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Sulfonic acid functionalized ordered nanoporous Na⁺ montmorillonite as an efficient and recyclable catalyst for the chemoselective methoxymethylation of alcohols

Farhad Shirini*, Manouchehr Mamaghani and Seyyed Vahid Atghia

Abstract

Sulfonic acid functionalized ordered nanoporous sodium montmorillonite was easily prepared by the reaction of sodium montmorillonite with chlorosulfonic acid. The new catalyst demonstrated efficient and chemoselective methoxymethylation reaction of alcohols with formaldehyde dimethyl acetal in chloroform under reflux conditions. This reaction affords corresponding ethers in good to excellent yields. The present method offers several advantages such as short reaction times, high yields, simple procedure, mild conditions, heterogeneous nature, and reusability of the catalyst.

Keywords: Methoxymethylation, Alcohols, Formaldehyde dimethyl acetal, Na⁺ montmorillonite, Solid acid catalyst, Heterogeneous catalysis

Background

Selective protection and deprotection of hydroxyl groups have occupied a unique position in organic synthesis because of the fundamental importance of hydroxyl groups in multistep synthesis of complex natural products [1]. Between 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 aluminum hydride, and Grignard reagents as well as easy removal of the MOM moiety by acid treatment. Generally, the formation of MOM ethers is carried out by the alkylation of alcohols with excess amounts of chloromethyl methyl ether (CME) in alkaline solution [2]. However, the potent carcinogenic property of CME limits the use of this method, and MOM ethers are prepared by the reaction of alcohols or phenols with formaldehyde dimethyl acetal (FDMA), as a cheap and commercially available compound. Even though the

handling of this reagent does not need special precautions and workup of the reaction mixture is not time-consuming, the low methoxymethylating power of FDMA is the main drawback for its application. To overcome this limitation, a number of catalysts such as *p*-toluenesulfonic acid [3], Nafion-H [4], TMSI [5], Envirocat [6], expansive graphite [2], sulfated metal oxides [7], silica sulfuric acid [8], Sc(OTf)₃ [9], Bi(OTf)₃ [10], Al(HSO₄)₃ [11], MoO₂(acac)₂ [12], H₃PMo₁₂O₄₀ [13], anhydrous FeCl₃ dispersed on 3A molecular sieve [14], TiO₂/SO₄²⁻ [15], H₃PW₁₂O₄₀ [16,17], melamine trisulfonic acid [18], benzyltriphenylphosphonium tribromide [19], and high-valent [Sn^{IV}(Br₈TPP)(OTf)₂] [20] 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 FDMA. Thus, the searches for new reagents and methods that utilize eco-friendly protocols are still in demand.

In recent years, clays as nanostructured materials have been widely used in organic transformations as solid acid catalysts [21-23]. The main reasons for use of clays are accessibility, easy modification, cheapness, non-

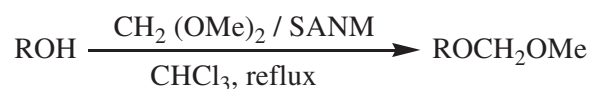
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corrosiveness, and recyclability. Montmorillonite (MMT) is one of the most widely used clays. Montmorillonite minerals have very small micron-sized particles, and they are extremely fine-grained and thin-layered [24]. Layers of MMT have a thickness of about 1 nm and a length of 100 nm or a little more. Broken bonds on the edge of MMT layers are common phenomena for layered silicates and lead to the free formation of hydroxyl groups [25,26], which can be utilized for chemical modification. The first attempt may be traced back in 1941 when Berger found that hydroxyl groups of montmorillonite could be methylated with diazomethane [27]. Many scientists then used this property for different modifications on the surface of montmorillonite [28,29].

Results and discussion

Recently, preparation of new catalysts for organic reactions, by modification of hydroxyl groups of various hetero- and homogenous compounds by sulfonic moiety, became an important part of our research program [30-33]. In continuation of these studies, we have found that chlorosulfonic acid can be used for the modification of Na⁺-MMT until -OH groups on the surface of this clay be converted to -SO₃H (Scheme 1). The reaction is easy and clean and needs no special precautions because HCl gas evolved from the reaction vessel immediately.

On the basis of the structure of sulfonic acid-functionalized ordered nanoporous Na⁺-MMT (SANM), we anticipated that this reagent would act as an efficient catalyst in the reactions that need the use of acidic reagents to speed up. In our first communication, we used this reagent as an efficient catalyst for *N*-*tert*-butoxycarbonylation of amines with di-*tert*-butyl dicarbonate [34], our procedure provided better activity with high yields compared to the heterogeneous ones in the *N*-*tert*-butoxycarbonylation of amines. Next, we have shown the catalytic application of our synthesized catalyst in the trimethylsilylation of alcohols and phenols with high chemoselectivity and yields [35]. Herein, we are reporting the promoting effect of SANM in the conversion of alcohols to their corresponding MOM ethers. All reactions were performed in CHCl₃ at reflux temperature under completely heterogeneous reaction



Scheme 2 Methoxymethylation of alcohols catalyzed by SANM.

conditions in good to high yields (Scheme 2, Table 1). Phenols remain intact under the same reaction conditions (entry 18 of Table 1). Therefore, the method can be useful for the chemoselective methoxymethylation of alcohols in the presence of phenols and primary alcohols in the presence of tertiary alcohols (entry 19 of Table 1).

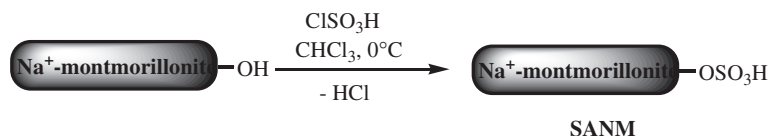
Investigation in the reusability of the catalyst showed that SANM is reusable four times (entries 1 and 2 of Table 1).

The possible mechanism for the methoxymethylation of various alcohols in the presence of SANM as a promoter is shown in Scheme 3. On the basis of this mechanism, SANM catalyzes the reaction by electrophilic activation of FDMA and by making the central carbon of FDMA susceptible to nucleophilic attack by the alcohol. Successive elimination of MeOH results in the formation of MOM-ether derivatives and regenerates SANM in the reaction mixture [7].

To illustrate the efficiency of the present method, Table 2 compares our results with some of those reported in the literature [8-12].

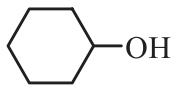
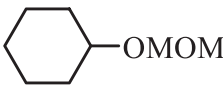
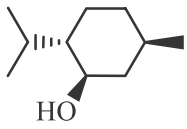
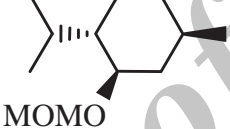
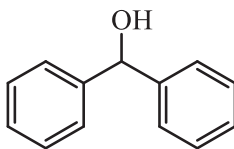
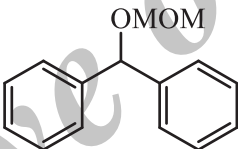
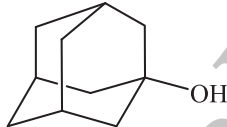
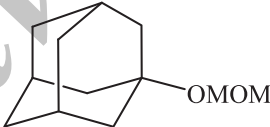
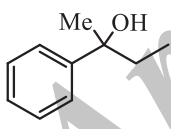
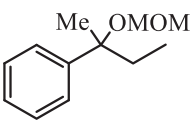
Conclusions

In conclusion, we have developed a simple and efficient protocol for the methoxymethylation of various alcohols using SANM as a novel heterogeneous catalyst. Good yields of the products, short reaction times, heterogeneous nature of reaction conditions, use of relatively small amounts of FDMA, ease of preparation, stability of the reagent, recyclability, and easy workup procedure are important features of the reported method. We are exploring further applications of SANM for the other types of functional group transformations in our laboratory.



Scheme 1 Preparation of SANM.

Table 1 Methoxymethylation of alcohols

Entry	Alcohol	MOM ether	Time(h)	Yield (%)
1	PhCH ₂ OH	PhCH ₂ OMOM	2	92 (90, 85, 80 ^a)
2	4-ClC ₆ H ₄ CH ₂ OH	4-ClC ₆ H ₄ CH ₂ OMOM	1.5	95 (92, 88, 86 ^a)
3	2-ClC ₆ H ₄ CH ₂ OH	2-ClC ₆ H ₄ CH ₂ OMOM	3	96
4	4-BrC ₆ H ₄ CH ₂ OH	4-BrC ₆ H ₄ CH ₂ OMOM	2	94
5	2-BrC ₆ H ₄ CH ₂ OH	2-BrC ₆ H ₄ CH ₂ OMOM	4.5	92
6	4-MeOC ₆ H ₄ CH ₂ OH	4-MeOC ₆ H ₄ CH ₂ OMOM	0.5	95
7	4- <i>tert</i> -butylC ₆ H ₄ CH ₂ OH	4- <i>tert</i> -butylC ₆ H ₄ CH ₂ OMOM	3	90
8	4-NO ₂ C ₆ H ₄ CH ₂ OH	4-NO ₂ C ₆ H ₄ CH ₂ OMOM	7.5	93
9	PhCH ₂ CH ₂ OH	PhCH ₂ CH ₂ OMOM	4	95
10	PhCH(OH)Me	PhCH(OMOM)Me	5	91
11	PhCH(OH)CH ₂ CH ₃	PhCH(OMOM)CH ₂ CH ₃	2	96
12	CH ₃ (CH ₂) ₅ CH ₂ OH	CH ₃ (CH ₂) ₅ CH ₂ OMOM	3.5	91
13			8	95
14			7.5	97
15			0.75	95
16			8	90
17			4	85
18	PhOH	PhOMOM	11	0
19	PhCH ₂ OH+PhOH	PhCH ₂ OMOM+PhOMOM	2.5	100 ^b +0 ^b

Products were characterized by comparison of their physical and spectral data with authentic samples [9,10,18,20] and isolated yields. ^aResults obtained using recycled catalyst; ^bConversion.

Methods

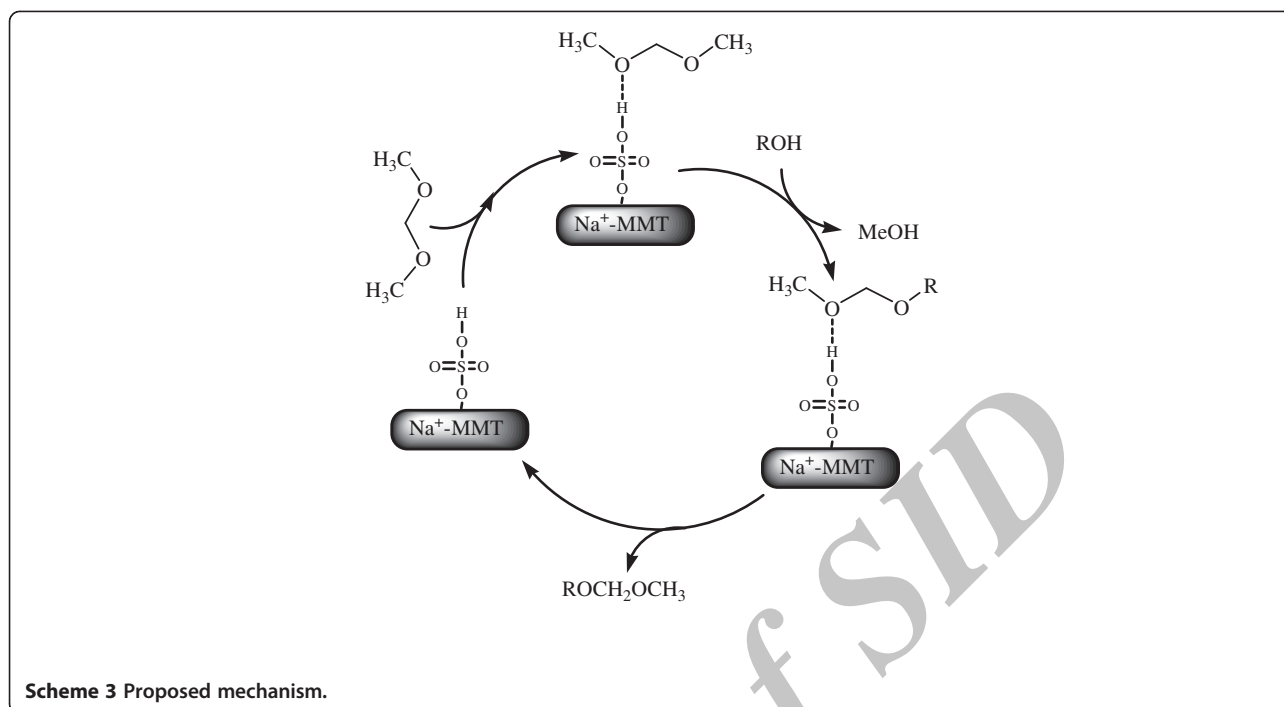
General

Chemicals were purchased from Southern Clay Products (Gonzales, TX, USA), Fluka (Buchs, Switzerland), Merck (Darmstadt, Germany), and Sigma-Aldrich (St. Louis, MO, USA) 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 was accompanied by gas chromatography or thin-layer

chromatography (TLC) on silica-gel polygram SILG-UV 254 plates.

Catalyst preparation

A 500-mL suction flask charged with 2.5 g Na⁺-montmorillonite (Southern Clay Products) and 10 mL CHCl₃ was equipped with a constant pressure dropping funnel containing chlorosulfonic acid (0.50 g, 9 mmol) and a gas inlet tube for conducting HCl gas into water as adsorbing solution. Chlorosulfonic acid was added dropwise over a period of 30 min while the reaction mixture



was stirred slowly in an ice bath (0°C). After addition was completed, the mixture was stirred for additional 30 min to remove all HCl. The mixture was then filtered, and the solid residue was washed with methanol (20 mL) and dried at room temperature to obtain SANM as white powder (2.58 g) [34,35].

Catalyst characterization

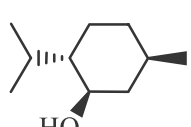
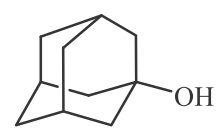
The synthesized catalyst was characterized by Fourier transform infrared spectroscopy, transmission electron microscopy, nitrogen sorption technique, X-ray

diffraction, thermogravimetric analysis, and elemental analysis [34,35].

General procedure

A mixture of the substrate (1 mmol), FDMA (6 mmol, 0.456 g), and SANM (3 mg) in CHCl₃ (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 Et₂O (5 mL) was added. The mixture was filtered, and the solid residue was washed with Et₂O (5 mL). The filtrate was washed with a saturated solution of NaHCO₃ and H₂O and dried over

Table 2 Comparison of some results obtained by our method (I) with those reported using various catalysts

Entry	Substrate	Time (h)/yield (%) /mmol of FDMA					
		I	II	III	IV	V	VI
1	PhCH ₂ OH	2/92/6	1.5/85/10	-	1/95/8	1.67/83/30	3/90/10
2	4-NO ₂ C ₆ H ₄ CH ₂ OH	7.5/93/6	12.5/80/10	5/94/50	-	12/75/30	4.5/83/10
3		7.5/97/6	16.5/78/10	7/80/50	4/85/8	17.5/85/30	-
4		8/90/6	8/70/10	7/77/50	-	8.5/75/30	5/75/30

Various catalysts used silica sulfuric acid (II) [8], Sc(OTf)₃(III) [9], Bi(OTf)₃ (IV) [10], Al(HSO₄)₃ (V) [11], and H₃Mo₁₂O₄ (VI) [12].

MgSO₄. Evaporation of the solvent afforded the requested MOM ether in high purity.

Competing interests

The authors declare that they have no competing interests.

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