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Efficient and Selective Protection of Alcohols and Phenols with Triisopropylsilyl Chloride/Imidazole Using Microwave Irradiation

Ali Khalafi-Nezhad,* Reza Fareghi Alamdari and Negar Zekri

Department of Chemistry, Faculty of Science, Shiraz University, Shiraz 71454, Iran

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Abstract—A very simple and efficient method is described for silylation of alcohols and phenols using triisopropylsilyl chloride and imidazole under microwave irradiation. High selectivity was observed for silylation of primary and secondary alcohols and also for structurally different phenols. © 2000 Published by Elsevier Science Ltd.

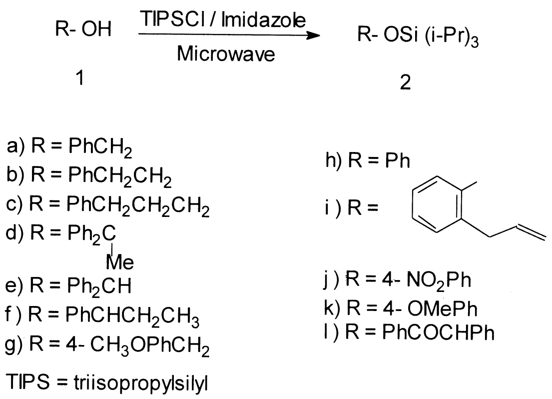
Introduction

Hydroxyl group protection is important in the synthesis of organic molecules. One way to protect hydroxyl groups is to transform the molecules to their corresponding silyl ethers.[1] A large number of silylating agents exist for the introduction of the trimethylsilyl (TMS) group into alcohols.[2] In general, the sterically least hindered alcohols are the most readily silylated, but these are also the most labile to hydrolysis with either acid or base. The *tert*-butyldimethylsilyl (TBDMS) group has been used for hydroxyl protection,[3] partly because of its specific and mild removal by either fluoride ion[3–5] or aqueous acid.[3] This protection is normally accomplished by using TBDMSCl as reagent with either imidazole[3] or 4-dimethylaminopyridine[6,7] as catalyst. One problem with TBDMS protection is the difficulty of silylation in the case of tertiary or hindered secondary alcohols. The triisopropylsilyl (TIPS) group is a exceedingly useful control element in organic synthesis. The three isopropyl substituents provide strong steric screening not only for the silicon to which they are attached, but also for the atom to which silicon is connected. However, the introduction of the TIPS group has been a problem because of the relative unreactivity of TIPSCl, for example, toward secondary hydroxyl groups or enolates.[8,9] In a study on the selective protection of hydroxyl groups in ribonucleosides, TIPSCl reacts almost exclusively with the primary 5′-hydroxy function.[8,10] Triisopropylsilyl triflate has also been used for silylation of primary and secondary alcohols, but tertiary alcohols are relatively resistant to silylation by this bulky silylating reagent.[11]

Several advantages can be envisioned for the use of the TIPS group as a hydroxyl-protecting moiety; (1) low cost and ready availability of pure TIPSCl, (2) greater stability of TIPS over TBDMS ethers, (3) more facile acidic deprotection of TIPS over TBDMS derivatives, and (4) relatively high volatility of TIPS ethers for purposes of gas chromatographic and mass spectral analysis.[9]

In recent years, the use of microwave irradiation in organic reactions is rapidly increasing, because of its short reaction times and operational simplicity. It has been reported that a variety of reactions such as Diels–Alder,[12] ene,[13] Claisen reactions,[14] Fischer cyclization,[15] hydrolysis of esters,[16] hydrogenation,[17] oxazoline formation,[18] could be facilitated by microwave as a good energy transferring medium.

In this paper, we wish to report that TIPS ethers can be obtained from the reaction of 1°, 2° and 3° alcohols and



Scheme 1.

Keywords: protection; alcohols; phenols; trimethylsilyl chloride; microwave.

* Corresponding author. Tel.: +98-071-22380; fax: +98-071-20027; e-mail: khalafi@chem.susc.ac.ir

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Table 1. Effect of different bases for the protection of benzyl alcohol with triisopropylsilyl chloride using microwave irradiation

Base	Subst./TIPSCl/base	Yield (%)[a]
Al_2O_3 (basic)	1:1.5:3	30
CaO	1:1.5:3	25
MgO	1:1.5:3	20
$Mg(OH)_2$	1:1.5:3	20
$NaHCO_3$	1:1.5:3	15
Imidazole	1:1.5:3	96

[a] Isolated yield after chromatography.

phenols with TIPSCl in the presence of imidazole under microwave irradiation and in the absence of solvent.

The reactions are outlined in Scheme 1.

To investigate the effect of different bases on the progress of this reaction, we examined several other bases than imidazole for silylation of benzyl alcohol. The obtained results show that imidazole is the most suitable base for this transformation (Table 1).

The results of protection of different alcohols and phenols are shown in Table 2.

As is shown in Table 2, primary and secondary aliphatic and benzylic alcohols are protected very easily by this method with excellent yields. An interesting feature of the present method is the conversion of 1,1-diphenyl ethanol as a tertiary alcohol (Table 2, Entry 4) to its corresponding TIPS ether in 72% yield in 80 s. Phenols are also successfully protected using this method by increasing the molar ratio of TIPSCl to the phenolic compound.

The selectivity of the presented method was also studied

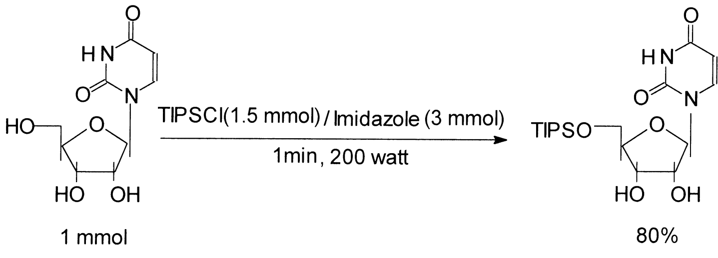
Table 2. Protection of alcohols and phenols with TIPSCL/imidazole under microwave irradiation

Entry	Substrate	Product	TIPSCl (mmol)	Imidazole (mmol)	Irradiation condition		Yield (%)[a]
					Time (s)	Power (W)	
(1)	**1a**	**2a**[19]	1.5	3	70	300	96
(2)	**1b**	**2b**	1.5	3	30	300	93
(3)	**1c**	**2c**[20]	1.5	3	40	300	96
(4)	**1d**	**2d**	2	4	80	700	72
(5)	**1e**	**2e**	2	3	90	500	90
(6)	**1f**	**2f**	2	3	120	400	90
(7)	**1g**	**2g**	1.5	3	90	300	92
(8)	**1h**	**2h**[21]	2	3	60	600	96
(9)	**1i**	**2i**	2	3	60	500	80
(10)	**1j**	**2j**[22]	2	3	30	600	96
(11)	**1k**	**2k**	2	3	60	600	95
(12)	**1l**	**2l**	3	4	90	700	70

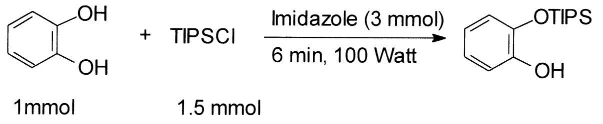
[a] Isolated yield after column chromatography.

Table 3. Selective silylation of alcohols with TIPSCL/imidazole under microwave irradiation

Entry	Substrate	Subst.1/subst.2/ TIPSCl/imidazole	Irradiation conditions		Yield (%)[a]
			Time (s)	Power (W)	
(1)	Benzyl alcohol 1-Phenyl-1-propanol	1:1:1.5:3	70	300	90 10
(2)	3-Phenyl-1-propanol 1-Phenyl-1-propanol	1:1:2:3	60	300	95 5
(3)	4-Nitrophenol Phenol	1:1:2:3	30	600	80 20
(4)	Benzyl alcohol Benzoin	1:1:1.5:3	70	300	100 0



Scheme 2.



Scheme 3.

between different hydroxyl compounds. This method shows high selectivity for silylation of primary alcohols versus secondary ones and also between structurally different phenols. The results obtained for some selective silylations are shown in Table 3.

Due to the importance of selective protection of hydroxyl groups in ribonucleosides, we further applied this method for protection in uridine. By our method, 5′-hydroxyl function of uridine was easily protected in minute. In comparison, when we repeated the literature method[8] for this protection in DMF, 5′-hydroxyl function of uridine was protected in 76% yield after 24 h (Scheme 2).

In order to further show the utility of this method, the selective monosilylation of catechol was also investigated. By using this method we were able to obtain monosilylated cathecol in 95% yield (Scheme 3).

Conclusion

The general procedure for triisopropylsilylation of alcohols suffers from prolonged reaction times and tedious and time consuming work-up due to the presence of DMF which must be removed by repeated extraction of the mixture with H_2O. We modified this method and took a short cut to Corey's procedure by the use of microwave irradiation. Elimination of DMF, which is a toxic solvent, accompanied with an easy work-up are worthy of mention as advantages for laboratory and large-scale operation of this method. We believe that the presented method which is very simple and offers high yields of the silylated products, is more useful than the available procedures for the protection of 1°, 2°, 3° alcohols and phenols with TIPSCl.

Experimental

Chemicals were either prepared in our laboratories or were purchased from Fluka, Merk, B. D. H. and Aldrich Chemical Companies. All yields refer to the isolated products. IR. spectra were recorded on a Perkin Elmer 781 spectrophotometer. NMR spectra were recorded on a Bruker DPX 250 MHz. The purity determination of the substrates and the reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates or GLC on a Shimadzu GC- 14A instrument.

General procedure for the protection of alcohols and phenols with TIPSCl under microwave irradiation

The alcohol (1 mmol), imidazole (3–4 mmol), and TIPSCl (1.5–2 mmol) were added successively and mixed in a dry flask and then irradiated at 100–700 W for 30–120 s in the microwave oven. The progress of the reaction was monitored by TLC. The resulting mixture was chromatographed on silica gel using petroleum ether as eluent. Evaporation of the solvent under reduced pressure gave the pure product.

Protection of 4-methoxybenzylalcohol with TIPSCl as a typical procedure (2g). *p*-Methoxybenzylalcohol (0.138 g, 1 mmol), imidazole (0.204 g, 3 mmol), and TIPSCl (0.28 g, 1.5 mmol) was added and mixed in a dry test tube and then irradiated at 300 W for 90 s in the microwave oven. TLC indicated completion of the reaction. The resulting mixture was purified by column chromatography (petroleum ether) to give the product (0.27 g, 92%) as a colorless liquid; [Found: C, 69.5; H, 10.4. $C_{17}H_{30}O_2Si$ requires C, 69.33; H, 10.27%]; R_f (*n*-Hexane) 0.33; ν_{max} (liquid film) 3050, 1500, 1375, 1245, 840 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.30–7.23 (4H, m, Ph), 4.5 (2H, s, PhC*H*$_2$OSi), 3.76 (3H, s, OC*H*$_3$), 1.24–1.19 (3H, m, Me$_2$C*H*Si), 1.04 (18H, d, *Me*$_2$CHSi).

Preparation of 5′-triisopropylsilyluridine

Uridine (0.244 g, 1 mmol), imidazole (0.204 g, 3 mmol), and TIPSCl (0.28 g, 1.5 mmol) were mixed in a dry flask and then irradiated at 200 W for 60 s in the microwave oven. TLC indicated the completion of the reaction. The resulting mixture was purified by column chromatography (10% $CHCl_3$/EtOAc) to give the product (0.32 g, 80%) as a white solid, mp 128°C (lit.[8] 126–127); [Found: C, 53.8; H, 8.05; N, 6.83. $C_{18}H_{32}N_2O_6Si$ requires C, 53.98; H, 8.06; N, 7.00%]; R_f (EtOAc) 0.48; ν_{max} (Nujol) 3600–3200 (br), 3150, 1670, 1620, 1200; δ_H (250 MHz, DMSO-d$_6$) 10.7 (1H, s, NH), 8.05 (1H, d, H-6), 5.93 (1H, d, H-1′), 5.61 (1H, d, H-5), 4.33 (1H, d, OH-2′), 4.13 (1H, d, OH-3′), 4.02–3.24 (5H,m, H-2′, H-3′, H-4′, H-5′), 1.18–1.13 (3H, m, Me$_2$C*H*), 1.07 (18H, d, *Me*$_2$CH); λ_{max} (EtOH) 262 nm (ϵ, 9,400); *m*/*z* 401 (MH$^+$).

2-[(Triisopropylsiloxy)ethyl]benzene (2b). (0.26 g, 93% yield) as a colorless liquid; [Found: C, 73.2; H, 10.7. $C_{17}H_{30}OSi$ requires C, 73.31; H, 10.86%]; R_f (*n*-Hexane) 0.7; ν_{max} (liquid film) 3070, 1510, 1470, 1150, 690 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.26–7.11 (5H, m, Ph), 3.86 (2H, t, C*H*$_2$OSi), 2.83 (2H, t, C*H*$_2$Ph), 1.21–1.16 (3H, m, Me$_2$C*H*Si), 1.02 (18H, d, *Me*$_2$CHSi).

[(Triisopropylsiloxy)-1,1-diphenyl]ethane (2d). (0.25 g, 72% yield) as a colorless liquid; [Found: C, 77.7; H, 9.5. $C_{23}H_{34}OSi$ requires C, 77.90; H, 9.66%]; R_f (*n*-Hexane) 0.71; ν_{max} (liquid film) 3090, 1525, 1370, 1260, 700 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.3–7.18 (10H, m, Ph), 2.3 (3H, s, Me),1.23–1.18 (3H, m, Me$_2$C*H*Si), 1.04 (18H, d, *Me*$_2$CHSi).

[(Triisopropylsiloxy)-1.1-diphenyl]methane (2e). (0.3 g, 90% yield) as a colorless liquid; [Found: C, 77.4; H, 9.3. $C_{22}H_{32}OSi$ requires C, 77.59; H, 9.46%]; R_f (*n*-Hexane) 0.45; ν_{max} (liquid film) 3100, 2900, 1530, 1235, 690 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.38–7.08 (10H, m, Ph), 5.2 (1H, s, Ph$_2$C*H*OSi), 1.2–1.12 (3H, m, Me$_2$C*H*Si), 1.02 (18H, d, *Me*$_2$CHSi).

1-[(Triisopropylsiloxy)propyl]benzene (2f). (0.26 g, 90%

yield) as a colorless liquid; [Found: C, 73.8; H, 11.2. $C_{22}H_{32}OSi$ requires C, 73.9; H, 11.03%]; R_f (*n*-Hexane) 0.59; ν_{max} (liquid film) 3050, 2890, 1510, 1460, 1365, 1170 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.32–7.2 (5H, m, Ph), 5.o7 (1H, t, $C\mathit{H}OSi$), 1.6 (2H, q, $C\mathit{H}_2CH_3$), 1.23–1.15 (3H, m, $Me_2C\mathit{H}Si$), 1.02– 0.96 (21H, m, $CH_2C\mathit{H}_3$, Me_2CHSi).

2-[(Triisopropylsiloxy)-3-propenyl]benzene (2i). (0.23 g, 80% yield) as a colorless liquid; [Found: C, 74.5; H, 10.3. $C_{17}H_{30}O_2Si$ requires C, 74.42; H, 10.41%]; R_f (*n*-Hexane) 0.62; ν_{max} (liquid film) 3060, 1650, 1520, 1220, 750 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.33–4.14 (5H, m, Ph), 5.79 (1H, m, $C\mathit{H}{=}CH_2$), 5.12 (2H, d, $CH{=}C\mathit{H}_2$), 4.90 (2H, d, $PhC\mathit{H}_2$), 1.28–1.19 (3H, m, $Me_2C\mathit{H}Si$), 1.08 (18H, d, Me_2CHSi).

4-[(Triisopropylsiloxy)]methoxybenzene (2k). (0.26 g, 95% yield) as a colorless liquid; [Found: C, 68.7; H, 10.2. $C_{16}H_{28}O_2Si$ requires C, 68.52; H, 10.07%]; R_f (*n*-Hexane) 0.32; ν_{max} (liquid film) 3080, 1500, 1370, 1170, 850 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.41–7.2 (4H, m, Ph), 3.63 (3H, s, $OC\mathit{H}_3$), 1.26–1.15 (3H, m, $Me_2C\mathit{H}Si$), 0.97 (18H, d, Me_2CHSi).

Triisopropylsiloxy benzoine (2l). (0.26 g, 70% yield) as a colorless oil; [Found: C, 74.8; H, 8.6. $C_{23}H_{32}O_2Si$ requires C, 68.52; H, 10.07%]; R_f (*n*-Hexane) 0.25; ν_{max} (liquid film) 3070, 1725, 1520, 1200, 700 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.63–7.37 (5H, m, PhCO), 7.28–7.2 (5H, m, $\mathit{Ph}CHOSi$), 5.87 (1H, s, $PhC\mathit{H}OSi$), 1.22–1.13 (3H, m, $Me_2C\mathit{H}Si$), 1.01 (18H, m, Me_2CHSi).

2-(Triisopropylsiloxy)phenol. (0.25 g, 95% yield) as a yellow liquid; [Found: C, 67.4; H, 9.78. $C_{15}H_{26}O_2Si$ requires C, 67.61; H, 9.84%]; R_f (*n*-Hexane) 0.36; ν_{max} (liquid film) 3500–3300 (br), 3010, 1510, 1175, 750 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.2–7.03 (5H, m, Ph), 5.68 (1H, s, OH), 1.32–1.23 (3H, m, $Me_2C\mathit{H}Si$); 1.12–1.07 (18H, d, Me_2CHSi).

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