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ZINC OXIDE CATALYZED EFFICIENT SYNTHESIS OF SULFONAMIDES UNDER MILD CONDITIONS

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ABSTRACT

A simple and efficient procedure for the synthesis of sulfonamides has been described. This method has been applied to a variety of substrates including nucleophilic and sterically hindered amines with excellent yields of sulfonamides. The remarkable selectivity under mild and neutral conditions, of this commercially available inexpensive catalyst is an attractive feature of this method.

Key words : Sulfonylation, Zinc oxide, Sulfonamides, Sulfonyl chlorides

INTRODUCTION

Developing easy-handling, efficient, environmentally compatible chemical processes or methodologies for widely used organic compounds from simple reagents is one of the major challenges for synthetic chemists. 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 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 in the absence of a strong base is necessary. In this communication, we report an efficient method for the sulfonylation of amines.

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EXPERIMENTAL

Procedure for sulfonylation of amines

A mixture of cyclohexylamine (2 m mol), p-toluenesulfonyl chloride (2 mmol) and 0.1 mmol (8 mg) zinc oxide (ZnO) was stirred magnetically in 5 mL of acetonitrile at room temperature and the progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of reaction, the mixture was poured into 30 mL of water and chloroform (30 mL). The solution was filtered and zinc oxide was isolated, which could be reused. The solution was extracted with chloroform (3 x 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.

N-(Cyclohexyl)-4-methyl benzene sulfonamidet (1b)

IR (KBr) (cm^{-1}) : 530, 692, 815, 1020, 1093, 1163, 1512, 1590, 1616 and 3270 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ : 1.2 (m, 2H, CH_2); 1.4 (m, 4H, CH_2); 1.6 (q, 4H, CH_2); 3.3 (m, 1H, CH); 1.8 (s, 1H, NH); 2.4 (s, 3H, CH_3); 6.9 (d, 2H, Ar-H) and 7.10 (d, 2H, Ar-H)., : **^{13}C NMR (100MHz, $CDCl_3$)** δ : 25.4, 27.3, 32.2, 35.2, 42.3, 1128.5, 129.5, 131.3 and 136.2.

N- (4-Methoxy phenyl) -4-methyl benzene sulfonamide (7b)

IR (KBr) (cm^{-1}) : 539, 679, 811, 910, 1090, 1159, 1509, 1597, 1611 and 3268 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ : 1.7 (s, 1H, NH); 2.4 (s, 3H, CH_3); 3.8 (s, 3H, O CH_3); 6.0 (d, 2H, Ar-H); 6.8 (d, 2H, Ar-H), 7.0 (d, 2H, Ar-H)., 7.2 (d, 2H, Ar-H) : **^{13}C NMR (100MHz, $CDCl_3$) δ :** 34.9, 67.1, 128.2, 129.4, 129.6, 130.5, 132.1, 132.5, 135.6 and 137.3.

N- (Phenyl)-4-methyl benzene sulfonamide (9b)

IR (KBr) (cm^{-1}) : 630, 665, 822, 915, 1092, 1166, 1512, 1596, 1620 and 3255 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ : 2.1 (s, 1H, NH); 2.7 (s, 3H, CH_3);; 7.11 (d, 2H, Ar-H), 7.16 (d, 2H, Ar-H) and 7.3 (m, 5H, Ar-H) : **^{13}C NMR (100MHz, $CDCl_3$) δ** : 35.3, 125.2, 127.3, 128.3, 129.3, 129.5, 130.2, 131.4 and 135.6.

N- (4-Bromophenyl) -4-methyl benzene sulfonamide (10b)

IR (KBr) (cm^{-1}) : 650, 691, 798, 919, 1095, 1163, 1512, 1592, 1625 and 3269

^{1}H NMR (300MHz, $CDCl_3$) δ : 1.9 (s, 1H, NH); 2.5 (s, 3H, CH_3), 6.7 (d, 2H, Ar-H), 6.8 (d, 2H, Ar-H), 7.21 (d, 2H, Ar-H) and 7.25 (d, 2H, Ar-H). : **^{13}C NMR (100MHz, $CDCl_3$) δ** : 34.6, 125.7, 126.4, 127.6, 129.2, 129.3, 129.5, 130.7 and 135.2.

N- (4-Nitrophenyl) -4-methyl benzene sulfonamide (14b)

IR (KBr) (cm^{-1}) : 536, 670, 749, 815, 1060, 1451, 1166, 1535, 1586, 1616 and 3274 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ : 2.0 (s, 1H, NH); 2.8 (s, 3H, CH_3); 6.8 (d, 2H, Ar-H), 7.0 (d, 2H, Ar-H)., 7.1 (d, 2H, Ar-H) and 7.15 (d, 2H, Ar-H) : **^{13}C NMR (100MHz, $CDCl_3$) δ** : 33.5, 124.5, 126.7, 127.5, 128.2, 128.7, 128.8, 130.7 and 136.2.

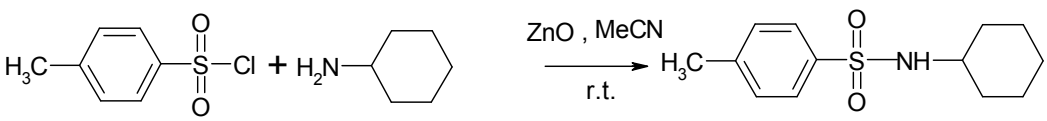
N- (4-Methylphenyl) -4-methyl benzene sulfonamide (19b)

IR (KBr) (cm^{-1}) : 610, 656, 815, 919, 1096, 1158, 1526, 1595, 1617, 3246 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ : 1.9 (s, 1H, NH); 2.9 (s, 3H, CH_3); 6.8 (d, 2H, Ar-H), 7.0 (d, 2H, Ar-H)., 7.05 (d, 2H, Ar-H) and 7.15 (d, 2H, Ar-H) : **^{13}C NMR (100MHz, $CDCl_3$) δ** : 34.4, 43.2, 125.1, 127.5, 128.1, 128.2, 128.5, 129.3, 130.7 and 135.8.

RESULTS AND DISCUSSION

The catalytic activity of zinc oxide for the sulfonylation of cyclohexylamine (2m mole) 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 zinc oxide in acetonitrile (5 mL) gave a moderate yield of the corresponding sulfonamide (Table 1, entries^{-1}, 2, 3), whereas the use of more than 0.1 mmol gave an excellent yield (Table 1, entries-4, 5, 6).



In order to find out the most effective sulfonylation, cyclohexylamine 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 ZnO 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 CH_3CN solvent to get an excellent yield (92%, entries, 7, 8)

Table 1: Catalytic effect of ZnO in the sulfonylation of cyclohexylamine with p-toluenesulfonyl chloride in the presence of zinc oxide in acetonitrile at room temperature

Entry	ZnO mmol (mg)	Time (h)	Yield (%)[a]
1.	0.005(0.4)	7	55
2.	0.01 (0.8)	5	60
3.	0.05 (4)	5	70
4.	0.10 (8)	1	90
5.	0.15 (12)	1	90
6.	0.20 (16)	1	90

[a]Isolated yield of the corresponding sulfonylated product

Table 2 : Sulfonylation of cyclohexylamine with p-toluene sulfonyl chloride in the presence of zinc oxide with different solvents.

Entry	ZnO mmol	Solvent	Time (h)	Yield[a] (%)
1.	1.0	THF	5	68
2.	1.0	CH_2Cl_2	2	85
3.	1.0	$CHCl_3$	2	70
4.	1.0	Et_2O	5	81
5.	1.0	EtOAc	3	78
6.	1.0	DMF	4	81
7.	1.0	CH_3CN	1	90[b]
8.	0.1	CH_3CN	1	90[b]

[a]Isolated yield

[b]CH_3CN solvent is more effective

In order to find out the most effective catalyst for sulfonation, we employed

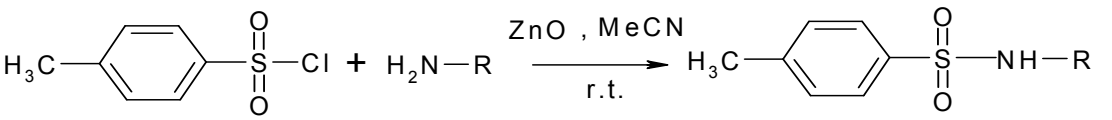
various metal oxides during the sulfonation of cyclohexylamine with p-toluene sulfonyl chloride (1 : 1 equimolar) at room temperature (Table 3). According to the results obtained, zinc oxide was found to be the most efficient catalyst. However, other metal oxides such as MgO, SiO_2 and CaO exhibit less significant catalytic properties in the sulfonylation of cyclohexylamine with p-toluene sulfonyl chloride.

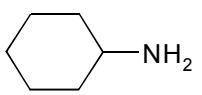
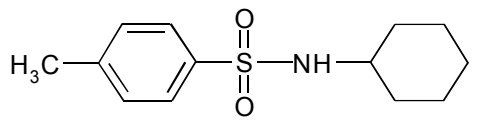
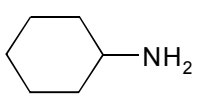
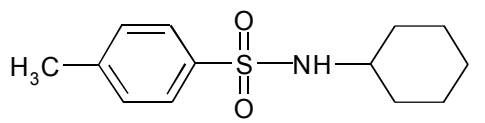
Table 3: Sulfonylation of cyclohexylamine with p-toluene sulfonyl chloride in the presence of different metal oxides with CH_3CN solvent

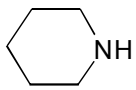
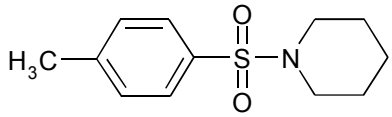
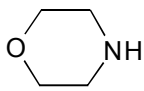
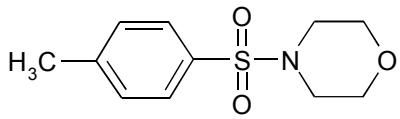
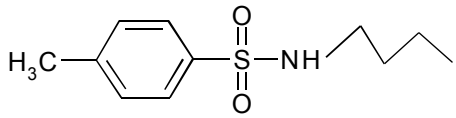
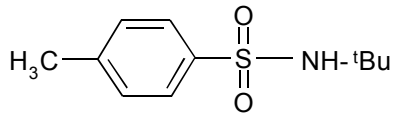
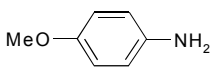
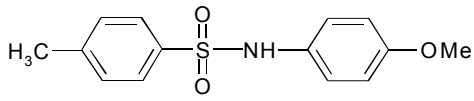
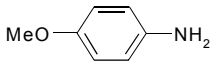
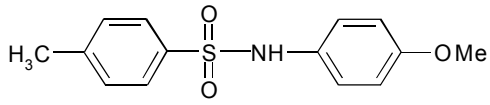
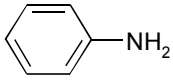
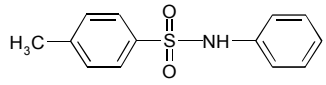
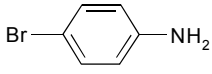
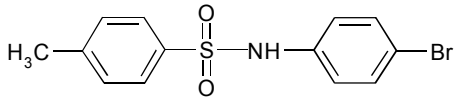
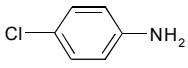
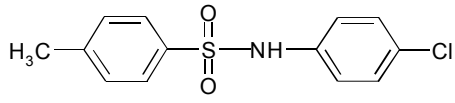
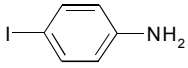
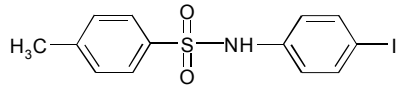
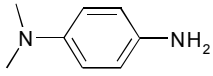
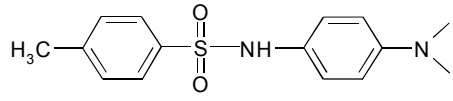
Entry	Metal oxide	mmol (mg)	Time (h)	Yield[a] (%)
1.	ZnO	0.1(8.1)	1	90
2.	ZnO	0.1(8.1)	0.5	90[b]
3.	MgO	0.2(8)	3	55
4.	SiO_2	0.1(6.0)	8	37
5.	CaO	0.1(5.6)	4	45

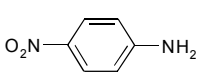
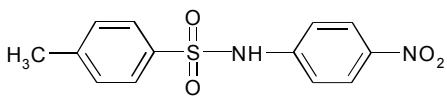
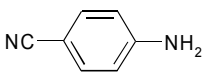
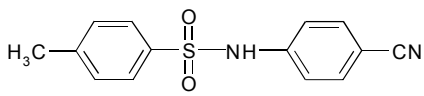
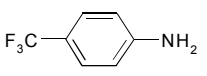
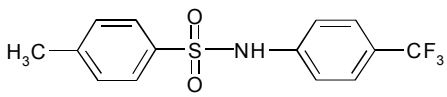
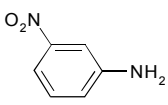
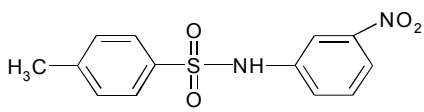
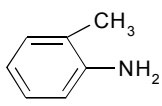
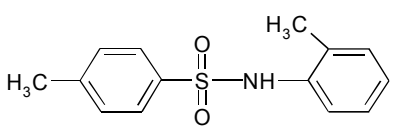
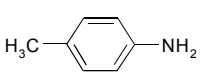
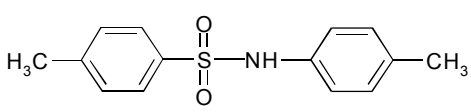
[a]Isolated Yield.
[b]Refluxed in CH_3CN

Table 4 : ZnO catalyzed sulfonylation of amines.



Entry	Amine	Product (b)	Time (h)	Yield[c] (%)
1.			1	90
2.			0.5	90

Entry	Amine	Product (b)	Time (h)	Yield[c] (%)
3.			1.5	89
4.			1.5	88
5.			1	88
6.			5	80
7.			1	90
8.			0.5	91
9.			2	90
10.			1.5	85
11.			1.5	84
12.			1.5	88
13.			2.0	85

Entry	Amine	Product (b)	Time (h)	Yield[c] (%)
14.			3	87
15.			4	75
16.			4	72
17.			5	85
18.			4	84
19.			3	87

[a] The substrate was treated with p-toluenesulfonyl chloride (2 mmol) by using 0.1 mmol of ZnO 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] Reflux in CH_3CN

We used a wide variety of compounds, to which optimal reaction conditions was applied to prepare a wide range of sulfonamides. The results are summarized in Table 4. The primary and secondary amines were sulfonylated under the CH_3CN solvent at room temperature with excellent yields (Table 4, entries 1-5). Aromatic amines, which were also sulfonylated under similar conditions gave excellent yields (Table 4, entries 7–19). Aromatic amines with an electron-donating group showed similar reactivity, whereas those with an electron-withdrawing group showed somewhat lower reactivity (Table 4, entries –14–17). Sulfonamide was obtained with a sterically-hindered amine (t-BuNH_2) at room temperature with considerable yields (Table 4, entry 6). However, the reaction involving reflux with MeCN reached to completion in 30 min (0.5 h) with an excellent yield of sulfonamide (Table 4, entries 2, 8).

In conclusion, this paper describes a method, in which ZnO is a highly efficient catalyst for the synthesis of sulfonamides by using various substrates as amines. 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 yields. 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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