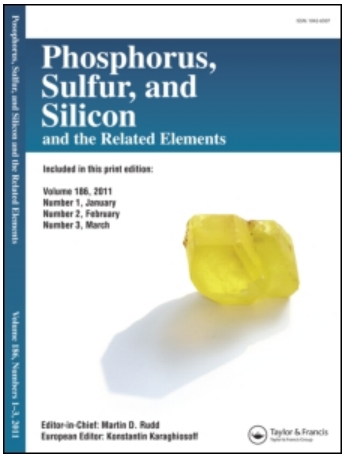

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Alumina Perchloric Acid (Al_2O_3-$HClO_4$) as an Efficient Heterogeneous Catalyst for Modified Preparation of Trimethylsilyl Ethers

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A highly efficient and mild procedure for the trimethylsilylation of a wide variety of alcohols, including primary, benzylic, secondary, hindered secondary, tertiary, phenols, and oximes with hexamethyldisilazane (HMDS) using alumina perchloric acid (Al_2O_3-$HClO_4$) as recyclable heterogeneous catalyst in excellent yields with short reaction times (3–65 min) under ambient conditions is described.

Keywords Alumina perchloric acid; heterogeneous catalyst; hexamethyldisilazane; hydroxyl groups; trimethylsilylation

INTRODUCTION

Trimethylsilylation of organic compounds having labile hydrogen atoms is an important organic transformation. It is a frequently used protection method in multi-step sequence synthesis of natural products due to the enhanced stability under a variety of conditions, solubility in non-polar solvents, thermal stability, and the ease of removal which is simply accomplished by acid or base induced hydrolysis giving only unreactive siloxane as by-product. It is also used extensively for the hydroxyl compounds to increase their volatility for gas chromatography and mass spectrometry.[1,2]

Several methods have been reported for this conversion, including the reaction of an alcohol with trimethylsilylhalides in the presence of a stoichiometric amount of a tertiary amine,[3] with trimethylsilyl

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triflate and trimethylsilylmethallylsulfinates, which are more reactive than the chloride,[4] allylsilanes in the presence of a catalytic amount of *p*-toluenesulfonic acid[4] iodine,[5] trifluoromethanesulfonicacid[6] and $Sc(OTf)_3$.[7] Hexamethyldisilazane (HMDS) is frequently used for the trimethylsilylation of hydroxyl groups. HMDS is an inexpensive and commercially available reagent. Its handling does not require special precautions, and the work-up is not time-consuming, because the by-product of the reaction is ammonia, which is simple to remove from the reaction medium. The low silylation power of HMDS is the main drawback to its application. Therefore, there are variety of catalysts for activating of this reagent, such as $(CH_3)_3SiCl$,[8] K-10 montmorillionite,[9] sulfonic acids,[10] zirconium sulfophenyl phosphonate,[11] $ZnCl_2$,[12] Envirocat EPZGO,[13] tungstophosphoric acid,[14] iodine,[15] lithium perchlorate,[16] cupric sulfate pentahydrate,[17] H–β Zeolite,[18] $MgBr_2$,[19] lithium perchlorate supported on silica gel,[20] $Al(HSO_4)_3$,[21] $Al(OTF)_3$,[22] magnesium triflate,[23] copper triflate,[24] $ZrCl_4$,[25] silica-$HClO_4$,[26] and silica chloride.[27] However, in most cases, a long reaction time, drastic reaction conditions, or tedious work-up is needed. In addition, trimethylsilyl azide is expensive and toxic. In continuation of our work[28] on the application of heterogeneous catalysts for the development of useful synthetic methodologies, we now show that O-trimethylsilylated compounds can be produced using Al_2O_3-$HClO_4$ as an efficient, recyclable heterogeneous catalyst under ambient conditions (Scheme 1).

$$2\ \text{R-OH} + \text{Me}_3\text{SiNHSiMe}_3 \xrightarrow[\text{Solvent-free}\\ \text{Room temperature}]{\text{Al}_2\text{O}_3\text{-HClO}_4\\ \text{(Catalyst)}} 2\ \text{R-OSiMe}_3 + \text{NH}_3$$

R= aryl, primary, secondary, tertiary and benzylic alcohol, oxime

SCHEME 1

This catalyst is safe, easy to handle, environmentally benign, presents fewer disposal problems and stable in reaction media. Al_2O_3-$HClO_4$ has been prepared from the reaction of neutral alumina with perchloric acid.

RESULTS AND DISCUSSION

First, silylation of benzyl alcohols with HMDS in the presence of solid Al_2O_3-$HClO_4$ as a catalyst in various solvents and also under solvent-free conditions at room temperature was investigated. The results were summarized in Table I. In Table I, we show that acetonitrile as a solvent is obviously the best choice for these reactions.

TABLE I Silylation of Benzyl Alcohols with HMDS in the Presence of Solid Al_2O_3-$HClO_4$(0.025 g) as Catalyst Under Solvent and Solvent-Free Conditions at Room Temperature

Entry	Solvent[a]	Substrate/HMDS Molar Ratio	Time (min)	GC Yield (%)	Yield (%)[b]
1	Dichloromethane	1/0.8	60	100	89
2	Chloroform	1/0.8	30	100	91
3	Ethyl acetate	1/0.8	40	100	87
4	Hexane	1/0.8	130	100	93
5	Acetonitrile	1/0.8	9	100	93
6	Solvent-Free	1/0.8	135	100	89

[a]Amount of solvent = 2 ml; and [b]isolated yield.

To determine the optimum quantity of Al_2O_3-$HClO_4$, the reaction of benzyl alcohol (1 equiv) and HMDS (0.8 equiv) was carried out under ambient conditions using different quantities of catalyst. The use of 50 mg of catalyst was resulted in the highest yield in 3 min (Table II). Thus, we prepared a range of O-trimethylsilated compounds under the optimized reaction conditions (Table III).

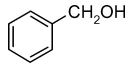
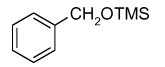
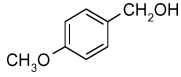
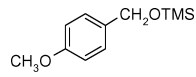
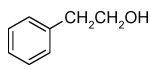
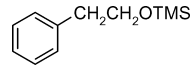
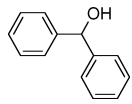
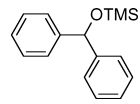
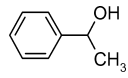
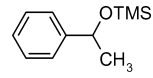
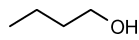
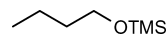
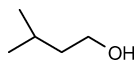
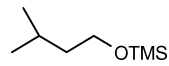
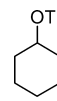
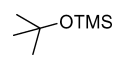
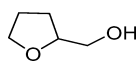
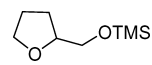
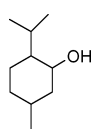
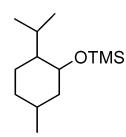
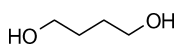
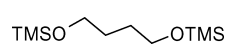
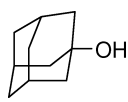
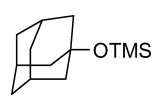
A wide range of structurally diverse and functionalized phenols, alcohols and oximes underwent silylation by this procedure to provide the corresponding TMS ethers in good to excellent isolated yields (Table III, Entries 1–24). Primary alcohols mostly reacted faster than secondary and tertiary alcohols. Generally, in the all cases of benzyl, primary, secondary, and tertiary alcohols, the reactions were completed within less than 65 min in solvent-free conditions, accompanied by evolution of NH_3 gas from the reaction mixture. Inspection of the data in Table III clearly shows that different types of hindered secondary, tertiary alcohols and oximes were successfully converted to the corresponding silyl ethers at ambient conditions (Table III). Amines (Table III, Entries 26–28), thiols (Table III, Entry 25) remained unaffected under the reaction conditions.

TABLE II Optimization of the Amount of Catalyst in the Synthesis of Benzyl Trimethylsilyl Ether

Entry	Al_2O_3-$HClO_4$(g)	Time(min)	Yield (%)[a]
1	0.05	3	95
2	0.025	9	93
3	0.01	19	90

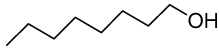
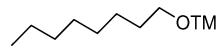
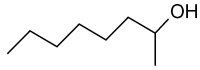
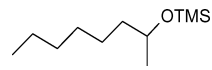
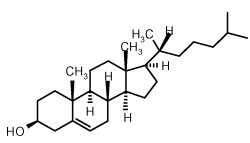
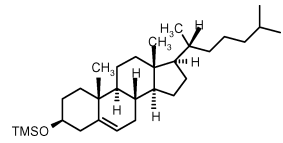
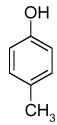
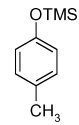
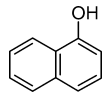
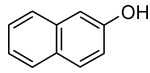
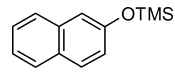
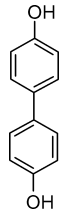
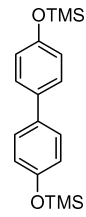
[a]Isolated yield.

TABLE III Silylation of Variety Hydroxyl Groups with HMDS in the Presence of Solid Al_2O_3-$HClO_4$ as Catalyst (0.05 g) Under Ambient Conditions

Entry	Substrate	Product	Molar ratio substrate/ HMDS	Time (min)	Yield (%)[a]
1			1/0.8	3	(91-95)[b]
2			1/0.8	3	94
3			1/0.8	8	98
4			1/0.8	7	91
5			1/0.8	7	93
6			1/0.8	9	83
7			1/0.8	6	85
8			1/0.8	13	92
9			1/0.8	65	87
10			1/0.8	7	93
11			1/0.8	11	97
12			1/1.6	5	91
13			1/0.8	17	97

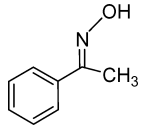
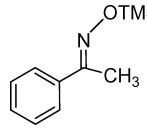
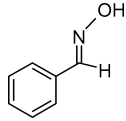
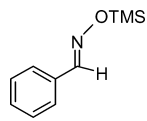
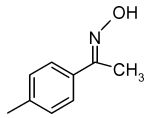
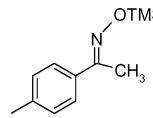
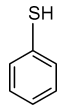
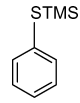
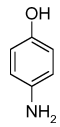
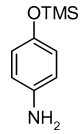
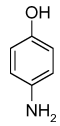
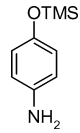
(Continued on next page)

TABLE III Silylation of Variety Hydroxyl Groups with HMDS in the Presence of Solid Al_2O_3-$HClO_4$ as Catalyst (0.05 g) Under Ambient Conditions *(Continued)*

Entry	Substrate	Product	Molar ratio substrate/ HMDS	Time (min)	Yield (%)[a]
14			1/0.8	4	96
15			1/0.8	9	95
16			1/0.8	6	96
17			1/0.8	4	95
18			1/0.8	4	96
19			1/0.8	4	93
20			1/0.8	3	94
21			1/1.6	4	96

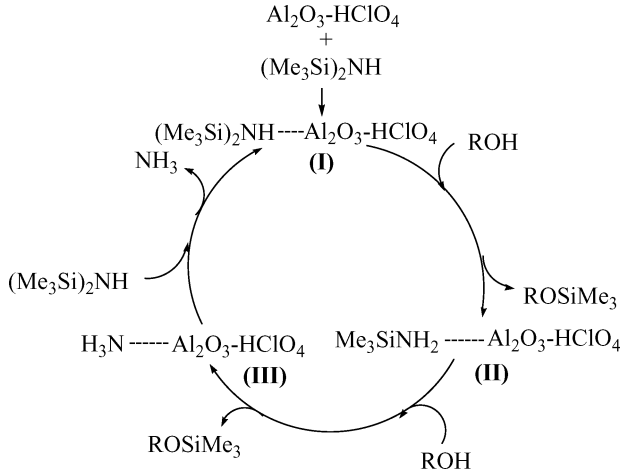
(Continued on next page)

TABLE III Silylation of Variety Hydroxyl Groups with HMDS in the Presence of Solid Al_2O_3-$HClO_4$ as Catalyst (0.05 g) Under Ambient Conditions *(Continued)*

Entry	Substrate	Product	Molar ratio substrate/ HMDS	Time (min)	Yield (%)[a]
22			1/0.8	6	93
23			1/0.8	6	88
24			1/0.8	5	91
25			1/0.8	7	—
26			1/0.8	5	90
27			1/1.6	5	90
28			1/0.8	7	—

[a]The pure isolated product(s) was characterized by comparison of their physical data with those of known compounds.[8–27 b] Yields after five times using recovered of the catalyst.

The suggested mechanism of the Al_2O_3-$HClO_4$ catalyzed silylation of hydroxyl groups is shown in Scheme 2. Al_2O_3-$HClO_4$ can act as Brønsted acid and also Lewis acid owing to the empty aluminum p orbital. Thus, in this mechanism, however operation process chart (OPC) of catalyst in this works is unknown nonetheless according to the observations such as evolution of NH_3in the reaction conditions, we have suggested that an acid-base interaction in Al_2O_3-$HClO_4$ as catalyst and nitrogen in HMDS polarizes N-Si bond of HMDS to produce a reactive silylating agent (**I**). A rapid reaction with alcohol then ensues, leading to the ammonium silylating species (**II**) with concomitant release of the corresponding silyl ether. Irreversible cleavage of (**II**) with alcohol led to the fast evolution of ROTMS and also formation of the unstable complexes of Al_2O_3-$HClO_4$ with ammonia (**III**). Cleavage of this complex with HMDS, led to the fast evolution of NH_3. Release of Al_2O_3-$HClO_4$ as catalyst from intermediate (**III**), re-enters catalytic cycle (Scheme 2).



SCHEME 2

The reusability of the catalysts is an important benefit and makes them useful for commercial applications. Thus, the recovery and reusability of Al_2O_3-$HClO_4$ was investigated. The recyclability of the catalyst in the reaction of benzyl alcohol and HMDS in the presence of Al_2O_3-$HClO_4$ was checked (Table III, Entry1). The separated catalyst can be reused after washing with CH_2Cl_2 and drying at 100^{o}C. The catalyst was recovered in excellent yields and catalyst was used in the mentioned reaction for five times; it showed the same activity such as fresh catalyst without any loss of its activity.

In conclusion, a reliable, rapid, and environmentally benign method for the preparation of trimethylsilyl ethers in a high to excellent yield under ambient conditions has been developed, which involves the use of recyclable Al_2O_3-$HClO_4$as an inexpensive and non-hazardous solid acid catalyst. In addition to the purity of the products, the short reaction times and ease of work-up make the method advantageous. We are currently exploring further applications of Al_2O_3-$HClO_4$ for other types of functional group transformations in our laboratories.

EXPERIMENTAL

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopy data (IR, ^{1}H NMR spectra). The NMR spectra were recorded on a Bruker Avance DPX 300 and 500 MHz instrument. The spectra were measured in $CDCl_3$ relative to TMS (0.00 ppm). GC analysis was run with Shimadzu GC-14A. IR spectra were recorded on a JASCO FT-IR 460plus spectrophotometer. TLC was performed on Silica-gel polygram SIL G/UV 254 plates.

Preparation of Al_2O_3-$HClO_4$

We prepared Al_2O_3-$HClO_4$ in a similar manner to that of the SiO_2-$HClO_4$ procedure first reported by Chakraborti and Gulhane.[29]

$HClO_4$ (1.045 g, 60% $HClO_4$) was added to the suspension of neutral alumina (Merck, 70–230 mesh, 11.85 g) in diethyl ether (75 mL). The mixture was concentrated and the residue dried under vacuum at 100^{o}C for 72 h to afford Al_2O_3-$HClO_4$ as a free flowing powder.

The amount of H^+ in the Al_2O_3-$HClO_4$ was determined by acid-base titration according to the following reaction (Equation 1).

$$Al_2O_3{-}HClO_4 \longrightarrow Al_2O_3{-}ClO_4 + H_3O \quad (1)$$

The librated H_3O^+ was titrated by standard NaOH and the amount of H^+ in Al_2O_3-$HClO_4$ was calculated (1 g of Al_2O_3-$HClO_4$ equal to 0.5 mmol H^+).

General Procedure for Silylation of Alcohols Using HMDS Catalyzed with Al_2O_3-$HClO_4$

To a stirred solution of alcohol (10 mmol), HMDS (8 mmol) and acetonitrile (5 ml) as solvent was added Al_2O_3-$HClO_4$ (0.5 g, 0.25 mmol) and the mixture was stirred at room temperature for the time specified in

Table II. The reaction was followed by TLC (n-Hexane-EtOAc, 9:1). After completion of the reaction, the heterogeneous catalyst was filtered, silica-gel (2 g) was added to the solution and the solvent was evaporated at reduced pressure. The resulting presorbed material was purified by column chromatography using silica gel. Then, the pad of silica in the column was washed with n-hexane (2 × 10 mL). Evaporation of the solvent under reduced pressure gave pure product(s) (Table I). The desired pure product(s) was characterized by comparison of their physical data with those of known compounds.[8–27]

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