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Tetrabutylammonium Bromide Promoted Efficient and Chemoselective Trimethylsilylation of Primary and Secondary Alcohols Under Mild Reaction Conditions

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This article is dedicated to Professor Habib Firouzabadi on the occasion of his 65th birthday, for his great contribution to the development of organic chemistry in Iran.

A mild and efficient method for trimethylsilylation of alcohols with hexamethyldisilazane (HMDS) catalyzed by tetrabutylammonium bromide is reported. The method is highly chemoselective for the o-protection of primary and secondary alcohols in the presence of amines, thiols and tertiary alcohols.

Keywords: Alcohols, Trimethylsilylation, Tetrabutylammonium bromide, Chemoselective, Hexamethyldisilazane

INTRODUCTION

Protection of the hydroxyl group of alcohols as an important process during a multi-step synthesis is attracted considerable attention of many organic chemists [1]. The conversion of hydroxyl groups to their corresponding trimethylsilyl ethers is one of the popular methods used for this purpose. Among the different reagents which are available for the silylation of alcohols [2-4], hexamethyldisilazane, as a cheap and commercially available reagent [5,6], is selected as one of the best candidates. Even though the handling of this reagent does not need special precautions and work-up of the reaction mixture is not time consuming, the low silylating power of HMDS is the main drawback for its application [7]. A variety of catalysts have been reported for the activation of HMDS [8-11]. Although these methods improve reaction conditions and shorten the reaction times, usually low selectivity, forceful conditions, tedious work-up and use of the expensive reagents have been observed in many of these reports.

EXPERIMENTAL

General

Chemicals were purchased from Fluka, Merck, and Aldrich Chemical Companies. All of the trimethylsilyl ethers are known compounds, and were characterized on the basis of their spectroscopic data (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.

General Procedure

Tetrabutylammonium bromide(0.05 mmol, 0.016 g) was added to a stirred solution of alcohol (1 mmol) and HMDS (0.7 mmol, 0.113 g) in CH_3CN (3 mL) at room

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temperature. The reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure. *n*-Hexane (5 mL) was added and the reagent was recovered by filtration and washed with *n*-hexane (5 mL). The filtrate was washed with water (10 mL) and organic layer was dried over $MgSO_4$. Evaporation of the solvent 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 to high yields.

RESULTS AND DISCUSSION

Recently F. Pizzo *et. al.* [12], have reported that the silylation of alcohols with trimethylsilyl azide is accelerated in the presence of tetrabutylammonium bromide. However, in most cases a long reaction time, drastic reaction conditions, or tedious work-up is needed. In addition, trimethylsilyl azide is expensive and toxic. On the basis of these drawbacks and in continuation of our ongoing effort to develop new methods for the protection of hydroxyl group [13-17], we were interested to investigate the applicability of tetrabutylammonium bromide in the promotion of the silylating ability of HMDS. Herein, we wish to report a mild and efficient method for the chemoselective trimethylsilylation of alcohols by using hexamethyldisilazane in the presense of catalytic amounts of tetrabutylammonium bromide (Scheme 1).

$$\mathrm{ROH} \xrightarrow[\mathrm{CH_3CN,\ r.t.}]{\mathrm{HMDS/n\text{-}Bu_4NBr}} \mathrm{ROTMS}$$

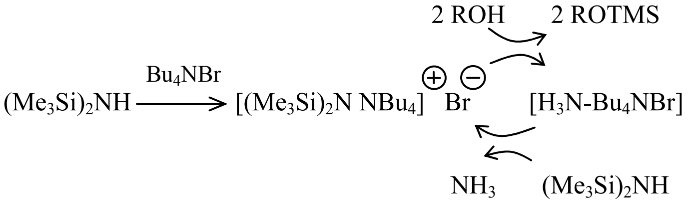
Scheme 1

Yields and reaction times are given in Table 1. Benzylic alcohols, including electron donating and withdrawing groups are converted to their corresponding trimethylsilyl ethers in good to high yields (Table 1, entries 1-17). Benzylic alcohols containing alkyl ethereal groups are protected as their trimethylsilyl ethers using this method, too, without cleavage of carbon-oxygen bond (Table 1, entries 10-12). This method is also very useful for the silylation of primary and secondary aliphatic alcohols (Table 1, entries 18-24). Tertiary alcohols became intact or gave poor yields under the same reaction conditions (Table 1, entries 25, 26). Under the selected conditions trimethylsilylation of amines and thiols was not successful and the starting material was recovered unchanged after 1h (Table 1, entries 27, 28).

The selectivity of a method determines it's broad of application in organic reactions. Because of the importance of this subject and on the basis of obtained results, the selective trimethylsilylation of benzylic, primary and secondary alcohols in the presence of amines, thiols and tertiary alcohols was investigated. The results obtained are reported in Table 2.

To illustrate the efficiency of the proposed method, Table 3 compares some of our results with some of those reported by the relevant reagents in the literature [10, 11, 14].

Also the mechanism of the reaction is not clear, but based on the previously reported methods [12, 15] and on the basis of our observations related to the fast evolution of NH_3 gas from the reaction mixture and the reusability of the catalyst , the mechanism which is shown in Scheme 2 is proposed for the clarification of the catalytic role of tetrabutylammonium bromide in the reported method.



Scheme 2

CONCLUSION

In conclusion, we have demonstrated that tetrabutylammonium bromide is an efficient catalyst for trimethylsilylation of alcohols using HMDS under mild reaction conditions. High yields of the products, relatively short reaction times, simple and easy work-up procedure and chemoselectivity can be considered as the main important advantages of the reported method.

ACKNOWLEDGEMENT

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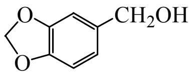
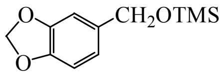
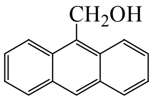
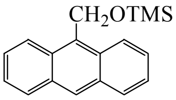
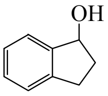
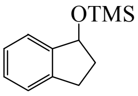
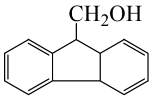
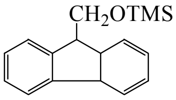
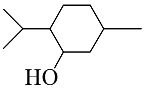
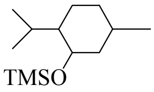
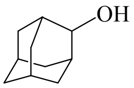
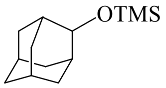
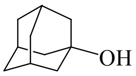
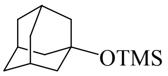
Table 1. Trimethylsilylation of Alcohols Catalyzed by Tetrabutylammonium Bromide. [a]

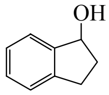
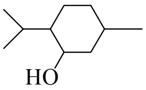
Entry	Substrate	Product	Time (min)	Yield (%) [b]
1	$4\text{-}ClC_6H_4CH_2OH$	$4\text{-}ClC_6H_4CH_2OTMS$	30	92
2	$2\text{-}ClC_6H_4CH_2OH$	$2\text{-}ClC_6H_4CH_2OTMS$	60	90
3	$4\text{-}BrC_6H_4CH_2OH$	$4\text{-}BrC_6H_4CH_2OTMS$	90	80
4	$2\text{-}BrC_6H_4CH_2OH$	$2\text{-}BrC_6H_4CH_2OTMS$	90	95
5	$3,4\text{-}Cl_2C_6H_3CH_2OH$	$3,4\text{-}Cl_2C_6H_3CH_2OTMS$	30	92
6	$2\text{-}MeC_6H_4CH_2OH$	$2\text{-}MeC_6H_4CH_2OTMS$	30	95
7	$4\text{-}Me_2CHC_6H_4CH_2OH$	$4\text{-}Me_2CHC_6H_4CH_2OTMS$	60	92
8	$4\text{-}Me_3CC_6H_4CH_2OH$	$4\text{-}Me_3CC_6H_4CH_2OTMS$	20	95
9	$2\text{-}NO_2C_6H_4CH_2OH$	$2\text{-}NO_2C_6H_4CH_2OTMS$	120	70
10	$3\text{-}MeOC_6H_4CH_2OH$	$3\text{-}MeOC_6H_4CH_2OTMS$	40	92
11			50	90
12	$4\text{-}PhCH_2OC_6H_4CH_2OH$	$4\text{-}PhCH_2OC_6H_4CH_2OTMS$	20	95
13			40	90
14	$PhCH(OH)CH_3$	$PhCH(OTMS)CH_3$	90	80
15	PhCH(OH)Ph	PhCH(OTMS)Ph	20	90
16	$4\text{-}ClC_6H_4CH(OH)Ph$	$4\text{-}ClC_6H_4CH(OTMS)Ph$	45	92
17			20	89
18	$PhCH_2CH_2OH$	$PhCH_2CH_2OTMS$	30	90
19	$PhCH_2CH_2CH_2OH$	$PhCH_2CH_2CH_2OTMS$	40	92
20	$PhCH(Me)CH_2OH$	$PhCH(Me)CH_2OTMS$	40	90
21			60	80
22	$PhCH_2CH(OH)CH_3$	$PhCH_2CH(OTMS)CH_3$	30	80
23			60	92
24			90	80
25			180	30
26	Ph_3COH	Ph_3COTMS	60	0
27	$4\text{-}MeC_6H_4NH_2$	$4\text{-}MeC_6H_4NH(TMS)$	60	0 [c]
28	$4\text{-}MeC_6H_4SH$	$4\text{-}MeC_6H_4STMS$	60	0 [c]

[a] Products were identified spectroscopically and also by the conversion of the silyl ethers to their corresponding alcohols. [b] Isolated yields. [c] Reaction was performed in the presence of 0.1 mmol of tetrabutylammonium bromide and under reflux conditions.

Table 2. Selective Trimethylsilylation of Alcohols.

Entry	Substrate	Product binary mixture	Time (min)	conversion
1	$4\text{-ClC}_6H_4CH_2OH$ + $4\text{-MeC}_6H_4NH_2$	$4\text{-ClC}_6H_4CH_2OTMS$ + 4-MeC_6H_4NHTMS	50	100 0
2	$4\text{-ClC}_6H_4CH_2OH$ + 4-MeC_6H_4SH	$4\text{-ClC}_6H_4CH_2OTMS$ + 4-MeC_6H_4STMS	40	100 0
3	$2\text{-BrC}_6H_4CH_2OH$ + Ph_3COH	$2\text{-BrC}_6H_4CH_2OTMS$ + Ph_3COTMS	120	100 0

Table 3. Comparison of Some of the Results Obtained by Our Method (1), with Some of Those Reported by Sulfonic Acid-functionalized Silica (2) [10], Trichloroisocyanuric Acid (3) [11], and $Al(HSO_4)_3$ (4) [14].

Entry	Substrate	Time (min) / Yield (%)			
		(1)	(2)	(3)	(4)
1		20 / 89	–	180 / 92	–
2	PhCH(OH)Ph	20 / 90	60 / 98	180 / 95	–
3	$PhCH_2CH_2OH$	30 / 90	40 / 100	180 / 90	90 / 90
4		60 / 92	–	180 / 95	60 / 95

REFERENCES

[1] a) L.F. Fieser, M. Fieser, Reagents for Organic Synthesis, Jhon Wiley and Sons Inc., New York, 1999; b) C.B. Reese, Protective Groups in Organic Chemistry, ed by J. F. McOmien, Plenum Press, London, 1973.

[2] J.M. Aizpurua, C. Palomo, Bull. Soc. Chim. Fr. Mem. (1982) 265.

[3] I. Nishiguchi, Y. Kita, M. Watanabe, Y. Ishino, T. Ohno and H. Maekawa, Synlett (2000) 1025.

[4] W. Verboom, G.W. Visser and D.N. Reinhoudt, Synthesis (1981) 807.

[5] S. Tarkelson, C. Ainsworth, Synthesis (1976) 722.

[6] J. Cossy, P. Pale, Tetrahedron Lett. 28 (1987) 6039.

[7] C.A. Bruynes, T.K. Jurriens, J. Org. Chem. 47 (1982) 3966.

[8] M. Curini, F. Epifano, M.C. Marcotullio, O. Rosati and U. Constantino, Synth. Commun. 29 (1999) 541.

[9] H. Firouzabadi, N. Iranpoor, K. Amani and F. Nowrouzi, J. Chem. Soc., Perkin Trans (2002) 2601.

[10] D. Zareyee, B. Karimi, Tetrahedron Lett. 48 (2007) 1277.

[11] A. Khazaei, M.A. Zolfigol, A. Rostami and A. Ghorbani Choghamarani, Catalysis Commun. 8 (2007) 543.

[12] D. Amantini, F. Fringuelli, F. Pizzo and L. Vaccaro, J. Org. Chem. 66 (2001) 6734.

[13] F. Shirini, M.A. Zolfigol and M. Abedini, Monatshefte fur Chemie 135 (2004) 279.

[14] F. Shirini, M.A. Zolfigol and M. Abedini, Bull. Chem. Soc. Jpn. (2005) 1982.

[15] F. Shirini, E. Mollarazi, Synth. Commun. 36 (2006) 1109.

[16] F. Shirini, M.A. Zolfigol and M. Paktinat, Synthesis (2006) 4252.

[17] F. Shirini, K. Marjani, H. Taherpour Nahzomi and M.A. Zolfigol, Phosphorus, Sulfur, and Silicon, 182 (2007) 1245.