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SYNTHESIS OF t-BUTYLDIMETHYLSILYL ENOL ETHERS FROM STERICALLY HINDERED KETONES

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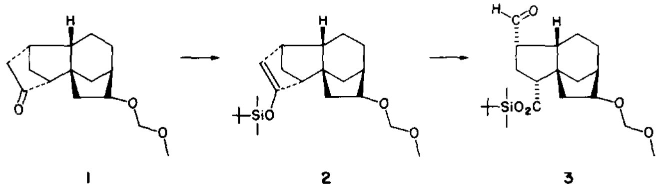
Summary: Ketones react rapidly with t-butyldimethylsilyl triflate and amine bases to form t-butyldimethylsilyl enol ethers in high yields.

Enol silyl ethers have proven to be extraordinarily versatile substrates for a wide variety of synthetic purposes, including [4+2] cycloadditions,[1] alkylations,[2] acylations,[3] aldol reactions,[4] hydroborations[5] and oxidative processes.[6,7] We were recently interested in preparing the enol silyl ether 2[8] with a view to preparing aldehyde 3 (Scheme 1), which we envisaged as an intermediate in the total synthesis of C_{20} gibberellins.[9] Our efforts to prepare 2 by published methods were unsuccessful, however, presumably because of a combination of steric hindrance with the characteristically low acidity of norbornanone derivatives.

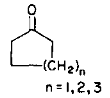
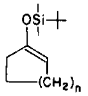
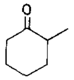
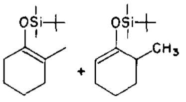
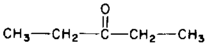
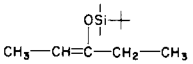
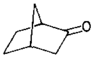
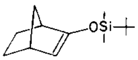
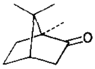
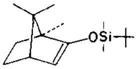
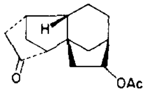
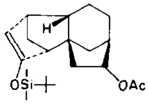
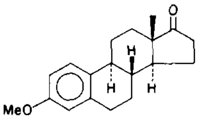
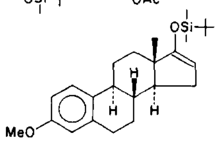
Scheme 1:

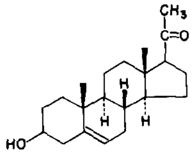
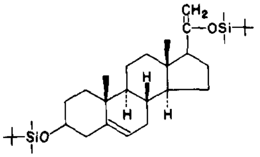
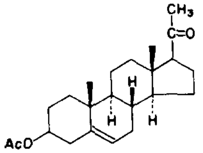
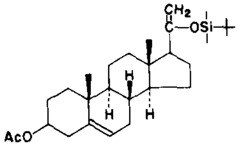
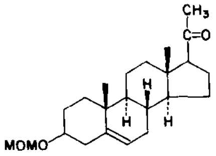
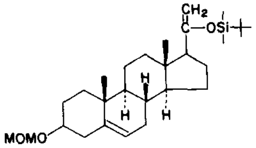
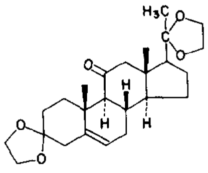
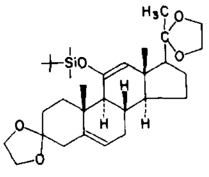
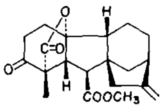
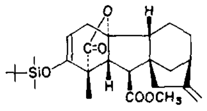
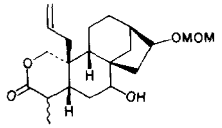
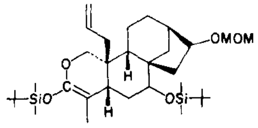


Trimethylsilyl triflate-triethylamine has been employed to silylate a variety of ketones under very mild conditions with rate constants of ∿10^8 relative to the chloride,[10] and even the highly hindered tri-isopropylsilyl derivatives may be prepared by using the triflate.[11] Although t-butyldimethylsilyl(TBDMS) triflate had been applied with considerable success to the silylation of hindered alcohols[11] and in the formation of allylic silyl ethers from epoxides,[12] there appeared to be no reports of the formation of enol silyl ethers from ketones with this reagent. We have found that TBDMS triflate in combination with triethylamine or 2,6-lutidine not only furnished TBDMS enol ether **2** under very mild conditions and in high yield, but appears to provide a completely general procedure as indicated by the formation of similar derivatives from the wide range of substrates outlined in Scheme 2.

The method is compatible with a wide range of functionality (entries 6,9-12)[13] and is especially valuable for sterically hindered substrates (entries 5,6,11,12). Selective formation of "kinetic" regioisomers was obtained with the steroidal substrates (entries 8-11), but not with simple ketones (entry 2), for which established procedures would be more satisfactory.[14] The scope of the present investigation has been largely confined to ketones, but preliminary studies indicate that esters and lactones (entry 13) may also be readily derivatized with these reagents.

Scheme 2.

ENTRY	SUBSTRATE	PRODUCT	TIME	YIELD (%)[a,b]
1			5 min	~100%
2		 64 36	5 min	~100%
3	 $CH_3—CH_2—\overset{O}{\overset{\|}{C}}—CH_2—CH_3$	 $CH_3—CH{=}\overset{OSi}{C}—CH_2—CH_3$ E + Z 17 : 83	5 min	~100%
4			5 min	~100%
5			5 min	100%
6			30 min	~95%
7			15 min	~98%

ENTRY	SUBSTRATE	PRODUCT	TIME	YIELD (%)^{a,b}
8			30 min	~98 %
9			30 min	~98 %
10			30 min	~98 %
11			12 hr	~94 %
12			12 hr	~93 %
13			2 hr	~90 %

[a] Isolated yields of chromatographically homogeneous products.

[b] Structures determined from ^{1}H-NMR spectra.

In a typical preparation, t-butyldimethylsilyl triflate (2-4 mmole) was added to a solution of the ketone (2.0 mmole) and triethylamine (3.0 mmole) in dichloromethane or 1,2-dichloroethane (5.0 ml). The progress of the reaction was monitored by thin layer chromatography and when complete, diluted with dichloromethane and washed with cold sodium bicarbonate. After the organic layer was dried over anhydrous sodium sulphate and concentrated on a rotovap, the residue was taken up in dry ether and separated from the insoluble triethylammonium triflate. The ether solution was then concentrated and chromatographed on neutral active alumina using 0-20% ether in hexane containing 1 drop of pyridine as eluent to give the pure product.

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5. G.L. Larsen, E. Hernandez, C. Alonso, and I. Nieves, Tetrahedron Lett., 4005 (1975).

6. G.M. Rubottom and J.M. Gruber, J. Org. Chem., **42**, 1051 (1977).

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8. The t-butyldimethylsilyl derivative was selected in anticipation of greater stability towards chromatography and reagents.

9. Cf. L. Lombardo and L.N. Mander, J. Org. Chem., **48**, 2298 (1983).

10. H. Emde, D. Domsch, H. Feger, U. Frick, A. Gotz, H.H. Hergott, K. Hofmann, W. Kober, K. Krageloh, T. Oesterle, W. Steppan, W. West, and G. Simchen, Synthesis, 1 (1982).

11. E.J. Corey, H. Cho, C. Rucker and D.H. Hua, Tetrahedron Lett., **22**, 3455 (1981).

12. S. Murata, M. Suzuki, and R. Noyori, J. Am. Chem. Soc., **101**, 2738 (1979).

13. All new compounds gave satisfactory ^{1}H-NMR, MS and HRMS data. Olefinic resonances associated with the enol silyl ether function were observed in the range δ 4.5-5.0 with the exception of entries 8-10 (δ 4.04) and entry 11(δ 5.56).

14. For the preparation of "kinetic" isomers see H.O. House, L.J. Czuba, M. Gall, and H.D. Holmstead, J. Org. Chem., **34**, 2324 (1969); E.J. Corey and A.W. Gross, Tetrahedron Lett., **25**, 495 (1984). For the preparation of "thermodynamic" isomers see M.E. Kraft and R.A. Holton, Tetrahedron Lett., **24**, 1345 (1983); J. Orban, J.V. Turner, and B. Twitchin, Tetrahedron Lett., in the press. See also J. Orban and J.V. Turner, Tetrahedron Lett., **24**, 2697 (1983).

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