Nano $Fe_3O_4@ZrO_2/SO_4^{2-}$: A highly efficient catalyst for the protection and deprotection of

hydroxyl groups using HMDS under solvent-free condition

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ABSTRACT

In this work, we introduce a new procedure for the protection and deprotection process of various types of alcohols and phenols by HMDS in the presence of nano magnetic sulfated zirconia (Fe₃O₄@ZrO₂/SO₄^{2–}) as a solid acid catalyst under very mild and solvent-free condition. This method has interesting advantages like short reaction times and a simple workup process. With regard to some outstanding benefits of this new heterogeneous catalyst such as excellent yield, reusability of the catalyst and easy thermal stability, high acidity, strong and excellent magnetic properties, this method can be very interesting in aspect of green chemistry Principles.

KEYWORDS

Magnetic nanocatalyst; $Fe_3O_4@ZrO_2/SO_4^{2-}$; trimethylsilyl ethers; HMDS; solvent-free condition

Introduction

Protection and deprotection of functional groups are indispensable processes in multi-step syntheses of complex organic molecules.¹ Protections of hydroxyl groups have received attention in recent years because of their role in synthetic organic and analytical chemistry.²⁻⁴ Conversion of alcohols to their corresponding silvlethers is one of the most popular and widely used strategies for protecting the hydroxyl groups.⁵ 1,1,1,3,3,3-hexamethyldisilazane (HMDS) has emerged as the most versatile reagent in recent years, for the trimethylsilyl (TMS) protection of alcohols and phenols. HMDS is a stable, commercially available and inexpensive compound. Its handling does not require special precautions and the workup is convenient because the only by product of the reaction is ammonia which is easily removed from the reaction medium.⁶ However, the low silvlation power of HMDS is the main drawback to its application,⁷ therefore several catalytic system have been developed to activate this reagent, such as (CH₃)₃SiCl, I₂, K-10 montmorillionite, ZnCl₂, Lithium perchlorate supported on silica gel. Silica sulfuric acid.⁷⁻¹⁷ Some of these protocols suffer from several aspects such as the use of expensive reagents, longer reaction times, harsh reaction conditions, tedious experimental procedures. Therefore, the development of simple, efficient, clean, high yielding and environmentally friendly approaches, using new catalysts for the protection of hydroxyl groups is an important task for organic chemists.

Deprotection of trimethylsilyl ethers to their corresponding hydroxyl compounds under mild condition is interesting for reactions in organic synthesis, and a wide variety of catalysts have been already reported for these conversions. Recently, to improve these reactions, many catalysts such as $BF_3 \cdot Et_2O$ -CHCl₃,¹⁸ aqueous acid,¹⁹ TiO₂-HClO₄,²⁰ silica sulfuric acid,²¹ montmorillonite K-10⁹ and silica chloride ²² have been developed. Despite of all reported studies, some of these methods suffer from one or more disadvantages like formation of large amounts of by-products, low yield of the products, hard workup, high cost or toxicity of the reagent and non-recyclability of the catalysts. Therefore, to overcome these drawbacks, enhancement of heterogeneous catalysts for the deprotection of trimethylsilyl ethers represents an attractive research task in organic chemistry.

In continuation of our research on one-pot multicomponent reactions,^{23, 24} we have recently reported the synthesis of nano magnetic sulfated zirconia $Fe_3O_4@ZrO_2/SO_4^{2-}$ and its application in the Strecker reaction as the first multicomponent reaction.^{25, 26} Herein, we wish to report the application of $Fe_3O_4@ZrO_2/SO_4^{2-}$ as an efficient catalyst for the silylation of hydroxyl groups under solvent-free condition at room temperature (see Scheme 1).

$$R-OH + Me_{3}Si^{N}SiMe_{3} \xrightarrow{Fe_{3}O_{4}@ZrO_{2}/SO_{4}^{2-}} R-OSiMe_{3}$$

r.t, Solvent-free

Scheme 1: *O*-Silylation of alcohols catalysed by $Fe_3O_4@ZrO_2/SO_4^{2-}$.

Results and discussion

Nano magnetic sulfated zirconia was prepared through the method that we have reported recently (for more details please see supporting information)^{25, 26}. The catalytic applicability of nano magnetic sulfated zirconia Fe₃O₄@ZrO₂/SO₄²⁻ in activation of HMDS for the protection of benzyl alcohol under solvent-free condition at room temperature was examined as a model reaction. To demonstrate the effect of the solid acid catalyst $Fe_3O_4@ZrO_2/SO_4^{2-}$, the reaction of HMDS and benzyl alcohol was examined in the absence of catalyst. However, this reaction remained incomplete and only 10% of the desired product was obtained after 120 min. Also, we evaluated the different amount of catalyst in this model reaction. When 80.0 mg of Fe₃O₄@ZrO₂/SO₄²⁻ was used the reaction went to completion in 15 min, and 90% of product was isolated (Table 1). In order to ensure the efficiency of $Fe_3O_4@ZrO_2/SO_4^{2-}$ in the protection reaction, we also investigated the treatment of other types of alcohols in the absence of catalyst, such as phenol, diphenylmethanol, naphthalen-2-ol and 2-methylbutan-2-ol. It seems that these reactions were not completed in the absence of the $Fe_3O_4@ZrO_2/SO_4^{2-}$. Therefore, these conditions were applied to the trimethylsilylation of other types of hydroxyl groups. The data in Table 2 clearly show that other types of alcohols, such as acid sensitive alcohols, as well as phenols and substituted phenols can be successfully converted to the corresponding trimethylsilyl ethers under these conditions (entries 9-17, Table 2).

[Insert Table 1]

[Insert Table 2]

O-Silylation of various primary alcohols including derivatives of benzyl alcohols with electron-donating or electron-withdrawing groups proceeds efficiently with notable isolated yield

(entries 1-8, Table 2). We extended our methodology to hindered secondary and tertiary alcohols. In the case of tertiary alcohols, the yield of TMS ethers was rather lower and longer reaction times were required than for less sterically hindered substrates. It should be noted that in the case of hindered tertiary alcohols, no elimination by-products were observed at all. Also, in the presence of an amino group, only the hydroxyl group reacts with HMDS to form the corresponding silylated product (entries 15, 16, Table 2). In the case of diols and dihydroxyarenes, only bis-silylated diols were formed (entries 5, 17, Table 2).

We also investigated the deprotection of corresponding silylethers in the presence of $Fe_3O_4@ZrO_2/SO_4^{2-}$ under solvent-free condition at room temperature (Table 3). The removal of the protective group can be carried out under mild reaction conditions as easily as the related protection process. The results have indicated the convenient efficiency of synthesized nano magnetic as catalyst in this reaction. Regarding to the structure of this catalyst, it exhibits both Brønsted and Lewis acid sites which can cause to improve the reaction. In general, benzylic trimethylsilyl ethers have shorter reaction times in comparison to phenolic trimethylsilyl ethers, and also for trimethylsilyl ethers substituted with electron-withdrawing groups decreased reaction rates are observed (Table 3). Table 4 shows the efficiency of $Fe_3O_4@ZrO_2/SO_4^{2-}$ in comparison with results reported in the literature. Short reaction time, solvent-free condition and simple recovery make our system better choice.

[Insert Table 3]

[Insert Table 4]

The recovery and reusability of the catalyst was investigated in the silylation of benzyl

alcohol with HMDS. After completing the reaction, the catalyst was easily separated by an external magnet, washed with ethanol and dried at room temperature and used directly for the next reaction. The isolated catalyst was reused for 5 runs without observable loss of its catalytic activity (Figure 1). This catalyst exhibits excellent selectivity in this reaction and can be used for the protection of OH groups in competition with NH₂ and COOH (Scheme 2). The suggested mechanism for the reaction is shown in Scheme 3.

[Insert Scheme 2]

[Insert Scheme 3]

[Insert Figure 1]

Conclusion

In conclusion, $Fe_3O_4@ZrO_2/SO_4^{2-}$ is found to be an efficient novel, heterogeneous catalyst for the selective silulation of various hydroxyl groups with HMDS under solvent-free condition. This method offers several advantages including high yields, short reaction times, easy workup procedure, reusability of catalyst and environmentally benign reaction conditions.

Experimental

Chemicals and Instruments

All chemicals used, such as iron(III) chloride, iron(II) chloride, zirconium(IV) chloride, ammonium sulfate, alcohols, HMDS and solvents were supplied by Merck and Aldrich chemical companies. FT-IR spectra were obtained over the region 400-4000 cm⁻¹ with a Nicolet IR 100 FT-IR instrument by use of spectroscopic grade KBr. ¹H NMR spectra were recorded using a

Avance Bruker DRX-500 spectrometer at 500 MHz in CDCl₃ as solvent. The powder X-ray diffraction pattern was recorded using a X-PERT-PRO diffractometer with CuK_{α} , ($\lambda = 1.54$ Å) irradiation, in the range of 5 to 80 (20) with a scan step of 0.026. The morphology of the catalyst was studied with scanning electron microscopy using SEM (KYKY, EM 3200) on gold coated samples. The magnetic properties of Fe₃O₄@ZrO₂/SO₄²⁻ nanoparticles were measured with a Vibrating Magnetometer/ Alternating Gradient Force Magnetometer (VSM/, MDKFD). The BET surface area and pore volume of Fe₃O₄@ZrO₂/SO₄²⁻ was determined with a Micromeritics ASAP 2020 apparatus using nitrogen as the analysis gas. The Supplemental Materials presented additional characterization information for the catalyst (Figures S 1 – S 7).

General procedure for the protection of hydroxyl groups using HMDS

To a mixture of alcohols (1.0 mmol) and HMDS (1.5 mmol) was added $Fe_3O_4@ZrO_2/SO_4^{2-}$ (80.0 mg) and the mixture was stirred at room temperature for an appropriate time (Table 2). After completion of the reaction, as indicated by thin-layer chromatography (TLC), the catalyst was separated by an external magnet and the products were obtained by evaporation of the volatile portion under reduced pressure. All compounds are known and were characterized on the basis of their spectroscopic data (IR, ¹H NMR) and by comparison with those reported in the literature.

General procedure for the deprotection of trimethylsilyl ethers (removal of TMS groups) using $Fe_3O_4@ZrO_2/SO_4^{2-}$

To a mixture of trimethylsilyl ether (1.0 mmol), 80.0 mg Fe₃O₄@ZrO₂/SO₄²⁻ was added and the

mixture was stirred at room temperature for an appropriate time (Table 3). After completion of the reaction, as indicated by thin-layer chromatography (TLC), 10.0 mL CCl₄ was added to the reaction mixture, the catalyst was separated by an external magnet, and the product was obtained by evaporation of the volatile portion under reduced pressure. All compounds are known and were characterized on the basis of their spectroscopic data (IR, ¹H NMR) and by comparison with those reported in the literature.

Spectroscopic data of representative compounds

2a. Table 2. Entry 1. IR: v = 1253, 1068, 643 cm⁻¹. ¹H NMR: $\delta = 0.16$ (s, 9H), 4.70 (s, 2H), 7.23-7.34 (m, 5H).

2b. Table 2. Entry 6. IR: v = 1253, 1095, 844 cm⁻¹. ¹H NMR: $\delta = 0.10$ (s, 9H), 4.72 (s, 2H), 7.19-7.31 (m, 4H).

2i. Table 2. Entry 9. IR: $v = 3057, 2960, 1468, 1255, 969, 928, 854 \text{ cm}^{-1}$.

2s. Table 2. Entry 19, IR: v = 1631, 1599, 1255, 854 cm⁻¹. ¹H NMR: $\delta = 0.39$ (s, 9H), 7.11-7.84 (m, 7H).

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Table 1: Optimization of *O*-silylation of benzyl alcohol using Fe₃O₄@ZrO₂/SO₄²⁻

Entry ^a	Catalyst (mg)	Time (min)	Yield (%) ^b
	$Fe_{3}O_{4}@ZrO_{2}/SO_{4}^{2}$		
1	-	120	10
2	10	43	75
3	40	35	80
4	80	15	92
5	90	30	90

^a Reaction conditions: benzyl alcohol (1.0 mmol), HMDS (1.5 mmol), catalyst, solvent-free. ^b Isolated yields.

Table 2: Silylation of various alcohols with HMDS in the presence of $Fe_3O_4@ZrO_2/SO_4^{2-}$ as the catalyst

Entry	Substrate	Draduat	Time	Yield
	Substrate	Product	(min)	$(\%)^{\mathrm{b}}$
1	ОН	OSiMe ₃	15	90

2	H ₃ C OH	H ₃ C OSiMe ₃ 2b	12	80
3	Н3СО ОН	H ₃ CO OSiMe ₃ 2c	10	90
4	ОН СН3	OSiMe ₃ CH ₃ 2d	12	90
5	ОН	OSiMe ₃ OSiMe ₃ 2e	100	85
6	O ₂ N OH	O ₂ N OSiMe ₃ 2f	25	90
7	OH NO ₂	OSiMe ₃ NO ₂ 2g	35	85
8	ОН	CI 2h	25	88
9	OH	OSiMe ₃	40	95
10	OH Cl	CI 2j	50	95
11	OH Cl	OSiMe ₃ Cl	75	90
12	OH Cl	Cl 2l	100	94
13	OH I	OSiMe ₃	120	87





^a Reaction conditions: alcohol (1.0 mmol), HMDS (1.5 mmol), catalyst (80 mg), solvent free. ^b Isolated yield.

Entry	Substrate	Product	Time (min)	Yield (%) ^b
1	OSiMe ₃	он За	10	85
2	OSiMe ₃	н ₃ с ОН 3b	10	80
3	H ₃ CO	H ₃ CO 3c	10	91
4	OSiMe ₃ CH ₃	CH ₃ 3d	10	85
5	OSiMe ₃	он Он Зе	50	80
6	O ₂ N OSiMe ₃	O ₂ N OH	20	85
7	OSiMe ₃ NO ₂	NO ₂ 3g	30	77
8	OSiMe ₃	СІ З	20	80

Table 3: Deprotection of silvlethers in presence of $Fe_3O_4@ZrO_2/SO_4^{2-}$ as the catalyst





^a Reaction conditions: Silylethers (1.0 mmol), $Fe_3O_4@ZrO_2/SO_4^{2-}$ (80.0 mg), solvent-free, room temperature. ^b Isolated yields.

Table 4: Comparison of the efficiency of $Fe_3O_4@ZrO_2/SO_4^{2-}$ with other catalysts for silvlation of benzyl alcohol using HMDS at room temperature

Entry	Catalyst	Solvent	Time	Yield	Ref.
			(min)	%a	
1	Sulfonic acid@nanoporous	CH ₂ Cl ₂	55	99	27
	silica				
2	LaCl ₃	-	180	91	28
3	LiClO ₄	-	25	90	29
4	$H_{3}PW_{12}O_{40}$	-	23	90	30
5	TCCA	CH ₂ Cl ₂	240	90	16
6	Poly(N-bromobenzene-1,3-	CH ₂ Cl ₂	90	90	31
	disulfonamide)				
7	$Fe_{3}O_{4}@ZrO_{2}/SO_{4}^{2-}$	-	15	90	This
					work

^a Isolated yields.



Figure 1: Recycling of $Fe_3O_4@ZrO_2/SO_4^{2-}$ for the protection of benzyl alcohols.



Scheme 1 O-Silylation of alcohols catalyzed by Fe₃O₄@ZrO₂/SO₄²⁻



Scheme 2: Selectivity of Fe₃O₄@ZrO₂/SO₄²⁻ in protection reactions



Scheme 3: Plausible mechanism for the *O*-silylation of alcohols with HMDS catalysed by $Fe_3O_4@ZrO_2/SO_4^{2-}$

Graphical Abstract

