Monatshefte für Chemie 132, 1101–1104 (2001)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Chemoselective Protection of Hydroxyl Groups and Deprotection of Silyl Ethers

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Summary. Trimethylsilylation of alcohols and phenols is carried out using hexamethyldisilazane and $LiClO_4$ under microwave irradiation and neutral conditions. The deprotection of silyl ethers is carried out similarly using natural kaolinitic clay and a few drops of water.

Keywords. Silyl ethers; Alcohols; Phenols; Protection; Deprotection.

Introduction

Trimethylsilylation is used extensively for the protection and derivatization of functional groups to increase volatility for gas chromatography and mass spectroscopy [1]. One of the most common reagents for silylation is hexamethyldisiazane (*HMDS*) which is cheap and commercially available. Its handling does not require special precaution, and work-up is not time consuming. The main drawback of this reagent is its poor silylating power, which frequently needs drastic conditions; reactions with tertiary alcohols do not take place [2]. The activity of *HMDS* has been increased by using *Lewis* acid catalysts, but usually – albeit there are some exceptions [3] – low selectivity and long reaction times are encountered. The use of acid catalysts for silylation is restricted when the substrate contains acid-sensitive functional groups. Most of the reported methods for the silylation of alcohols and phenols involve acid [4] or basic [5] catalysts. The development of new methods which allow silylation under essentially neutral conditions should increase the synthetic potential of the reaction. We report here for the first time a selective silylation of alcohols and phenols with *HMDS* under microwave irradiation without solvent using $LiClO_4$ as an essentially neutral catalyst.

Results and Discussion

Various alcohols and phenols were silylated with *HMDS* under microwave irradiation without solvent using $LiClO_4$ as a neutral catalyst; the results are presented in Table 1. Primary, secondary, tertiary, and benzylic alcohols as well as phenols undergo smooth silylation under these reaction conditions. It is worth

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Table 1. Silylation of hydroxyl groups and cleavage of silyl ethers; yields refer to pure isolated products which were characterized by comparison of their spectroscopic properties (IR, ^{1}H NMR) with those of authentic samples

$$2R\mathrm{OH} + \underset{\mathbf{1}}{\mathrm{Me_3SiNHSiMe_3}} \underset{\text{MW, clay, H}_2\text{O}}{\overset{\text{MW, LiClO}_4}{\rightleftharpoons}} \underset{\mathbf{2}}{2R\mathrm{OSiMe_3}} + \mathrm{NH_3}$$

Entry	1	2	Protection		Deptrotection	
			Time min	Yield %	Time min	Yield %
1	$CH_3(CH_2)_5OH$ (**1a**)	$CH_3(CH_2)_5O$*TMS* (**2a**)	1.5	83	1.5	82
2	$HO(CH_2)_5OH$ (**1b**)	$TMSO(CH_2)_5O$*TMS* (**2b**)	3.0	75	1.0	72
3	$PhCH{=}CHCH_2OH$ (**1c**)	$PhCH{=}CHCH_2O$*TMS* (**2c**)	1.0	70	1.2	72
4	$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2OH$ (**1d**)	$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2O$*TMS* (**2d**)	1.0	67	1.5	87
5	$(CH_3)_2CHCH(OH)C{\equiv}CH$ (**1e**)	$(CH_3)_2CHCH(O$*TMS*$)C{\equiv}CH$ (**2e**)	1.0	78	1.0	78
6	Menthol (**1f**)	Menthyl *TMS* ether (**2f**)	3.0	76	1.0	68
7	Ph-COCH(OH)Ph (**1g**)	Ph-COCH(O*TMS*)Ph (**2g**)	4.2	80	2.0	62
8	$(CH_3)_3COH$ (**1h**)	$(CH_3)_3CO$*TMS* (**2h**)	4.0	58	2.5	58
9	$4\text{-Cl–}C_6H_4CH_2OH$ (**1i**)	$4\text{-Cl–}C_6H_4CH_2O$*TMS* (**2i**)	1.8	67	1.0	88
10	$MeOC_6H_4CH_2OH$ (**1j**)	$MeOC_6H_4CH_2O$*TMS* (**2j**)	1.3	69	1.2	85
11	$3,4\text{-}CH_2(O)_2C_6H_3CH_2OH$ (**1k**)	$3,4\text{-}CH_2(O)_2C_6H_3CH_2O$*TMS* (**2k**)	1.0	70	2.0	63
12	$4\text{-OH–}C_6H_4CH_2OH$ (**1l**)	$4\text{-OH–}C_6H_4CH_2O$*TMS* (**2l**)	1.0	68	1.5	82
13	$4\text{-}NH_2\text{–}C_6H_4CH_2OH$ (**1m**)	$4\text{-}NH_2\text{–}C_6H_4CH_2O$*TMS* (**2m**)	1.0	74	1.0	67
14	$4\text{-}CH_3\text{–}C_6H_4OH$ (**1n**)	$4\text{-}CH_3\text{–}C_6H_4O$*TMS* (**2n**)	1.4	62	1.5	68
15	β-Naphthol (**1o**)	β-Napthyl *TMS* ether (**2o**)	1.6	75	2.0	75
16	$4\text{-}NH_2\text{–}C_6H_4OH$ (**1p**)	$4\text{-}NH_2\text{–}C_6H_4O$*TMS* (**2p**)	3.0	70	2.5	63
17	$4\text{-COOH–}C_6H_4OH$ (**1q**)	$4\text{-COOH–}C_6H_4O$*TMS* (**2q**)	3.0	77	2.5	79

mentioning that the selective silylation of benzylic alcohols was carried out in the presence of a phenol group (entry 12) as well as an aromatic primary amine (entry 13). Similarly, the phenolic OH group was selectively protected in the presence of an amino group (entry 16) or a carboxylic group (entry 17). It is also important to note that C=C (entries 3, 4), C≡C (entry 5), methoxy (entry 10, 11), and methylenedioxy groups (entry 11) remain intact during silylation under these conditions.

Attempts were made to silylate alcohols and phenols with *HMDS* in toluene at 110°C. However, these reactions remained incomplete, resulting in low yield of products (20–30%) even after heating for 12 h. Nevertheless, silylation of alcohols carried out by conventional heating (110°C) using trimethylsilyl chloride as a more reactive silylating reagent and $LiClO_4$ as the catalyst resulted in moderate yield of products (50–60%; reaction time: 1–5 h).

For the cleavage of silyl ethers, various reagents have been reported in the literature [6]. However, each of them shows more or less severe limitations. Attempts to deprotect silyl ethers using $LiClO_4$ and a few drops of water under microwave irradiation failed. Employing natural kaolinitic clay and few drops of water settled the problem. Obviously, natural kaolinitic clay in water serves as an eco-friendly catalyst for the deprotection of silyl ethers under microwave irradiation.

Experimental

Natural kaolinitic clay was obtained from the Padappakara mine (Quilon district, Kerala, India) and was purified and characterized [7] by FTIR, XRD, UV, EPR, SEM, EDX, and AAS. Composition: (*i*) determined by wet chemical analysis: $SiO_2 = 67.45\%$, $Al_2O_3 = 22.2\%$, $Fe_2O_3 = 6.1\%$, $TiO_2 = 3.45\%$, $K = 0.8\%$; (*ii*) determined by electron dispersive X-ray (EDX) analysis: $SiO_2 = 62.8\%$, $Al_2O_3 = 24.92\%$, $Fe_2O_3 = 7.5\%$, $TiO_2 = 3.79\%$, $K = 0.4\%$. Natural kaolinitic clay was supplied by Dr. *Lalithambika*, RRL, Trivandrum, India and used as obtained without any pretreatment or activation.

Solvents were distilled before use. All chemicals were of analytical grade. A microwave oven (Kelvinator, T-37 model) with 100% efficiency at 760 W and 2450 MHz was used.

Silylation

A mixture of 10 mmol alcohol, 5 mmol *HMDS*, and 1 mmol $LiClO_4$ in a beaker covered with a watch glass was irradiated for the specified time (Table 1). After completion of the reaction, 10 cm^3 petroleum ether were added, and the catalyst was removed by filtration and washed twice with 10 cm^3 petroleum ether. Removal of the solvent under reduced pressure gave the desired product. The results of elemental analyses (C, H, Cl, Si) agreed with the calculated values within experimental error.

4-Chlorobenzyl trimethylsilyl ether (**2i**; $C_{10}H_{15}ClOSi$)

Oil; IR (neat): $\nu = 670, 710, 770, 810, 842, 874, 1014, 1087, 1160, 1252, 1330, 1450, 1491, 1540, 2860, 2910, 2951\ cm^{-1}$; ^1H NMR (300 MHz, δ, $CDCl_3$): 0.2 (s, 9H, $Si(CH_3)_3$), 4.7 (s, 2H, CH_2), 7.3 (d, 2H, Ar-H), 7.5 (d, 2H, Ar-H) ppm.

Deprotection of silyl ethers

A mixture of 5 mmol *TMS* ether and 100 g natural kaolinitic clay moistened with H_2O was irradiated with microwaves for the time period specified in Table 1. After completion of the reaction, the product was extracted three times with 5 cm^3 of diethyl ether. The ether layer was dried over anhydrous Na_2SO_4. Removal of the solvent furnished a crude product which was further purified by column chromatography (petroleum ether:ethyl acetate = 9:1).

3,4-Methylenedioxybenzyl alcohol (**1k**; $C_8H_8O_2$)

M.p.: 58°C; IR (KBr): $\nu = 766, 803, 860, 919, 936, 1015, 1034, 1098, 1123, 1191, 1245, 1329, 1413, 1490, 1503, 1604, 2907, 3314\ cm^{-1}$; ^1H NMR (300 MHz, δ, $CDCl_3$): 2.49 (s, 1H, OH), 4.49 (s, 2H, CH_2), 5.9 (s, 2H, OCH_2O), 6.7 (s, 2H, Ar-H), 6.80 (s, 2H, Ar-H) ppm.

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Received March 1, 2001. Accepted (revised) April 17, 2001

Verleger: Springer-Verlag KG, Sachsenplatz 4–6, A-1201 Wien. – Herausgeber: Österreichische Akademie der Wissenschaften, Dr.-Ignaz-Seipel-Platz 2, A-1010 Wien, und Gesellschaft Österreichischer Chemiker, Eschenbachgasse 9, A-1010 Wien. – Redaktion: Währinger Straße 38, A-1090 Wien. – Satz und Umbruch: Thomson Press Ltd., New Delhi, India. – Offsetdruck: Manz Crossmedia, A-1051 Wien. – Verlagsort: Wien. – Herstellungsort: Wien. – Printed in Austria.