Tetrahedron Letters,Vol.30,No.46,pp 6413-6416,1989
Printed in Great Britain

0040-4039/89 $3.00 + .0
Pergamon Press plc

THE DIETHYLISOPROPYLSILYL GROUP: A NEW PROTECTING GROUP FOR ALCOHOLS

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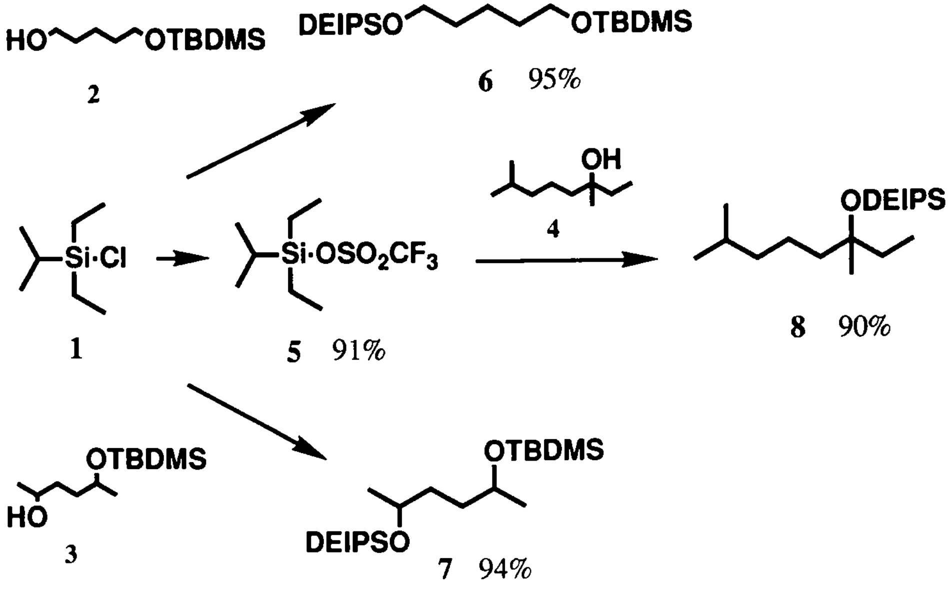
Summary: The diethylisopropylsilyl (DEIPS) group which is a new protective group for alcohols has been first characterized. DEIPS group can be distinguished from t-butyldimethylsilyl, triethylsilyl, tetrahydropyranyl groups and 2-deoxy glycoside with high selectivity in removing under mild acidic condition, although DEIPS group has high stability to many useful organic synthetic reaction conditions.

Although silyl ethers such as t-butyldimethysilyl (TBDMS) and t-butyldiphenylsilyl (TBDPS) have been widely used as protective group for alcohols and a large number of protecting groups for hydroxy function are now available$^{1)}$, new protecting groups with different selectivities are sometimes required, especially in the synthesis of large, complex and unstable compounds. Taking into account Sommer's study on the rate of acidic and basic hydrolysis of silyl ethers as function of the ligands on silicon$^{2)}$, we have recently developed new silyl protecting group, diethylisopropylsilyl (DEIPS) group in our first total synthesis of elaiophylin$^{3)}$. A silylating reagent of DEIPS group, DEIPS-Cl (**1**), was easily prepared from dichlorodiethylsilane and isopropyllithium in high yield$^{3b)}$. Herein, we wish to report the characterization of DEIPS group as protecting group for alcohols in organic synthesis.

First, we examined the formation of DEIPS ethers (Scheme 1). The three compounds **2**$^{4)}$, **3**$^{4)}$ and **4** were tested as examples of primary, secondary and tertiary alcohols, respectively. In case of primary and secondary alcohols, the DEIPS group was easily attached to each of these substrates by reaction with 1.2 equiv. of DEIPS-Cl (**1**) and 1.3 equiv. of imidazole in CH_2Cl_2 at room temperature. Tertialy alcohol was silylated with the more reactive DEIPS-trifluoromethanesulfonate$^{5)}$ (**5**) (1.2 equiv) in the presence of 2,6-lutidine (1.5 equiv) as base in CH_2Cl_2 at room temperature in high yield.

Our next attention turned to the selective distinction of DEIPS group from TBDMS, TES (triethylsilyl) and THP group in the removing under mild acidic condition. The mixtures of AcOH-H_2O-THF with the appropriate ratio were useful for this purpose as summarized in Table 1 and 2. The results showed that DEIPS group could be distinguished from all these groups with high selectivity in case of primary position. On the other hand, in secondary position, DEIPS group could be distinguished from THP with high selectivity and TBDMS and TES with



Scheme 1. Formation of DEIPS ethers [9]

acceptable selectivity. The DEIPS ether were also effectively removed even in the presence of acid-sensitive O-glycosidic linkage of 2-deoxy sugar moiety such as 2-deoxy-α-L-fucose and 4-O-carbamoyl-2-deoxy-β-D-rhamnose under mild acidic condition as significant steps in our macrolide syntheses [3,6].

Although isopropyldimetylsilyl (IPDMS) ether[7], the reagent of which is now commercially available, has simillar properties under mild acidic conditions[8], it is unfortunately well known to be unstable to some basic, nucleophilic, oxidative and reductive organic reaction conditions[1,7]. Finally, we examined the stability of the DEIPS group to these reaction conditions. The results (Scheme 2) showed that DEIPS ether has high stability to many useful organic reaction conditions except Jone's oxidation[10].

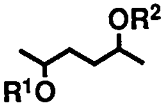
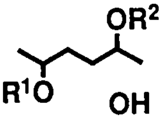
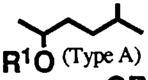
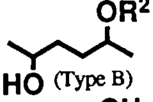
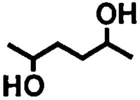
In conclusion, several advantages can be envisioned for the use of the DEIPS group as a hydroxy-protecting group and, further DEIPS group should find wide application especially in complex organic synthesis.

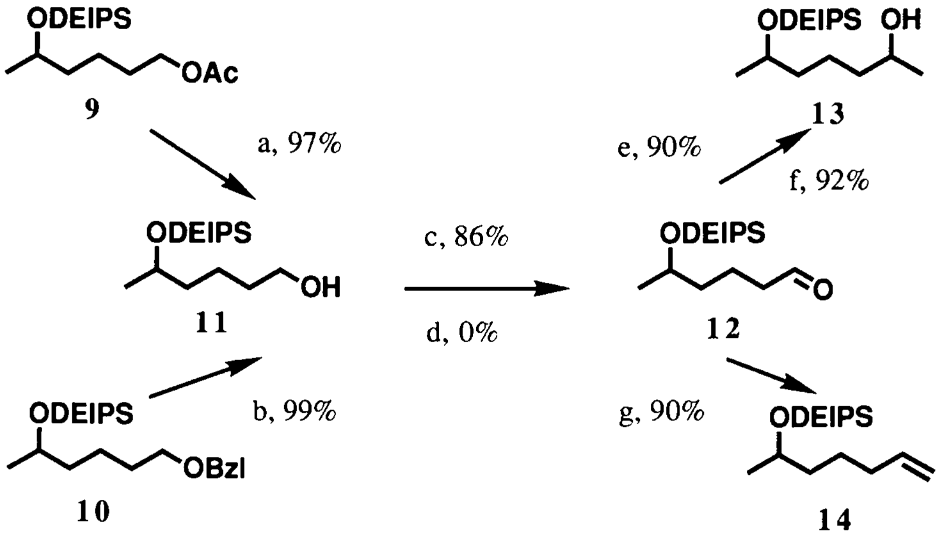
Acknowledgement: We are grateful to the Institute of Microbial Chemistry for the generous support of our program. Financial support by the Ministry of Education, Science and Culture (Grant-in-Aid Scientific Research) is gratefully acknowledged.

Table 1.[11)]

	Entry 1	Entry 2	Entry 3
	R^1=TBDMS R^2=DEIPS	R^1=THP R^2=DEIPS	R^1=TES R^2=DEIPS
Reaction Condition / Products	AcOH-H_2O-THF (4 : 1 : 4) 26°C, 80min	AcOH-H_2O-THF (4 : 1 : 4) 26°C, 105min	AcOH-H_2O-THF (8 : 1 : 8) 26°C, 50min
	11%	2%	0%
 (Type A)	81%	81%	1.3%
 (Type B)	1.3%	0%	75%
	5%	0%	9%

Table 2.[11)]

	Entry 1	Entry 2	Entry 3
	R^1=TBDMS R^2=DEIPS	R^1=THP R^2=DEIPS	R^1=TES R^2=DEIPS
Reaction Condition / Products	AcOH-H_2O-THF (4 : 1 : 4) 26°C, 105min	AcOH-H_2O-THF (4 : 1 : 4) 26°C, 230min	AcOH-H_2O-THF (8 : 1 : 8) 26°C, 80min
	14%	7%	14%
 (Type A)	69%	80%	0.1%
 (Type B)	0.2%	0%	62%
	7%	6%	16%



Scheme 2. Stability of DEIPS gruop [9)]

(a) 1.2 equiv 1NNaOH, 1:1 THF-MeOH, 26°C, 1h; (b) cat. $Pd(OH)_2$, dioxane, 26°C, 15h; (c) 2.0 equiv PCC, MS 4A, CH_2Cl_2, 26°C, 1h; (d) Jone's reagent, acetone, 0°C, 30min, (c) 2.0 equiv MeLi, Et_2O, 0°C, 1h; (f) 3.0 equiv MeMgBr, Et_2O, 26°C, 1h; (g) 2.0 equiv CH_2=PPh_3, benzene, 26°C, 1h.

References and Notes:

1). T. W. Green, *"Protective Groups in Organic Synthesis"*, John Willy and Sons, New York, 1981.

2). L. H. Sommer, *"Stereochemistry, Mechanism and Silicon"*, McGraw-Hill, New York, 1965, pp. 127-138.

3). (a) K. Toshima, K. Tatsuta, and M. Kinoshita, Tetrahedron Lett., 27, 4741 (1986): (b) K. Toshima, K. Tatsuta, and M. Kinoshita, Bull. Chem. Soc. Jpn., 61, 2369 (1988).

4). Mono-silyl ethers were prepared by treatment of the corresponding diols with 2.0 equiv. of imidazole followed by reaction with 1.0 equiv. of TBDMS-Cl.

5). DEIPS-Cl and trifluoromethanesulfonic acid were heated at 60°C for 5h and the resulting silyl ester was isolated by distillation. bp 60-62°C/2.5mmHg.

6). K. Toshima, M. Misawa, K. Ohta, K. Tatsuta, M. Kinoshita, Tetrahedron Lett., following paper.

7). E. J. Corey and R. K. Varma, J. Am. Chem. Soc., 93, 7319 (1971).

8). M. Lalonde and T. H. Chan, Synthesis., 1985, 817.

9). All new products were purified by silica gel column chromatography and were fully characterized by spectroscopic means and elemental analyses.

10). DEIPS group of **11** was cleaved completely under this condition.

11). Isolated yield after column chromatography on slica gel. The ratio of type A and type B was determined by gas chromatograph (GC) analysis. GC analysis was carried out on a 2m silicon SE-30 5% column (0.3 mm id) using helium as carrier gas at a flow rate of 20 ml min^{-1}. The column temperature was held at 170°C.

(Received in Japan 1 August 1989)