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Melamine Trisulfonic Acid (MTSA): A New Efficient Catalyst for the Chemoselective Methoxymethylation of Alcohols

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MELAMINE TRISULFONIC ACID (MTSA): A NEW EFFICIENT CATALYST FOR THE CHEMOSELECTIVE METHOXYMETHYLATION OF ALCOHOLS

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Melamine trisulfonic acid, which is easily prepared by the reaction of melamine with neat chlorosulfonic acid, is able to efficiently catalyze the chemoselective methoxymethylation of alcohols with dimethoxymethane (DMM). All reactions were performed under mild and completely heterogeneous reaction conditions in good to high yields.

Keywords: Alcohols; heterogeneous reaction conditions; melamine; melamine trisulfonic acid; methoxymethylation

Between the several methods available for the protection of the alcoholic hydroxyl groups, methoxymethylation has attracted the attention of many organic chemists. This considerable attention can be attributed to the stability of the produced methoxymethyl (MOM) ethers against reagents such as strong bases, butyl lithium, lithium aluminium hydride, and Grignard reagents as well as easy removal of the MOM moiety by acid treatment. Generally, the formation of methoxymethyl ethers is carried out by the alkylation of alcohols with excess amounts of chloromethyl methyl ether (CME) in alkaline solution.[1] However, the potent carcinogenic properties of CME limits the use of this method.

Dimethoxymethane (DMM), a cheap and commercially available reagent, is the other compound that can be used for the methoxymethylation of alcohols. Handling of this reagent is easy, but its main drawback is its poor methoxymethylating power. For the activation of DMM, a variety of catalysts, such as expansive graphite,[2] $Sc(OTf)_3$,[3] phenylsulfonic acid functionalized mesoporous silica,[4] $Bi(OTf)_3$,[5] silica sulfuric acid,[6] and metal hydrogen sulfates,[7] have been reported. Although these methods are improvements, most of them suffer from disadvantages such as harsh reaction conditions, long reaction times, poor yields, poor selectivity, use of toxic or expensive reagents, and use of large amounts of DMM. Thus, the search for new reagents and methods is still of practical importance.

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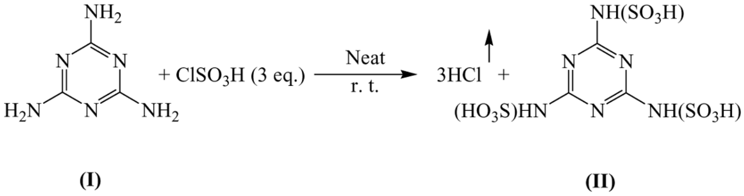
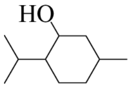
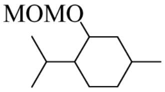
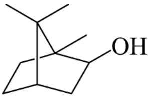
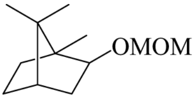
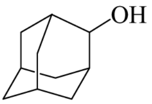
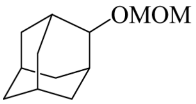
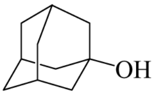
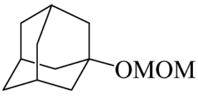


Scheme 1. Preparation of MTSA.

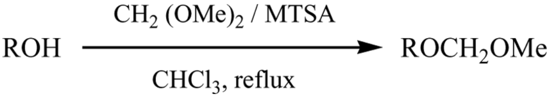
Table 1. Methoxymethylation of alcohols[a,b]

Entry	Substrate	Product	Time (h)	Yield (%)
1	PhCH$_2$OH	PhCH$_2$OMOM	0.58	92
2	2-BrC$_6$H$_4$CH$_2$OH	2-BrC$_6$H$_4$CH$_2$OMOM	0.2	90
3	4-ClC$_6$H$_4$CH$_2$OH	4-ClC$_6$H$_4$CH$_2$OMOM	0.42	95
4	4-MeOC$_6$H$_4$CH$_2$OH	4-MeOC$_6$H$_4$CH$_2$OMOM	0.13	92
5	4-NO$_2$C$_6$H$_4$CH$_2$OH	4-NO$_2$C$_6$H$_4$CH$_2$OMOM	1.5	85
6	PhCH(OH)Me	PhCH(OMOM)Me	0.7	90
7	PhCH$_2$CH$_2$OH	PhCH$_2$CH$_2$OMOM	0.3	92
8	PhCH$_2$CH$_2$CH$_2$OH	PhCH$_2$CH$_2$CH$_2$OMOM	0.3	90
9	MeCH$_2$CH$_2$CH$_2$OH	MeCH$_2$CH$_2$CH$_2$OMOM	0.3	87
10	MeCH$_2$CH(OH)Me	MeCH$_2$CH(OMOM)Me	0.5	90
11			0.7	90
12			1	80
13			0.53	95
14	Ph$_3$COH	Ph$_3$COMOM	1	82
15			0.92	90
16	PhOH	PhOMOM	1	0
17	PhCH$_2$OH + PhOH	PhCH$_2$OMOM + PhOMOM	0.6	100[c] + 0[c]

[a] Products were characterized by comparison of their physical and spectral data with authentic samples.[4,11,13,14]

[b] Isolated yields.

[c] Conversion.



$$\text{ROH} \xrightarrow[\text{CHCl}_3\text{, reflux}]{\text{CH}_2\text{(OMe)}_2\text{ / MTSA}} \text{ROCH}_2\text{OMe}$$

Scheme 2. Methoxymethylation of alcohols catalyzed by MTSA.

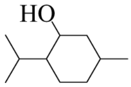
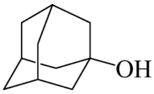
In recent years, the introduction of new methods and reagents for protection of alcoholic hydroxyl groups became an important part of our research program.[8–11] In continuation of these studies, we have found that melamine (I), a cheap and commercially available reagent, reacts with neat chlorosulfonic acid to give melamine trisulfonic acid (II) at room temperature. The reaction is easy and clean and needs no special workup procedure (Scheme 1).

The structure of MTSA assured us that this reagent can act as an efficient catalyst in reactions that need acidic reagents to speed them up. Our investigations clarified that this prediction is correct, and the conversion of alcohols to their corresponding MOM ethers is efficiently promoted in the presence of MTSA (Table 1, Scheme 2). All reactions were performed in $CHCl_3$ at reflux temperature under completely heterogeneous reaction conditions in good to high yields. Phenols remain intact under the same reaction conditions (Table 1, entry 16). Therefore, the method can be useful for the chemoselective methoxymethylation of alcohols in the presence of phenols (Table 1, entry 17).

The efficiency of the present method is illustrated by the comparison of some of our results with some of those reported in the literature (Table 2).[3–7]

In conclusion, melamine trisulfonic acid, a newly prepared reagent, is efficiently able to catalyze the methoxymethylation of alcohols with DMM. Good yields of the products, short reaction times, heterogeneous nature of the reaction conditions, use of the relatively small amounts of DMM, ease of preparation, stability of the reagent, and easy workup procedure are important features of the reported method.

Table 2. Comparison of some of the results obtained by our method (I) with those reported using $Sc(OTf)_3$ (II),[3] phenylsulfonic acid functionalized mesoporous silica(III),[4] $Bi(OTf)_3$ (IV),[5] silica sulfuric acid (V),[6] and $Al(HSO_4)_3$ (VI)[7]

		Time (h)/yield (%)/DMM–substrate					
Entry	Substrate	I	II	III	IV	V	VI
1	$PhCH_2OH$	0.58/92/4	—	—	1/95/8	1.5/85/10	1.67/83/30
2	$4\text{-}NO_2C_6H_4CH_2OH$	1.5/85/4	5/94/50	6/28.4/5	—	12.5/80/10	12/75/30
3		0.7/90/4	7/80/50	—	4/85/8	16.5/78/10	17.5/85/30
4		0.92/90/4	7/77/50	—	—	8/70/10	8.5/75/30

EXPERIMENTAL

General

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. All of the products are known compounds and were characterized by spectral analyses, comparisons with authentic samples (IR and NMR), and regeneration of the corresponding alcohols. All yields refer to the isolated products. The purity determination of the substrate and reaction monitoring were accompanied by gas chromatography (GC) or thin-layer chromatography (TLC) on silica-gel polygram SILG/UV 254 plates.

Preparation of MTSA

A 250-mL suction flask charged with chlorosulfonic acid (5 mL, 75.2 mmol) was equipped with a gas inlet tube for conducting HCl gas over an adsorbing solution (i.e., water). Melamine (3.16 g, 25.07 mmol) was added in small portions over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately (Scheme 1). After completion of the addition of melamine, the mixture was shaken for 30 min; meanwhile, the residual HCl was removed by suction. Melamine trisulfonic acid (7.9 g, 87%) was obtained as a white solid, which was stored in a capped bottle. Mp: 142–144 °C; IR: $\bar{\nu} = 3133, 2621, 1654, 1509, 1175, 1069\,\text{cm}^{-1}$. Anal. calcd. for $C_3H_6N_6O_9S_3$ (366.3): C, 9.83%; N, 22.95%; H, 1.64%. Found: C, 9.81%; N, 22.95%; H, 1.64%.

General Procedure

A mixture of the substrate (1 mmol), DMM (4 mmol, 0.304 g), and MTSA (0.1 mmol, 0.04 g) in $CHCl_3$(3 mL) was stirred at reflux temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated, and Et_2O (5 mL) was added. The mixture was filtered, and the solid residue was washed with Et_2O (5 mL). The filtrate was washed with a saturated solution of $NaHCO_3$ and H_2O and dried over $MgSO_4$. Evaporation of the solvent afforded the requested MOM ether in high purity.

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