Article

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A Mild and Highly Efficient Method for the Preparation of Silyl Ethers using $Fe(HSO_4)_3/Et_3N$ by Chlorosilanes

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A very efficient and mild procedure for preparation of silyl ethers from benzylic, allylic, propargilic alcohols, phenols, naphtoles and some of phenolic drugs with trimethylsilylchloride (TMSCl), triethylsilylchloride (TESCl) and t-buthyldimethylsilyl chloride (TDSCl) ethers in the presence of $Fe(HSO_4)_3/Et_3N$ in room temperature in excellent yields is reported. This procedure also allows the excellent selectivity for silylation of alcohols and phenols.

Keywords: Silyl ethers; Phenolic drugs; TMSC; TESCl; TDSCl; Fe $(HSO_4)_3$.

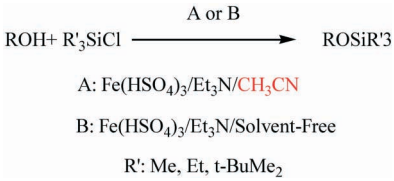
INTRODUCTION

The protection of hydroxyl groups in the synthesis of poly functional compounds, and several chemical conversions and multiple sequence synthesis is important process, which is under considerable attention of organic chemists.[1] Trimethylsilylation is used extensively for the protection and derivatization of functional groups to increase volatility for gas chromatography and mass spectroscopy.[2] And as a silyl ether is widely used in the chemistry of drugs, steroids, sugars and natural product synthesis.[3-6] A large number of reagents and methods have been reported for the preparation of trimethylsilyl ethers e.g. hexamethyldisiloxane,[7] allylsilanes,[8-9] chlorotrimethylsilane/lithium disulfide,[10] N-trimethyl-2-oxazolidinone,[11] $TMSCl/K_2CO_3$/phase transfer catalyst,[12] trimethylsilylazid,[13] allyltrimethylsilane,[14] and trimethylacetate,[15] are examples.

1,1,1,3,3,3-Hexamethyldisilazane (HMDS) is frequently used for the trimethylsilylation of hydroxyl groups. HMDS is a stable, commercially available, and cheap reagent,[16] and in workup does not require special precautions, because the byproduct of the reaction is ammonia. However, the low silylation power of HMDS is a main drawback for its application which needs forceful conditions and long reaction times in many instances. Therefore, a variety of catalysts have been reported for activating of this reagent.[17]

Recently, the use of metal hydrogensulfates in organic reactions became an important part of our research program.[18-22] In continuation of these studies, we were interested to investigate the applicability of $Fe(HSO_4)_3$ in organic synthesis.[23] Here in we wish to report an efficient method for the synthesis of silyl ethers by alcohols and phenols with chlorosilanes in the presence of $Fe(HSO_4)_3/Et_3N$, both in solution and under solvent-free conditions (Scheme I).

Scheme I Preparation of silyl ethers with $Fe(HSO_4)_3/Et_3N$ reagent in solution and under solvent-free condition



EXPERIMENTAL

Synthesis of silyl ethers were carried out under dry argon to exclude oxygen and moisture from the reaction systems.

Materials

Chemicals were purchased from Fluka, Merk and Aldrich chemical companies. All of trimethylsilyl ethers and some of triethylsilyl ethers and tert-buthyldimethylsilyl ethers are known compounds, and were characterized by spectra 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.

Measurements

^{1}H-NMR spectra were recorded on a Brucker 400 AC spectrometer in $CDCl_3$. The Infrared spectra were recorded

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on a Shimadzu FT IR-408 spectrophotometer.

General procedure for the preparation of silyl ethers in CH_3CN

To a mixture of the substrate (1 mmol), triethylamine (1 mmol) and $Fe(HSO_4)_3$ (0.03 mmol) in CH_3CN (5 mL), chlorosilane (1 mmol) was added dropwise within 10 min with stirring at room temperature. After completion of the reaction, (TLC or GC), water was added (10 mL) and the organic layer was separated, dried ($MgSO_4$) and filtered. Evaporation of the solvent gave under reduced pressure afforded the silylated compounds in high purity. Further purification was proceeded by vacuum distillation or recrystallization to afford the pure silyl ethers in good high yields.

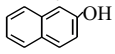
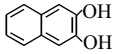
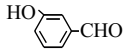
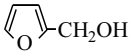
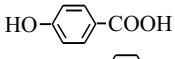
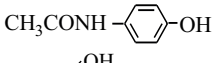
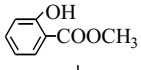
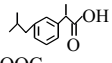
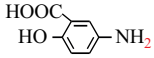
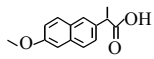
General procedure for the preparation of silyl ethers under solvent-free conditions

A mixture of the substrate (1 mmol), triethylamine (1 mmol) and $Fe(HSO_4)_3$ (0.03 mmol), chlorosilane (1 mmol) was stirred at room temperature. The progress of the reaction was monitored by TLC. Water (10 mL) was added and the mixture extracted with diethyl ether (3 × 7 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave almost pure product(s). Further purification was proceeded by vacuum distillation or recrystallization to afford pure silyl ether.

RESULTS AND DISCUSSION

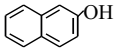
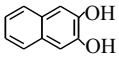
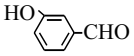
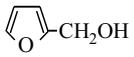
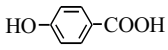
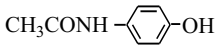
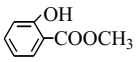
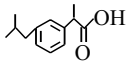
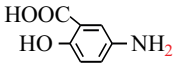
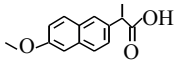
In our development of new methods for functional

Table 1. Trimethylsilylation of alcohols and phenols in solution and under solvent-free conditions[a]

Entry	Substrate	Silylation in CH_3CN		Solvent-free silylation	
		Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	$C_6H_5CH_2OH$	20	98	15	98
2	2-$BrC_6H_4CH_2OH$	25	95	16	95
3	2-$ClC_6H_4CH_2OH$	20	90	15	90
4	4-$ClC_6H_4CH_2OH$	20	95	15	95
5	2-$NO_2C_6H_4CH_2OH$	10	90	5	95
6	3-$NO_2C_6H_4CH_2OH$	12	90	5	90
7	4-$NO_2C_6H_4CH_2OH$	8	95	4	95
8	4-$NH_2C_6H_4CH_2OH$	20	85	15	85
9	C_6H_5OH	20	90	17	95
10	4-$NH_2C_6H_4OH$	40	80	30	80
11	4-$NO_2C_6H_4OH$	10	85	5	85
12	4-ClC_6H_4OH	20	80	20	85
13		10	70	8	75
14		50	70	40	70
15	CH_2=$CHCH_2OH$[c]	30	70	20	70
16	CH=CCH_2OH[c]	15	65	10	70
17		10	95	10	90
18		45	80	30	90
19		12	90	5	95
20		10	75	10	75
21		20	70	10	80
22		50	30	30	30
23		55	40	30	45
24		20	35	20	40

[a] Products were characterized by their physical constant, IR, NMR and Mass spectroscopy.
[b] Isolated yield. [c] Triethylsilylation was performed at reflux and 80 °C, respectively.

Table 2. Triethylsilylation of alcohols and phenols in solution and under solvent-free conditions[a]

Entry	Substrate	Silylation in CH_3CN		Solvent-free silylation	
		Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1	$C_6H_5CH_2OH$	25	95	20	95
2	$2\text{-}BrC_6H_4CH_2OH$	30	95	20	95
3	$2\text{-}ClC_6H_4CH_2OH$	26	95	20	95
4	$4\text{-}ClC_6H_4CH_2OH$	25	95	22	95
5	$2\text{-}NO_2C_6H_4CH_2OH$	10	90	5	95
6	$3\text{-}NO_2C_6H_4CH_2OH$	12	90	5	95
7	$4\text{-}NO_2C_6H_4CH_2OH$	8	95	3	95
8	$4\text{-}NH_2C_6H_4CH_2OH$	30	80	25	85
9	C_6H_5OH	10	95	7	95
10	$4\text{-}NH_2C_6H_4OH$	30	80	25	80
11	$4\text{-}NO_2C_6H_4OH$	20	85	18	85
12	$4\text{-}ClC_6H_4OH$	30	75	25	80
13		30	80	15	80
14		100	60	90	65
15	$CH_2{=}CHCH_2OH$[c]	50	70	40	70
16	$CH{\equiv}CCH_2OH$[c]	30	60	20	70
17		15	90	10	90
18		15	80	13	90
19		10	90	5	95
20		80	95	60	98
21		60	70	20	80
22		40	30	30	30
23		90	45	20	45
24		30	30	30	30

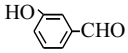
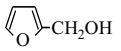
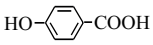
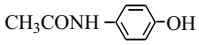
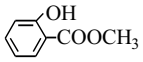
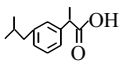
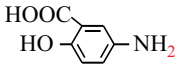
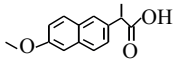
[a] Products were characterized by their physical constant, IR, NMR and Mass spectroscopy.
[b] Isolated yield. [c] Triethylsilylation was performed at reflux and 80 °C, respectively.

group transformation, we have already introduced ferric hydrogensulfate as new reagent system for the silylation of hydroxyl groups with HMDS.[23] Even though the activity of HMDS has been increased drastically in the presence of this reagent, the method suffer from limitations. With $Fe(HSO_4)$/HMDS, trimethylsilylation of alcohols and phenols in solution and under solvent-free conditions were performed at reflux and 90-100 °C, respectively.

In view of this, we decided to overcome these limitations by conducting the silylation reactions in the presence of $Fe(HSO_4)_3/Et_3N$ with chlorosilanes instead of silazanes. In this method not only trimethylsilylether but also other hindered silylethers such as triethylsilyl and tert-buthyldimethylsilyl ethers are synthesized. In order to optimized the reaction conditions, we first examined the effect of different ratios of ROH/TMSCl or TESCl/$Fe(HSO_4)_3/Et_3N$, employing the 1/1/0.03/1 mmol ratio gave the best result and produced trimethylsilyl, triethylsilyl and tert-buthyldimethylsilyl ethers in quantitative yields. The reactions were completed within 20-150 min in acetonitrile or solvent-free conditions in room temperature.

Trimethylsily, triethylsilyl and tert-buthyldimethylsilyl ethers of benzylic alcohols including acid sensitive and electron-donating or-with drawing groups were pro-

Table 3. Tert-buthyldimethyl silylation of alcohols and phenols in solution and under solvent-free conditions[a]

Entry	Substrate	Silylation in CH_3CN		Solvent-free silylation	
		Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1	$C_6H_5CH_2OH$	60	100	20	95
2	2-$BrC_6H_4CH_2OH$	33	95	20	95
3	2-$ClC_6H_4CH_2OH$	25	95	20	95
4	4-$ClC_6H_4CH_2OH$	20	95	19	95
5	2-$NO_2C_6H_4CH_2OH$	30	100	5	95
6	3-$NO_2C_6H_4CH_2OH$	18	95	5	95
7	4-$NO_2C_6H_4CH_2OH$	13	95	3	95
8	4-$NH_2C_6H_4CH_2OH$	22	90	22	90
9	C_6H_5OH	80	90	7	95
10	4-$NH_2C_6H_4OH$	30	80	25	80
11	4-$NO_2C_6H_4OH$	30	85	18	85
12	4-ClC_6H_4OH	80	70	25	80
13		60	90	25	90
14		150	60	110	85
15	CH_2=$CHCH_2OH$[c]	60	70	40	70
16	CH=CCH_2OH[c]	50	60	20	75
17		120	90	20	90
18		80	70	15	95
19		45	100	30	100
20		180	95	60	100
21		120	70	30	80
22		60	25	20	40
23		100	60	20	60
24		80	30	40	40

[a] Products were characterized by their physical constant, IR, NMR and Mass spectroscopy.
[b] Isolated yield. [c] Triethylsilylation was performed at reflux and 80 °C, respectively.

ceed efficiently with high isolated yields (Table 1, 2, 3 entries 1-8). Phenols also undergo silylation easily using this method and their corresponding silyl ethers isolated in good to high yields (Table 1, 2, 3 entries 9-12). Some of phenolic drugs were, also, successfully converted to their corresponding silyl ethers in almost quantitative yields at room temperature (Table 1, 2, 3 entries 20, 21) in solution and solvent-free conditions. This method is not useful for the silylation of ibuprofen, mesalazine and naproxen (Table 1, 2, 3 entries 22, 23 and 24 respectively) because the protection of hydroxyl group in carboxylic acid is very difficult.

In all case the trimethylsilyl, triethylsilyl and tert-buthyldimethylsilyl ethers derivatives were isolated in high yields (60-98%), and the reactions were completed in a relatively short time (8-100 min).

Although by omitting of the solvent the reaction times and the yields of the products were not changed considerably, the need for the solvent is avoided and the work-up procedure become easier.

We have found that $Fe(HSO_4)_3$ is a reusable catalyst and even after five runs for the condensation reactions the activity of the reagent was almost the same as that of the freshly used reagent.

In order to show the efficiency of this method Table 4 compares some of the results with some those reported in

Table 4. Comparison of some of the results obtained by the present method

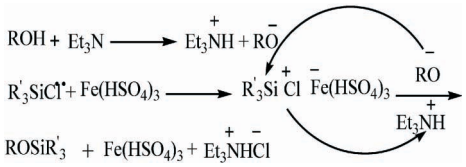
Entry	R1	(t/min)		(Yield %)	
		Silylation in CH_3CN		Solvent-free silylation	
		(1)	(2)	(1)	(2)
1	$C_6H_5CH_2OH$	(20)(98)	(102)(70)	(15)(98)	(15)(90)
2	$2\text{-}BrC_6H_4CH_2OH$	(25)(95)	(120)(60)	(16)(95)	(12)(90)
3	$2\text{-}ClC_6H_4CH_2OH$	(20)(90)	(114)(60)	(15)(90)	(15)(95)

(1) (Trimethylsilylation) with some of those reported by $Fe(HSO_4)_3$/HMDS (2)[23]

the literature.[23]

Although the mechanism for these transformations is unclear, but it seems that the Et_3N acts as a base, and polarize the O-H bond in ROH. Then chlorosilane react with $Fe(HSO_4)_3$ as a Lewis acid to produce the silylating agent. A rapid reaction with RO^-, and the concomitant release of the corresponding silyl ether, is a feature of this mechanism that is shown in Scheme II.

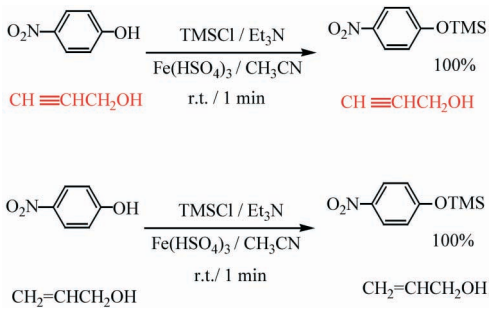
Scheme II The mechanism of preparation of silyl ethers with $Fe(HSO_4)_3/Et_3N$ reagent



This method was also found to be useful for trimethyl, triethyl and tert-buthyldimethyl silylions of allyl and propargyl alcohols, but at the reflux conditions (Table 1, 2, 3 entries 15). Therefore we observed the selective and competitive silylation of phenols in the presence of allyl and propargyl alcohols.

In a control experiment, when the trimethylsilylation reaction of 4-nitrophenol and allyl alcohol or propargyl alcohol were performed with below conditions, the nitro phenol underwent chemoselectivity trimethylsilylation and gives trimethylsiloxy-4-nitro phenol (100%), whereas the allyl alcohol or propargyl alcohol remained intact (Scheme III).

Scheme III The selective and competitive silylation of phenols in the presence of allyl and propargyl alcohols



CONCLUSION

In conclusion we have described a simple and efficient method for the synthesis of silylethers by using a reusable $Fe(HSO_4)_3$ in the presence of Et_3N with chlorosilanes, both in solution and under solvent free conditions. The method offers several advantages including simple, easy and clean work-up procedure, short reaction times and good to high yields of the products, which make it a useful addition to the present methodologies for the synthesis of chlorosilanes.

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