Zinc Mediated Reactions in Organic Synthesis: Efficient Synthesis of Silyl Ethers under Mild Conditions

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General and practical method for the synthesis of silyl ethers in the presence of zinc powder under mild conditions has been described.

Keywords: Silyl ethers; Selectivity; Protection; Zinc powder; Alcohol; TMSCl.

INTRODUCTION

The protection of alcohols as a trimethylsilyl group has been frequently and widely used in organic synthesis,¹⁻³ and this derivatization is also applicable to increase volatility for analysis in liquid or gas-chromatography and mass spectrometry.⁴ A number of methods have been reported for this purpose, using for example trimethylsilyl chloride (TMSCl) or hexamethyldisilazane (HMDS) pyridine or triethyl amine,¹⁻⁸ TMSCl/Et₃N/catalyst,⁹ TMSCl/lithium sulfide,¹⁰ TMSCl/ K₂CO₃/phase transfer catalyst,¹¹ trimethylsilyl azide,¹² allyltrimethylsilane,¹³ ethyl trimethylacetate,¹⁴ N-trimethylsilyl-2-oxazolidinone,¹⁵ N-(trimethylsilyl)imidazoles¹⁶ N,N-bis-(triethylsilyl)urea,¹⁷ ketene methyltrialkylsilyl acetals,¹⁸ and hexamethyldisilyloxane.¹⁹ Sterically hindered tertiary alcohols are in general not or only partly transformed into their O-trimethylsilylated derivatives by most of these methods. Exceptions among them are the reactions using TMSCl/Et₃N/ catalyst,⁹ N-trimethylsilyl-2-oxazolidinone,¹⁵ N-(trimethylsilyl)imidazoles,¹⁶ and N,N-bis(trimethylsilyl)trifluoroace tamide.²⁰ Some difficulties may be, however, sometimes encountered because of the basic conditions for the first method and expensiveness of the reagents for the latter three cases. The method which allows O-silylation under mild conditions should heighten the synthetic potentiality of the reaction. We now report here for the first time a zinc mediated efficient and general method of O-silylation of a variety of alcohols (Scheme I).

Scheme I

$$R-OH \xrightarrow{Zn, 25^{\circ}C} R-OSiMe_{3}$$

RESULTS AND DISCUSSION

Trace of HCl in TMSCl reacted with zero-valent zinc to generate a trace amount of ZnCl₂, which activates silyl chloride in a halophilic manner to make silylchloride much more electrophilic.

 $Zn + 2 HCI \longrightarrow ZnCl_2 + H_2$ TMSCI + $ZnCl_2 \longrightarrow TMSCI - ZnCl_2$ TMSCI -ZnCl_2 + ROH \longrightarrow ROTMS + HCI + ZnCl_2

Thus-generated HCl is again trapped by zinc.

$Zn + 2 HCI \longrightarrow ZnCl_2 + H_2$

In order to confirm this mechanism, the reaction is performed in the presence of a trace amount of base, triethylamine or Na_2CO_3 , and it was observed that the corresponding O-silylated product is not formed even after stirring the mixture for a longer time (10 h). This indicates that a trace amount of HCl in trimethylsilyl chloride plays an important role in initiating the reaction.

Use of readily available and inexpensive reagents, facile procedure, mild conditions and easy and selective applica-

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bility for alcohols having other substituents which may be labile under basic conditions are important features of this method.

Under these reaction conditions, primary, secondary, tertiary, benzylic, allylic and propargylic alcohols were efficiently and conveniently transformed into the corresponding silyl ethers (Table 1) in excellent yields. Using less than a stoichiometric amount of zinc powder resulted in a decrease in the yield of O-silylated product. When attempts were made to carry out O-silylation in the absence of zinc powder, it resulted in almost a quantitative recovery of the starting alcohols. It is important to note that O-silylation of benzylic alcohols (Table 1, entries 1-4), allylic alcohols (Table 1, entry 5) and propargylic alcohols (Table 1, entries 6, 12) is very fast as compared to O-silylation of primary, secondary and tertiary alcohols (Table 1, entries 7-11).

It may also be quite interesting that the presence of a carbonyl group (Table 2, entry 3), halogen atoms (Table 2, entries 1, 2, 6, 7 and 10) or a ester group, (Table 2, entry 4) which may show some reactivity under the basic conditions of conventional methods, did not give any disturbance to the present reaction. It is worth noting that various other functional groups such as C=C, C=C, methoxy, methylenedioxy remain unaltered during silylation under these reaction conditions.

One of the most noteworthy features of this method is that chemoselective o-silylation of benzylic primary alcohols occurred in the presence of primary alkanols (Table 2 entries 6-7). Similarly benzylic primary alcohols are chemoselectively O-silylated in the presence of secondary alkanols (Table 2, entry 8), tertiary alkanols (Table 2, entry 9) and phenols (Table 2 entry 5). Other silylating reagents are also equally effective for silylation of benzyl alcohols (equations 1 and 2). It is also important to note that tertiary alcohols (equations 3 and 4) efficiently silylated even by using sterically hindered reagents such as t-butyl/phenyl dimethylsilyl chloride.



In conclusion, mild conditions tolerance of other sensitive functional groups and chemo selectivity using inexpensive zinc dust are important features of this method.

EXPERIMENTAL SECTION

Activation of Zinc

4 g of commercial Zinc powder was stirred with 1.5 mL of 10% HCl for 2 minutes, filtering and washing with 30 mL of water followed by 10 mL acetone.

A typical procedure

A mixture, activated zinc dust (5 mmol) and tri-methyl silyl chloride (5 mL) was stirred at room temperature (25 °C)

Entry	Substrate	Product	Time (min)	Yield ^{a,b} (%)
1	Benzyl alcohol	TMS benzyl ether	5	91
2	4-chloro benzyl alcohol	TMS 4-chloro benzyl ether	5	96
3	4-methoxy benzyl alcohol	TMS 4-methoxy benzyl ether	10	94
4	3,4-dioxymethylene benzyl	TMS 3,4-dioxymethylene	10	91
	alcohol	benzyl ether		
5	Cinnamyl alcohol	TMS cinnamyl ether	5	94
6	3-methyl-1-pentyn-3-ol	TMS 3-(trimethyl silyl)-3- methyl-1-pentyne ether	10	91
7	t-Butyl alcohol	TMS t-Butyl ether	120	88
8	Triphenyl carbinol	TMS triphenyl methyl ether	150	82
9	Menthol	TMS menthyl ether	90	82
10	Tetrahydro furfuryl alcohol	TMS tetrahydrofurfuryl ether	600	91
11	3-methyl-1-butanol	TMS 3-methyl-1-butyl ether	420	98
12	Propargyl alcohol	TMS propargyl ether	5	92

Table 1. Zinc mediated O-silylation of alcohols

^a Yields of isolated products.

^b Products are characterised by spectral analysis and comparision with authentic samples.

Entry	Substrate	Product	Time	Yield ^{ab} (%)
1 2 3	6-chloro-1-hexanol 5-bromo-1-pentanol Benzoin	TMS 6-chloro-1-hexyl ether TMS 5-bromo-1-pentyl ether TMS-benzoin ether	8 h 7 h 2 h	91 87 97
4	OH COOET	OTMS COOET	3 h	85
5	4-hydroxy-3-methoxy benzyl alcohol	TMS 4-hydroxy-3-methoxy benzyl ether	10 min	87
6	СІОН + СН ₃ (СН ₂)4ОН	CI OTMS + CH ₃ (CH ₂) ₄ OH	10 min	77 + 00
7	BrOH + CH ₃ (CH ₂) ₆ OH	Br OTMS + CH ₃ (CH ₂) ₆ OH	5 min	90 + 00
8	NC-OH + OH		10 min	92 + 00
9	O ₂ N- + Ph ₃ COH	O ₂ N- + Ph ₃ COTMS	10 min	93 + 00
10			5 h	82

Table 2. Zinc mediated selective O-silylation of alcohols

^a Yields of isolated products.

^b Products are characterised by spectral analysis²² and comparision with authentic samples.¹⁻⁸

for one minute and then benzyl alcohol (5 mmol) was added in it. Spontaneous and exothermic reaction took place which was controlled by cooling the reaction mixture in an ice bath. After completion of the reaction (TLC) the mixture was diluted with CH₂Cl₂ and filtered. Solvent was removed under vacuum to afford the crude product, which was further purified by column chromatography on silica gel (hexane: ethyl acetate = 9:1). A large excess of TMSCl is used because it is highly volatile and acted as a solvent for the reaction. A stoichiometric amount of TMSCl under this reaction condition resulted in lowering the yield of product. However, a stoichiometric amount of TMSCl in dichloromethane or acetonitrile as a solvent worked well for this reaction.

ACKNOWLEDGEMENT

SSP thanks UGC, New Delhi for teacher fellowship.

Received March 8, 2004.

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