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Metal oxide in aqueous organic solution promoted chemoselective *N*-sulfonylation of hydrophilic amino alcohols

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Abstract—The reaction of hydrophilic amino alcohols with sulfonyl chlorides in the presence of metal oxide (MgO, CuO, Ag_2O) in aqueous organic solution cleanly provided alkanolsulfonamide. Advantages of this method were mild, neutral reaction conditions, chemoselectivity and easy isolation of the final product.

Organic sulfonamides are very important protected intermediates of amines,[1,2] which are also found in a variety of biologically active compounds.[3,4] They are usually prepared by treating the corresponding amine with sulfonyl chloride and various base in organic solvent.[5] Although the use of this method was successful for the simple sulfonylation of amines or alcohols, the lack of chemoselectivity was presented in case of amino alcohols. Although the use of dibutylstannylene acetal intermediate has been reported in a few cases,[6,7] simple and efficient method for the selective *N*-sulfonylation of amino alcohols has not been established. Recently, we have found an efficient method for the chemoselective *N*-acylation of amino alcohols promoted by MgO in aqueous organic solution.[8]

In the context of this ongoing research, we tried to apply the chemoselective *N*-acylation method to sulfonyl chloride and other metal oxide (CuO and Ag_2O). A series of experiments were performed on the 1,3-bis[(hydroxymethyl)amino]propan-2-ol (BHAP, **1**) with benzenesulfonyl chloride (2.2 equiv.) under various reaction conditions (entries 1–5 in Table 1). However, only a slight amount of desired sulfonamide was obtained in these attempted conditions. Next, we tested MgO (5.0 equiv.) suspended in aqueous organic solution, which has been used for the chemoselective *N*-acylation of amino alcohols. Treatment of BHAP **1** with MgO (5.0 equiv.) in THF/H_2O (v/v = 4:1) solution with vigorously stirring at 25°C followed by addition of benzenesulfonyl chloride gave the desired disulfonamide (**2**) in 80% yield.[9] Of the metal oxide tested, the best choice was 5 equiv. of magnesium oxide. Using copper oxide and silver(I) oxide, compound **2** was also obtained in high yield (entries 8 and 9). We could not discriminate the critical difference of metal oxide (MgO, CuO and Ag_2O) in this reaction. As solvent, THF/H_2O (4:1) was preferred even if dioxane/H_2O (4:1) was also effective. The reaction temperature is important factor for the chemoselective *N*-sulfonylation. The

Table 1. Conditions for chemoselective disulfonamide (**2**) formation

Entry	Solvent	Base[a]	Time (h)	Yield (%)[b]
1	CH_2Cl_2	TEA (2.2)	3.5	0
2	CH_2Cl_2	Pyridine (2.2)	3.5	0
3	DMF	TEA (2.2)	3	10
4	DMF	Pyridine (2.2)	3	12
5	H_2O	NaOH (2.2)	2.5	20
6	THF/H_2O (4:1)	MgO (5.0)	2.5	80
7	Dioxane/H_2O (4:1)	MgO (5.0)	2.5	78
8	THF/H_2O (4:1)	CuO (5.0)	3	75
9	THF/H_2O (4:1)	Ag_2O (5.0)	4	74

[a] The molar equivalents are given in parentheses.
[b] Isolated yields.

Keywords: amino alcohols; sulfonamide; sulfonyl chloride; metal oxide; aqueous organic solution.

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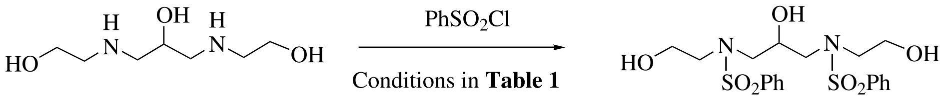
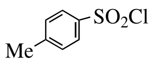
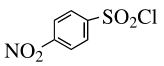
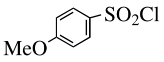
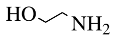
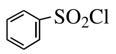
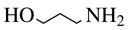
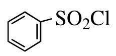
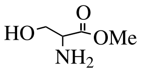
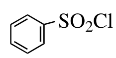
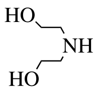
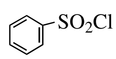


1 **2**

Scheme 1.

Table 2. Conditions for chemoselective sulfonamide formation[a]

Entry	Substrate	Sulfonyl chloride	Yield (%)
1	**1**		75
2	**1**		73
3	**1**		70
4			82
5			85
6			80
7			82

[a] All the reaction were run with 1.1 equivalent of sulfonyl chlorides in THF/H_2O (4:1) except of entry 1, 2 and 3. In case of entry 1, 2 and 3, 2.2 equivalent of sulfonyl chloride was used.

best temperature was around 25°C. When the temperature was elevated to above 25°C, *O*-sulfonyl disulfonamide has been observed as a side product. The formation of the *O*-chemoselective sulfonate has not been detected in any case examined (Scheme 1).

Metal oxide[10] mediated reaction showed several advantages over the organic base used methods. For instance, the reaction occurs in neutral condition and necessitates simple isolation process. The sulfonamide is often isolated pure after a simple filtration, evaporation, and precipitation or short column chromatography. We extended this optimized reaction condition to other sulfonyl chlorides and hydrophilic substrates. The results are summarized in Table 2.

In case of NsCl, *p*-methoxy benzenesulfonyl chloride and TsCl, the desired disulfonamide products were obtained in high yield (entries 1–3 in Table 2). Although the reason for *N*-sulfonylation induced by metal oxide has not been clarified, the reaction mechanism was similar to that of selective *N*-acylation.[8] The coordination of metal ion to the double bond of S=O of sulfonyl chloride activates the leaving ability of chloride.[11] More nucleophilic amino groups may only react with activated sulfonyl chloride.[12] The activating ability of CuO and Ag_2O for sulfonyl chloride was similar to that of MgO. The reaction also worked well for the other hydrophilic amine such as ethanolamine, propanolamine, DL-serine methyl ester and diethanolamine.

In summary, we have developed an efficient and chemoselective *N*-sulfonylation reaction by the treatment of amino alcohols with various sulfonyl chlorides in the presence of metal oxide in aqueous organic solution. The use of metal oxide afforded several advantages such as neutral reaction condition, short reaction time, easy handling and simple isolation of product.

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9. Typical procedure: To a solution of 1,3-bis[(hydroxymethyl)amino]propan-2-ol (1.0 g, 5.6 mmol) in H_2O (2 mL) was added MgO (1.13 g, 28.0 mmol), THF (6 mL), and stirred vigorously for 30 min at 25°C. To a suspension of reaction mixture, benzenesulfonyl chloride (2.17 g, 12.3 mmol) in THF (2 mL) was added dropwise for 1 h. After additional stirring for 1 h at 25°C, the reaction mixture was filtered through the bed of Celite. The filtrate was evaporated and extracted with ethyl acetate (50 mL), washed with water. The solvent was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography to give desired product **2** (2.9 g, 80%) IR ν_{max} (CH_2Cl_2 solution) 3362, 1446, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.86 (m, 4H), 7.55 (m, 6H), 5.42 (bs, 1H), 4.24 (m, 1H), 4.02 (bs, 2H), 3.88 (m, 4H), 3.35 (m, 4H), 3.20 (m, 4H). MS-FAB (*m*/*e*) 459 (M^++1). Anal. calcd for $C_{19}H_{26}N_2O_7S_2$: C, 49.77; H, 5.72; N, 6.11; S, 13.99. Found: C, 49.71; H, 5.67; N, 6.06; S, 13.94.
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