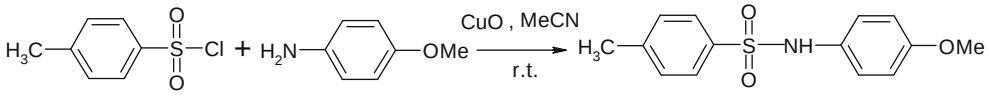
Entry	Amine[a]	Product[b]	Time (h)	Yield[c] (%)
1			1	92
2[d]			0.5	90
3			2	88
4			1.5	86
5			1.5	84
6			1.5	87
7			2.0	88
8			4	85

Table 4 (*continued*)

Entry	Amine[a]	Product[b]	Time (h)	Yield[c] (%)
9			4	75
10			4	70
11			5	83
12			4	82
13			3	83
14			2	92
15[d]			0.5	92
16			2	90
17			1.5	92
18			2	91
19	*t*Bu–NH_2		5	80

[a] The substrate was treated with *p*-toluene sulfonyl chloride (2 mmol) by using 0.1 mmol of CuO in the presence of acetonitrile under neat conditions at room temperature.
[b] All products were identified by their IR and ^{1}H NMR spectra.
[c] Isolated yields.
[d] The reaction was reflux in CH_3CN.



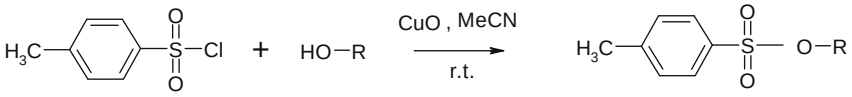
Scheme 1.

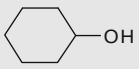
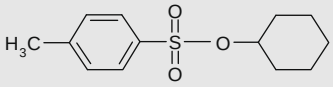
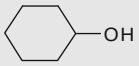
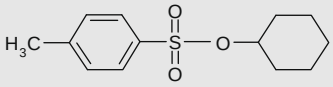
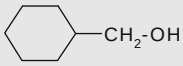
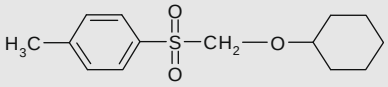
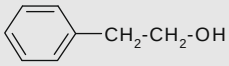
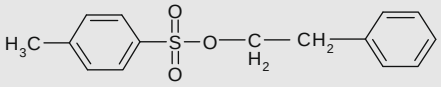
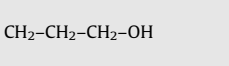
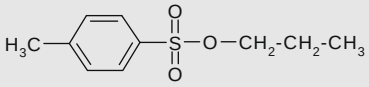
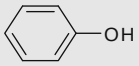
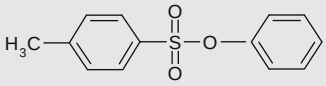
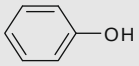
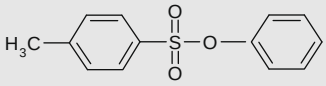
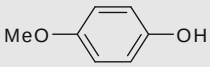
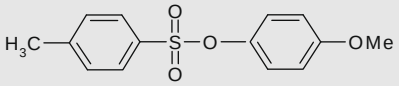
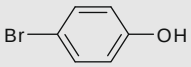
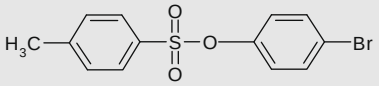
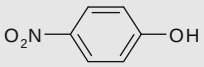
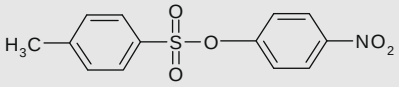
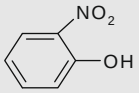
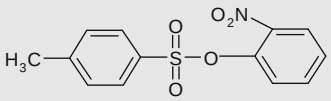
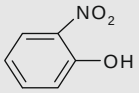
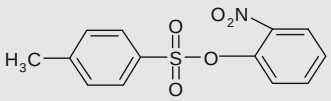
reaction offers the possibility of *B*-elimination in basic reaction conditions.

In order to expand the scope of this new protocol to synthesize sulfonic esters from sulfonyl chloride with alcohols, we investigated the reaction of sulfonyl chloride and alcohols in the presence of cupric oxide (Table 5).

It is very interesting to note that when *p*-toluene-sulfonyl chloride was allowed to react with cyclohexanol in the presence of CuO (10 mol % relative to amine) at room temperature, a moderate yield of the corresponding sulfonic esters was obtained (scheme in Table 5) at a longer reaction time of 5 h (Table 5, entries 1). However, the reaction refluxing with MeCN reached

Table 5
CuO-catalyzed sulfonylation of alcohols and phenols[a]



Entry	Alcohol/phenol[a]	Product[b]	Time (h)	Yield[c] (%)
1			5	87
2[d]			2	88
3			5	90
4			6	86
5			7	50
6			5	92
7[d]			2	90
8			3	88
9			3	87
10			7	85
11			8	70
12[d]			2	90

[a] The substrate was treated with *p*-toluene sulfonyl chloride (2 mmol) by using 0.1 mmol of CuO in the presence of acetonitrile under neat conditions at room temperature.
[b] All products were identified by their IR and ^{1}H NMR spectra.
[c] Isolated yields.
[d] The reaction was reflux in CH_3CN.

completion in two hours (2 h) with an excellent yield of sulfonic ester (Table 5, entries 2).

Phenol itself and phenols with an electron-donating group produced the corresponding sulfonic esters with moderate yields, while phenols with an electron-withdrawing group gave somewhat lower yields of sulfonic esters (Table 5, entries 6–12). The comparison of the results (Table 5, entries 10–12) indicates that the sulfonylation of substrates bearing a NO_2 group adjacent to the phenolic OH required a longer time due to the steric hindrance offered by the group with a smaller yield. However, when refluxing with MeCN, the yield of sulfonamide increased significantly (Table 5, entry 12).

3. Conclusions

In conclusion, this Letter describes a method in which CuO is a highly efficient catalyst for the synthesis of sulfonamides and sulfonic esters by using various substrates as amines, alcohols, phenols. The advantages include low cost, ease of catalyst handling, requirement of a very small amount of catalyst as 0.1 mmol (8 mg), mild reaction conditions and reactions carried out at room temperature with excellent yield. The remarkable selectivity under mild and neutral conditions of this commercially available inexpensive catalyst is an attractive feature of this method.

Acknowledgement

We thank the faculty of chemistry, University of Mumbai, for supporting this work.

References and notes

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9. *Typical experimental procedure for sulfonylation of amines*: A mixture of *p*-anisidine (2 mmol), *p*-toluenesulfonyl chloride (2 mmol) and 0.1 mmol (8 mg) cupric oxide (CuO) was stirred magnetically in 5 ml of acetonitrile at room temperature and the progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was diluted with water (30 ml) and extracted with chloroform (3 × 30 ml). The combined chloroform extracts were dried with Na_2SO_4 and concentrated under reduced pressure. In all the cases, the product obtained after the usual work up gave satisfactory spectral data.Product (**11b**): IR (KBr): 539, 679, 811, 910, 1090, 1159, 1509, 1597, 1611, 3268 cm^{-1}. ^1H NMR (300 MHz, $CDCl_2$): δ 1.7 (s, 1H, NH); 2.4 (s, 3H, CH_3); 3.8 (s, 3H, O CH_3); 6.8 (d, 2H, Ar-H), 7.0 (d, 2H, Ar-H), 7.2 (d, 2H, Ar-H), 7.6 (d, 2H, Ar-H).