

Silylation and Tetrahydropyranylation of Alcohols Catalyzed by $Al(HSO_4)_3$

Farhad Shirini,* Mohammad Ali Zolfigol,[1] and Masoumeh Abedini

Department of Chemistry, College of Science, Guilan University, Rasht 41335, Iran

[1]Department of Chemistry, College of Science, Bu-Ali Sina University, Hamadan 65174, Iran

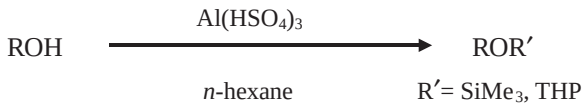
Received April 5, 2004; E-mail: shirini@guilan.ac.ir

Trimethylsilylation and tetrahydropyranylation of alcohols are efficiently catalyzed by $Al(HSO_4)_3$. All reactions were performed under mild and completely heterogeneous conditions in good-to-high yields.

The hydroxy group is present in a number of compounds of biological and synthetic interest. Protection of this functional group during a multi-step synthesis is an important process, which is under considerable attention of organic chemists.[1] The conversion hydroxy groups to their corresponding trimethylsilyl and tetrahydropyranyl ethers is one of the popular methods used for this purpose. 1,1,1,3,3,3-Hexamethyldisilazane (HMDS) as a cheap and commercially available material is one of the reagents that is used for the silylation of alcohols.[2,3] It's handling does not need special precaution, and work-up of the reaction mixture is not time consuming. However, the low silylating power of HMDS is a main drawback for its application, which needs forceful conditions and long reaction time in a many instances.[4] For the activation of HMDS, a variety of catalysts, such as Me_3SiCl,[5] zirconium sulfophenylphosphonate,[6] K-10 montmorillonite,[7] and silicon chloride,[8] have been reported.

Although, using these reagents causes a considerable enhancement in the activity of HMDS, in most cases the reaction with hindered alcohols do not take place,[5] or requires forceful conditions and prolonged reaction times.[4]

Because of the remarkable stability of tetrahydropyranyl ethers towards a variety of conditions, such as strongly basic media, Grignard reagents and alkyllithiums, reduction with hydride, oxidation, oxidative alkylation, and acylation reactions,[9] tetrahydropyranylation has found a wide variety of applications in protecting the hydroxy group of alcohols. A variety of reagents have been developed for the tetrahydropyranylation of hydroxy functions, which include mainly protic acids,[10] Lewis acids,[11] ion exchange resins (Amberlyst H15[12] and Nafion-H[13]), I_2,[14] $CuCl_2$,[15] zinc chloride on alumina,[16] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),[17] lithium triflate,[18] calcium chloride,[19] sulfuric acid on silica gel,[20] dialkylimidazolium tetrachloroaluminates,[21] bis(trimethylsilyl sulfate),[22] and H-Y zeolite.[23] Although these methods are satisfactory for many molecules, some have limitations, such as the use of strongly acidic media, expensive reagents, tedious and time-consuming work-up procedures, refluxing conditions, high catalyst to substrate ratio, long reaction times, the formation of polymeric byproducts of the dihydropyran, and isomerization. Thus, there is still a need for a mild and efficient alternative method, especially using heterogeneous catalysts for the protection of alcohols as THP ethers.



Scheme 1.

In recent years, we were interested to develop the application of hydrogensulfate salts in organic chemistry.[24–26] In continuation of these studies, herein, we wish to report an efficient method for the trimethylsilylation and tetrahydropyranylation of alcohols in the presence of a catalytic amounts of $Al(HSO_4)_3$,[27,28] under mild and completely heterogeneous reaction conditions (Scheme 1).

Different types of benzylic alcohols having both electron-withdrawing and -donating groups were trimethylsilylated with HMDS in the presence of a catalytic amounts of $Al(HSO_4)_3$ in *n*-hexane under reflux conditions in good-to-high yields (Table 1, Entries 1–7). Primary and secondary aliphatic alcohols were also efficiently converted to their corresponding trimethylsilyl ethers under the same reaction conditions (Table 1, Entries 8–10). This method was found to be useful for the protection of hindered secondary and tertiary alcohols (Table 1, Entries 11–14). This method is also useful for the silylation of allylic alcohols (Table 1, Entry 15).

The mechanism of the reaction is not clear, but the fast evolution of NH_3 gas from the reaction mixture and the reusability of the catalyst for three times without any considerable loss of activity, directed us to accept the mechanism that is shown in Scheme 2 as a most probable one.

In order to show the efficiency of this method, we have compared some of the results with some of those reported in the literature (Table 2).[8,29]

The tetrahydropyranylation of alcohols with DHP was performed in the presence of catalytic amounts of $Al(HSO_4)_3$ in *n*-hexane at room temperature and under completely heterogeneous reaction conditions, to produce the desired tetrahydropyranyl ether in good-to-high yields (Table 3). Benzylic, allylic, primary, and secondary alcohols were protected without the

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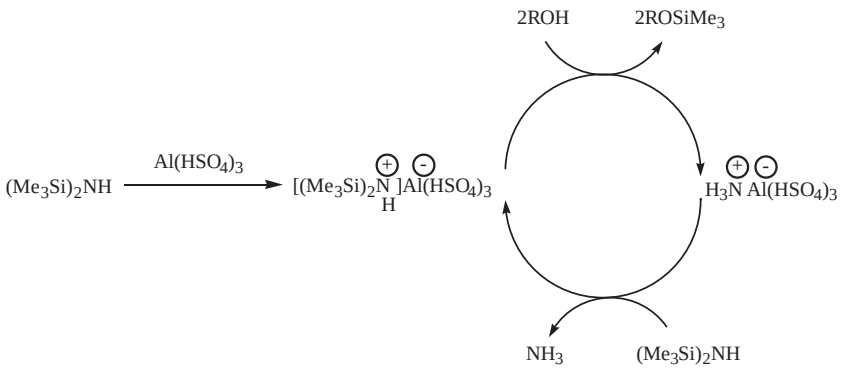
Table 1. Silylation of Alcohols Using HMDS in the Presence of $Al(HSO_4)_3$[a)]

Entry	Substrate	HMDS:$Al(HSO_4)_3$	Time/h	Yield/%[b)]
1	2-Chlorobenzyl alcohol	0.6:0.04	1	90
2	4-Chlorobenzyl alcohol	0.6:0.04	0.67	92
3	2-Bromobenzyl alcohol	0.6:0.04	1.5	85
4	2-Methylbenzyl alcohol	0.6:0.04	0.83	90
5	2-Nitrobenzyl alcohol	0.75:0.06	4	78
6	4-*tert*-Butylbenzyl alcohol	0.6:0.04	0.42	80
7	2-Phenylethanol	0.6:0.04	1.5	90
8	3-Phenyl-1-propanol	0.75:0.06	0.42	91
9	2-Phenyl-1-propanol	0.6:0.04	0.83	89
10	1-Phenyl-2-propanol	0.6:0.04	0.5	80
11	(−)-Menthol	0.75:0.06	1	95
12	1-Adamantanol	0.75:0.06	4	90
13	2-Adamantanol	0.75:0.06	4	85
14	Cholesterol	0.75:0.06	4	80
15	Cinnamyl alcohol	0.75:0.06	1.7	70

a) Products were identified spectroscopically and also by the conversion of the products to their corresponding alcohols. b) Isolated yields.



Scheme 2.

Table 2. Comparison of Some of the Results Obtained by Silylation of Alcohols with HMDS in the Presence of $Al(HSO_4)_3$ (1), with Some of Those Reported by $LiClO_4$ (2)[29] and Silicon Chloride (3)[8]

Entry	Substrate	(Time/min)(Yield/%)(Substrate:HMDS:Catalyst)		
		1	2	3
1	(−)-Menthol	(60)(95)(1:0.75:0.06)	(3)(76)(1:0.5:0.1)	—
2	4-Chlorobenzyl alcohol	(40)(92)(1:0.6:0.04)	(1.8)(67)(1:0.5:0.1)	(30)(92)(1:1:0.05)

formation of any other side products in the presence of 0.035 mol equiv of the catalyst. Tertiary alcohols gave poor yields under the same reaction conditions (Table 3, Entry 17). We then investigated the possibility for the selective tetrahydropyranylation of the above-mentioned alcohols in the presence of the tertiary ones. This is exemplified by the competitive reaction between benzyl alcohol and 1-adamantanol (Table 3, Entry 18).

To illustrate the efficiency of the proposed method, Table 4 compares some of our results with some of those reported by the relevant reagents in the literature.[18,30]

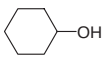
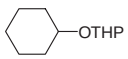
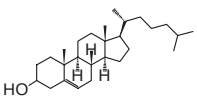
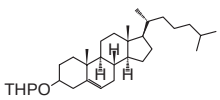
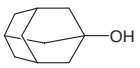
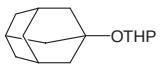
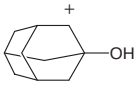
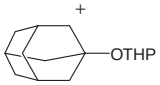
In conclusion, in this study, we developed a simple, mild, and efficient procedure for the conversion of alcohols to their corresponding trimethylsilyl and tetrahydropyranyl ethers. In addition, the availability of the reagent, short reaction times, high yields of the products, easy work-up, and heterogeneous reaction conditions are other advantages of the present method, which make this procedure a useful and attractive addition to the currently available methods.

Experimental

Chemicals were purchased from Fluka, Merck, and Aldrich Chemical Companies. All of the trimethylsilyl and tetrahydropyranyl ethers are known compounds, and were characterized by spectral analyses, comparisons with authentic samples (IR and NMR), and also by regeneration of the corresponding alcohols. All yields refer to the isolated products. The purity determination of the substrate and reaction monitoring were accompanied by TLC on silica-gel polygram SILG/UV 254 plates.

General Procedure for Silylation of Alcohols. To a mixture of the substrate (10 mmol) and $Al(HSO_4)_3$ (0.4–0.6 mmol) in hexane (30 mL), HMDS (6–7.5 mmol) was added dropwise within 5

Table 3. Tetrahydropyranylation of Alcohols in the Presence of $Al(HSO_4)_3$[a)]

Entry	Substrate	Product	Time/h	Yield/%[b)]
1	$C_6H_5CH_2OH$	$C_6H_5CH_2OTHP$	0.17	92
2	4-$ClC_6H_4CH_2OH$	4-$ClC_6H_4CH_2OTHP$	0.33	90
3	2-$ClC_6H_4CH_2OH$	2-$ClC_6H_4CH_2OTHP$	0.27	95
4	2-$BrC_6H_4CH_2OH$	2-$BrC_6H_4CH_2OTHP$	0.25	95
5	2-$MeC_6H_4CH_2OH$	2-$MeC_6H_4CH_2OTHP$	0.25	90
6	4-$PhCH_2OC_6H_4CH_2OH$	4-$PhCH_2OC_6H_4CH_2OTHP$	3	70
7	4-$Me_3CC_6H_4CH_2OH$	4-$Me_3CC_6H_4CH_2OTHP$	0.5	85
8	$C_6H_5CH(OH)C_6H_5$	$C_6H_5CH(OTHP)C_6H_5$	0.92	92
9	$C_6H_5CH(OH)COC_6H_5$	$C_6H_5CH(OTHP)COC_6H_5$	4	65
10	$C_6H_5CH_2CH_2OH$	$C_6H_5CH_2CH_2OTHP$	0.33	90
11	$C_6H_5CH_2CH_2CH_2OH$	$C_6H_5CH_2CH_2CH_2OTHP$	0.5	85
12	$C_6H_5CH(CH_3)CH_2OH$	$C_6H_5CH(CH_3)CH_2OTHP$	0.25	95
13	$C_6H_5CH_2CH(OH)CH_3$	$C_6H_5CH_2CH(OTHP)CH_3$	0.5	85
14			1.5	90
15			3	90
16	$PhCH{=}CHCH_2OH$	$PhCH{=}CHCH_2OTHP$	0.33	75
17			1	10
18	$C_6H_5CH_2OH$ + 	$C_6H_5CH_2OTHP$ + 	0.17	100[c)] + Trace[c)]

a) Products were identified spectroscopically and also by the conversion of the products to their corresponding alcohols. b) Isolated yields. c) GC yield.

Table 4. Comparison of Some of the Results Obtained by Tetrahydropyranylation of Alcohols in the Presence of $Al(HSO_4)_3$ (1), with Some of Those Reported by $ZrCl_4$ (2)[30] and LiOTf (3)[16]

Entry	Substrate	(Time/h)(Yield/%)		
		1	2	3
1	Benzyl alcohol	(0.17)(92)	(3)(92)	(2.5)(96)
2	Benzhydrol	(0.92)(95)	(3)(90)	(4)(95)
3	Cyclohexanol	(1.5)(90)	(3)(95)	—

min with stirring under reflux condition. After completing the reaction (TLC or GC), the mixture was filtered through a silica-gel pad and filter cake was washed with hexane (2×10 mL). Evaporation of the solvent gave almost pure product(s). Further purification proceeded by bulb-to-bulb distillation under reduced pressure or recrystallization to afford pure silyl ether.

General Procedure for Tetrahydropyranylation of Alcohols. A mixture of alcohol (1 mmol), 3,4-dihydro-2*H*-pyran (1.4 mmol), and $Al(HSO_4)_3$ (0.035 mmol, 0.011 g) in *n*-hexane (5 mL) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a silica-gel pad, and the solid residue was washed by *n*-hexane (5 mL). Evaporation of the solvent gave the desired products in good-to-high yields.

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