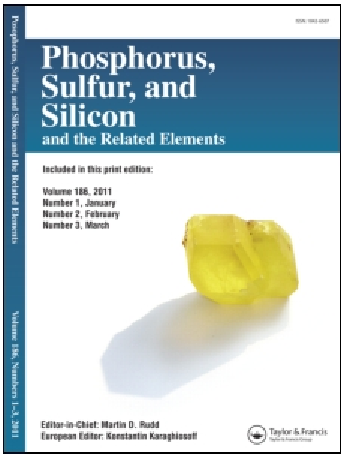

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EFFICIENT AND CHEMOSELECTIVE PROTECTION OF ALCOHOLS AND PHENOLS WITH *Tert*-BUTYLDIMETHYLCHLOROSILANE (TBDMCS) UNDER SOLVENT-FREE CONDITIONS

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EFFICIENT AND CHEMOSELECTIVE PROTECTION OF ALCOHOLS AND PHENOLS WITH *Tert*-BUTYLDIMETHYLCHLOROSILANE (TBDMCS) UNDER SOLVENT-FREE CONDITIONS

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(Received 10 September, 1998)

Various types of primary and secondary alcohols and phenols can be converted efficiently to their corresponding TBDMS ethers using TBDMCS/imidazole under solvent-free conditions. Elimination of DMF, accompanied with an easy non-aqueous work-up and a high rate enhancement of the reaction are worthy to be mentioned for the presented method. The reactions show absolute chemoselectivity for the protection of primary in the presence of secondary alcohols.

Keywords: Silylation; Protection; Protecting groups; Silyl Ethers; TBDMS Ethers; Solvent-Free Condition

INTRODUCTION

The sterically hindered *tert*-butyldimethylsilyl group has been widely utilized as a protecting group for hydroxy functions[1,2]. Since the introduction and application of this group by Stork[3] and Corey[4] there have been explosive challenges in the development of new procedures for the preparation of TBDMS ethers. A variety of reagents and methods have been established for this process, such as TBDMCS/Imidazole/DMF[4],

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* Corresponding Author.

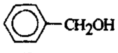
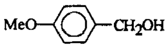
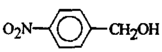
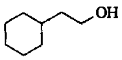
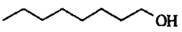
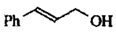
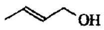
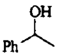
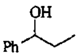
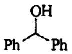
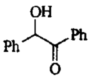
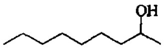
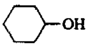
tert-butyldimethylsilyl perchlorate in the presence of pyridine[5], TBDMCS/ DMAP/DMF[6], TBDMCS/Li_2S/CH_3CN[7], O-silylated ketenacetal/CH_3CN[8], allyl trialkylsilane/ TsOH[9], TBDMS-enol ether[10], TBDMCS/ $AgNO_3$/pyridine[11] and TBDMCS/KH/18-Crown-6 in THF which has been studied exclusively for the protection of sterically hindered alcohols[12], TBDMSCN[13], TBDMSOTf/2,6-lutidine in CH_2Cl_2[14], TBDMCS/DBU[15] and etc[1]. However, many of these methods require forceful conditions, prolonged reaction times and the yield are not always satisfactory. On the other hand some of the previously reported reagents such as TBDMSOTf, TBDMSCN, $TBDMSClO_4$ are expensive and should be handled with special precaution due to their high moisture sensitivity or explosive character. However, the generally used procedure for the preparation of TBDMS ethers involved treatment of alcohols with TBDMCS in the presence of imidazole in DMF solution[4]. Although in most cases in this method the reactions proceed at room temperature to give excellent yields of the corresponding TBDMS ethers, the reaction times are too long (12–15h) and the requirement of DMF which is claimed to be toxic are also drawbacks of the method. Aqueous work-up of the reaction mixture and contamination of the products with *t*-butylditmethylsilanol which results in the aqueous work-up is also a problem [8].

RESULTS AND DISCUSSION

In this report we wish to represent a simple and useful modification to the previously reported procedure[4] for the selective silylation of varieties of structurally different alcohols and phenols under solvent-free condition[16] (Table I).

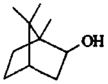
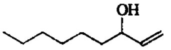
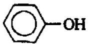
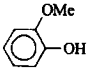
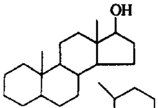
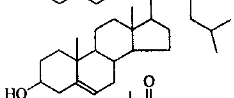
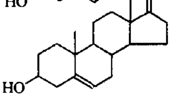
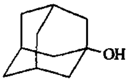
Examination of the data shows that the formation of TBDMS ethers of primary and secondary aliphatic, benzylic, allylic alcohols as well as phenols occurred almost immediately at room temperature by simple mixing of the alcohol with TBDMCS (1.2–2.5 equiv.) and imidazole (1.5–3 equiv.) in the absence of solvent (Table I). Silylation of benzhydrol, benzoin, and borneol is sluggish at room temperature, but at 50–55°C, proceeded almost immediately and the desired TBDMS ethers were obtained in good to excellent yields (Table I, entries 11, 12, 15).

TABLE I Silylation of Alcohols and Phenols with TBDMCS/Imidazole under Solvent-Free Conditions

Entry	Substrate	Subst./ TBDMCS/ Imidazole	Condition[a]	Yield[b] (%)
1		1 : 1.2 : 1.5	A	97
2		1 : 1.2 : 1.5	A	95
3		1 : 1.5 : 1.5	A	93
4		1 : 1.2 : 1.5	A	95
5		1 : 1.5 : 1.5	A	96
6		1 : 2 : 2	A	95
		1 : 1.2 : 1.5	B	97
7		1 : 1.2 : 1.5	A	95
8		1 : 1.5 : 1.5	A	93
9		1 : 2.5 : 3	A	85
		1 : 1.8 : 1.8	B	97
10		1 : 2.5 : 3	A	80
		1 : 1.8 : 1.8	B	95
11		1 : 2.5 : 3	A	50
		1 : 1.8 : 1.8	B	95
12		1 : 2.5 : 3	A	60
		1 : 2 : 2	B	93
13		1 : 2.5 : 3	A	89
		1 : 1.2 : 1.5	B	94
14		1 : 1.5 : 1.5	A	93

An interesting feature of this procedure is conversion of steroidal alcohols such as cholesterol, dehydroepiandrosterone, and 5α-androstane-17β-ol to their corresponding TBDMS ethers in excellent yields almost immediately (Table I, entries 19–21). Even, 1-adamantanol, a highly strically hindered alcohol is converted to its TBDMS ether in 54%

TABLE I Continued

15		1 : 2.2 : 2.2	B	80
16		1 : 2 : 2 1 : 1.5 :1.5	A B	90 95
17		1 : 1.5 : 1.5	A	92
18		1 : 1.8 : 1.8 1 : 1.2 : 1.5	A B	97 97
19		1 :2.2 : 2.2	B	89
20		1 : 2.2 : 2.2	B	98
21		1 : 2.2 : 2.2	B	97
22		1 : 2.2 : 2.2	B	54

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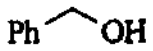
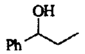
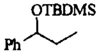
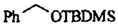
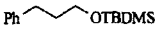
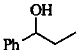
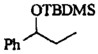
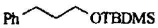
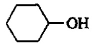
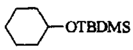
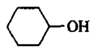
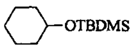
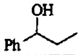
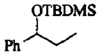
[a] Reaction was completed after mixing; A = room temperature; B = 50-55 °C. [b] Yields refer to isolated pure products.

yield in an immediate reaction. We have also found that primary alcohols in the presence of secondary alcohols are protected with absolute chemoselectivity by the presented method (Table II).

In order to show the usefulness of the solvent-free method in comparison with those that have been performed in DMF, the reactions of some selected alcohols have been studied in our laboratory. Although the in-solution procedure, as shown in Table III, is of equal efficiency for transformation of steroidal alcohols with the non-solvent method, it suffers from prolonged reaction time (12–15h) and from a tedious and a time consuming work-up due to the presence of DMF. In case of 1-adamantanol, the solvent-free method is more efficient than the in solution procedure (Table III).

TABLE II Selective Silylation of Primary vs. Secondary Alcohols with TBDMCS/Imidazole under Solvent-Free Conditions

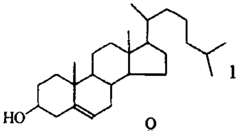
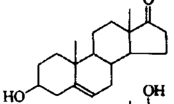
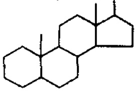
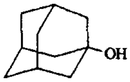
Entry	Substrate	Product	Subst. 1/Subst. 2/ TBDMCS/Imidazole	Yield(%)[a]
1			1 : 1 : 1.2 : 1.5	100
				0
2			1 : 1 : 1.2 : 1.5	60
				40
3			1 : 1 : 1.2 : 1.5	100
				0
4			1 : 1 : 1.2 : 1.5	100
				0
5			1 : 1 : 1.2 : 1.5	66
				34

[a] Yields based on GC and NMR spectra of the isolated products.

CONCLUSION

In conclusion, high rates of the reactions, high yields of the desired products accompanied with high selectivity, easy non-aqueous work-up, and the avoidance of DMF which is claimed to be toxic,[17] are the advantages of the presented method. In this method because of the absence of water for the work-up, silanol formation is not possible and the excess of TBDMCS and imidazole are absorbed easily on silica-gel surface and do not interfere in the purification process. The reaction of TBDMCS with alcohols in the presence of imidazole is not so exothermic, therefore, the method could be used for multi-gram laboratory scales. The method should also not be harmful to heat sensitive compounds.

TABLE III Comparison of Solvent-Free Method with in DMF Solution Procedure

Substrate	TBDMCS/Imidazole/DMF[a]		TBDMCS/Imidazole/50-55 °C	
	Time (h)	Yield(%)[b]	Time	Yield(%)[b]
	12	95	Immediate Reaction	98
	12	95	"	97
	12	85	"	89
	15	10	"	54

[a] Substrate/TBDMCS/Imidazole; 1 : 1.2 : 2.5. [b] Isolated yields.

EXPERIMENTAL

General

All yields refer to isolated pure products unless otherwise stated. Chemicals were either prepared in our laboratories or were urchased from Fluka, BDH and Merck chemical companies. Most of the products were purified by short column chromatography, vacuum distillation or recrystallization and were identified by the comparison of their mp, bp, IR, MS, and NMR with those reported for the authentic samples and also by the conversion to their parent alcohols using tetrabutylammonium fluoride. The purity determination of the products was accomplished by GLC on a Shimadzu model GC-8A instrument with a flame-ionization detector using a column of 15% carbowax 20m chromosorb-W acid washed 60–80 mesh or by TLC on silica-gel polygram SIL G/UV 254 plates. Mass spectra were run on a Shimadzu GC MS-QP 1000 EX. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. The NMR spectra were recorded on a Bruker Avance DPX instrument (250 MHz).

Preparation of tert-Butyldimethylsilyl Ethers with TBDMCS in the Presence of Imidazole under Solvent-Free Conditions

General Procedure

The alcohol (10 mmol), imidazole (15–25 mmol), and TBDMCS (12–25 mmol) were mixed together in a dry mortar by a pestle at room temperature (condition A), or at 50–55 °C (condition B). It is important to note that all solid pieces of the mixture collapsed. The formation of a homogeneous paste is an indication of the completion of silylation reaction. To the resulting paste petroleum ether (20 ml, 60–80 °C) was added and the mixture was magnetically stirred for a few minutes, and filtered through a short silica-gel column, and the filter cake was washed with petroleum ether (100 ml, 60–80 °C). Evaporation of the solvent under reduced pressure gave the desired pure product. Further purification was achieved by vacuum distillation or recrystallization from appropriate solvent to afford the proper silyl ether (Table I).

Acknowledgements

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