Tetrahedron Letters, Vol. 22, No. 14, pp 1299 - 1302, 1981
Printed in Great Britain

0040-4039/81/141299-04$02.00/0

A CLASS OF NEW SILYLATING REAGENTS. I. A MILD METHOD FOR INTRODUCTION OF THE TERT-BUTYLDIMETHYLSILYL GROUP.

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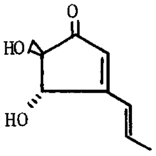
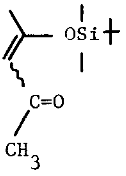
Abstract. t-Butyldimethylsilyl enol ethers of pentane-2,4-dione and methyl acetoacetate react rapidly at room temperature to give high isolated yields of the t-butyldimethylsilyl ethers of a variety of alcohols.

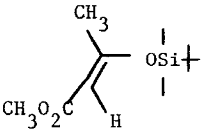
The t-butyldimethylsilyloxy group is well known to be more stable than the trimethylsilyloxy and dimethylisopropylsilyloxy groups towards solvolysis in protic media and against other widely employed reagents.[1] These facts led to its introduction as a protective group into organic synthesis by Corey and Venkateswarlu[1d] and it has found widespread use since then, especially in prostaglandin synthesis. Efficient introduction of this group into a molecule, however, to the best of our knowledge, requires the use of a base catalyst.[2,3] Therefore, its introduction into base sensitive molecules poses some problems. Indeed, our efforts to introduce this group into terrein (1) using the normal procedure gave very poor results. Therefore, we sought for a reagent which would accomplish this under neutral and/or mildly acidic conditions. We report herein our success in developing blocked enolic trisubstituted silyl enols as transfer reagents of considerable convenience, ease of preparation, and reactivity.



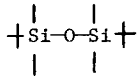
1



2a



2b

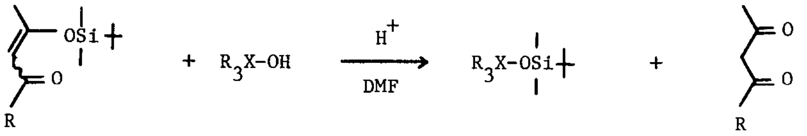


3

Reagent 2a was prepared as follows: t-butyldimethylchlorosilane (10.0 g; ∿66 mmoles; Petrarch Systems, Inc.) dissolved in 20 ml dry THF was added to a mixture of imidazole (4.8 g; 70 mmoles) in 40 ml of dry THF under an argon atmosphere in a rigorously dried two-necked reaction flask fitted with a reflux condenser and a rubber septum. A jelly-like precipitate immediately formed. Distilled 2,4-pentanedione (6.9 g; 69 mmoles) was injected through the septum and the septum was then replaced by a teflon-lined glass stopper. The reaction mixture was magnetically stirred under gentle reflux until all the jelly-like matter disappeared (crystalline imidazole hydrochloride appears; 7-12 hours). Cooling, filtration through a sintered glass funnel, and then concentration under reduced pressure (dry argon back flush) gave a yellowish liquid which was quickly pressure filtered through a pad (2 x

2.5 cm) of silica gel to remove the excess imidazole. The pad was washed with dry ether (2 x 6 ml) to insure total recovery of product. Ether removal gave a faintly yellow liquid as the crude product. Distillation, using a 15 cm Vigreaux distilling head, gave 2a as a clear liquid (12.34 g; 87% yield): b.p. 59-63/0.06 mm Hg. Analysis by nmr[4] showed a cis to trans ratio of 1:6. The peaks and the relative areas recorded in the nmr spectrum are as follows: (CCl_4) τ 9.78 (s, 42), 9.07 (s, 63), 8.0 (s, 24), 7.8 (s, 18), 4.78 (s, 1), and 4.5 (s, 6). Ir (neat) 2980, 2955, 2905, 2890, 1730, 1484, 1470, 1415, 1380, 1355, 1275, 1250, 1150, 1025, 995, 850, 830, 820, 800, 770, 710 and 650 cm^{-1}. Eims (m/e) 199, 158, 157(base), 139, 127, 115, 99, 89, 76, 73 and 43. Calculated for C, 61.62; H, 10.35. Found: C, 61.56; H, 10.60. The preparation of 2b was carried out by the same procedure described above, however, using 4.6 g of imidazole, 7.9 g methyl acetoacetate, and 9.1 g of t-butyldimethylchlorosilane in 50 ml dry THF. The reaction was over in 7 hours. Distillation of the crude product gave 2.1 g (15%) of slightly contaminated and 10.2 g (74%) of gas chromatographically pure product consisting of the trans isomer only; b.p. 54-5/0.04 mm Hg; nmr (neat) τ 9.8 (s, 9H), 9.08 (s, 6HO, 7.8 (s, 3H), 6.53 (s, 3H), and 4.9 (s, 1H). Ir (neat) 2980, 2950, 2910, 2880, 1720, 1630, 1470, 1430, 1380, 1330, 1280, 1250, 1130, 1030, 935, 870, 830, 810, 795, and 770 cm^{-1}. Eims (m/e) 215, 199, 175, 174, 173, 141, 115, 99, 91, 90, 89(base), 75, 73 and 59. Calculated for C, 57.34; H, 9.62. Found: C, 57.47; H, 9.89.

Their reactions with alcohols or silanols proceed as shown in Scheme 1. As expected the reaction is facilitated by more polar solvents (DMF>Acetonitrile>THF>Dichloromethane), DMF being the solvent of choice. Also the higher the temperature the faster the reaction is, however, a slight molar excess of 2a gave consistently excellent yields of products at room temperature in DMF with a catalytic amount of tosic acid. Under similar conditions 2a shows greater reactivity and a higher susceptibility to solvolysis compared to 2b. (See Table 1.) For example, the addition of water to a solution of 2a in DMF or acetonitrile results in hydrolysis of the reagent to t-butyldimethylsilanol and 2,4-pentanedione while 2b is stable under these conditions, hydrolyzing only after the solution is acidified. The results obtained with representative substrates are given in Table 1. It is important to note that 1,3-di-t-butyl-1,1,3,3-tetramethyldisiloxane (3), a highly sterically crowded disiloxane which defied synthesis until only very recently,[5] can easily be obtained in almost quantitative yield with this new procedure.



R=CH_3, OCH_3
X=C, Si

Scheme 1

The following examples demonstrate the typical procedure used and the utility of these reagents. An excess of reagent 2a (300 mg; 1.4 meq.) was added to a solution of terrein (77 mg; 1.0 meq.) and 6 mg of p-toluenesulfonic acid monohydrate in 2 ml dry DMF. The reaction mixture was stirred overnight at room temperature and then distributed between 3 ml petroleum ether and 2 ml water followed by separation of the phases and further extraction of the aqueous phase with five like portions of petroleum ether. The combined organic extracts were dried (Na_2SO_4) and evaporated to give 192 mg of a brownish red viscous product. This was nearly pure and could be further purified by column chromatography over silica gel in methylene chloride to give 144 mg of gas chromatographically[6] and

Substrate	Reagent	Conditions for Quantitative Conversion to Product as Judged by glc.[5]	Isolated Yield
2-phenylethanol	2a	24 hr., DMF, 50°C	83%
	2a	1 hr., DMF, cat. tosOH, r.t.	
	2b	2 hr., DMF, cat. tosOH, r.t.	
trans-2-methylcyclopentanol	2a	7-10 hrs., DMF, tosOH, r.t.	86%
terrein (**1**)	2a	8-14 hrs., DMF, tosOH, r.t.	92%
t-butyldimethylsilanol	2a	8-10 hrs., DMF, tosOH, r.t.	85%
	2b	5-6 hrs., DMF, tosOH, 75°C	

analytically pure terrein di-*t*-butyldimethylsilyl ether as a very viscous yellowish compound: nmr (CCl_4) τ 9.80 (s, 12H), 9.10 (s, 18H), 8.o0 (d, J=5 Hz, 3H), 5.95 (d, J=2.5 Hz, 1H), 5.35 (d, J=2.5 Hz, 1H), 4.10 (s, 1H), and 3.30-3.80 (m, 2H); ir (CCl_4) 2980, 2950, 2910, 2870, 1720, 1645, 1595, 1480, 1460, 1355, 1245, 1130, 1094, 944, 890, 855, and 820 cm^{-1}; eims (m/e) 384, 383, 382, 381, 372, 341, 327, 326, 325(base), 313, 281, 251, 193, 147, 133, 75, 73, and 43. Calcd.: C, 62.77; H, 10.01. Found: C, 62.57; H, 10.20. An additional 31 mg of slightly contaminated product was also eluted. Another typical preparation follows: A mixture of 2b (2.665 g; 11.5 mmoles), *t*-butyldimethylsilanol (1.825 g; 20% molar excess), *p*-toluenesulfonic acid monohydrate (29 mg) in 10 ml dry DMF was heated at 75°C for 5 hours. (Quantitative conversion to product as judged by GLC.) After cooling, the addition of 15 ml water was followed by extraction with pentane (4 x 10 ml). The combined pentane extracts were shaken with 15 mls of 5% H_2SO_4, then washed successively with sat. sodium carbonate and water until the washes were neutral to pH paper. Drying (Na_2SO_4), concentration and finally fractional distillation at atmospheric pressure using a micro Vigreaux distilling head gave **3** in better than 85% yield: b.p. 191-3; nmr (CCl_4) τ 10.0 (s, 12), and 9.14 (s, 18); ir (CCl_4) 2980, 2950, 2905, 2880, 1470, 1385, 1360, 1245, 1060, 1045, 995, 930, and 825 cm^{-1}; eims (m/e) 246 (M^+), 231 ($M-CH_3$), 191, 190, 189 (M^+-*t*-butyl), 149, 148, 147(base), 133, 131, 117 and 73. Calcd.: C, 58.45; H, 12.26. Found: C, 58.58; H, 12.30.

The ease of preparation of these reagents and their high reactivity under exceptionally mild conditions persuade us that these new reagents will find substantial use in organic synthesis; especially for hindered and/or sensitive compounds.

Acknowledgement: This research was supported by USPHS Grant GM/HL 26553.

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2a) See also: K. K. Ogilvie and D. J. Iwacha, *Tetrahedron Lett.*, **1973**, 317; b) T. J. Barton and C. R. Tully, *J. Org. Chem.*, **43**, 3649 (1978); and, c) S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*,

1979, 99.

3. During the preparation of this manuscript allyl-t-butyldimethylsilane was reported as a new and effective reagent for introducing the t-butyldimethylsilyl group. Its reaction with cyclohexanol requires heating at 70-80°C for 2.5 h in the presence of TsOH and it should be a welcome addition to the armamentarium of the organic chemist. See: T. Morita, Y. Okamoto and H. Sakurai, Tetrahedron Lett., 1980, 835. Also, recently, ketene methyl trialkylsilyl acetals were reported to be effective silylating agents under neutral or acidic conditions. See Y. Kita, J. Haruta, J. Segawa and Y. Tamura, Tetrahedron Lett., 1979, 4311. Our attempts to prepare the analogous t-butyldimethylsilyl acetal failed. Instead we obtained only the silylated condensation product of methyl propionate.
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5. L. H. Sommer and L. J. Tyler, J. Am. Chem. Soc., 76, 1030 (1954); G. W. Ritter, II, and M. E. Kenney, J. Organometal. Chem., 157, 75 (1978).
6. The reactions were monitored and purity was established in all cases using a Varian Model 3700 Gas Chromatograph; flame ionization detector; He; a 10 x 1/8", 3% SE-30 on Chromasorb W 80/100 column; and column temperatures of 70-210°C (either isothermally or temperature programmed).

(Received in USA 3 November 1980)