Facile Procedure for Acetalization Using Diols, Alkoxysilane and a Catalytic Amount of Trimethylsilyl Trifluoromethanesulfonate

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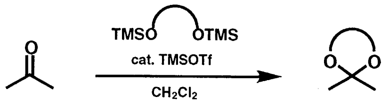
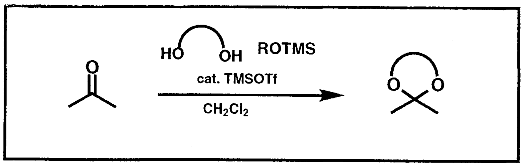
In the presence of *sec*- or *tert*-alkoxysilane and a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf), carbonyl compounds react with various diols to give acetals in high yields.

The acetal group is not only the most widely used protective group for carbonyl compounds[1] but also an efficient chiral auxiliary group for enantioselective synthesis.[2] Acetalization using alkoxysilane and TMSOTf as a catalyst (eq. I) has been reported by Noyori et al.[3] Noyori's method is useful for the synthesis of acetals, especially under mild conditions, but trimetylsilylated diols must be prepared. This report describes a convenient procedure for acetalization of carbonyl compounds using a diol, a *sec*- or *tert*-alkoxysilane and a catalytic amount of TMSOTf without the need to prepare the silylated diols. (eq. II)



(I)

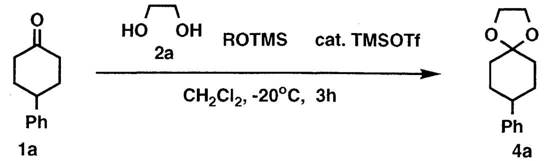


(II)

The reaction of the ketone **1a** with ethylene glycol and an alkoxysilane[4] (isopropoxytrimethylsilane, *sec*-phenethyloxytrimethylsilane or *tert*-buthoxytrimethylsilane) in the presence of a catalytic amount of TMSOTf proceeded smoothly at -20 °C to give the corresponding acetal in high yield. (Table 1)

The results of the acetalization of carbonyl compounds with various diols are summarized in Table 2. Notably, acetalization using chiral diols has been achieved (entry 1,2,4,5,7) and 2-cyclohexenone as typical α,β-unsaturated ketone is acetalized

Table 1.



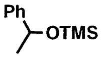
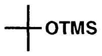
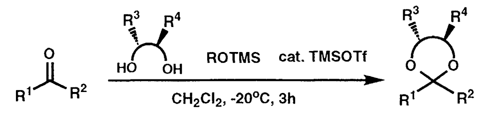
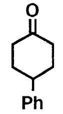
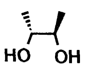
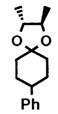
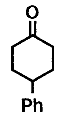
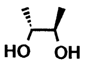
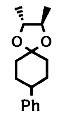
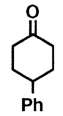
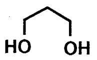
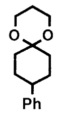
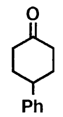
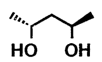
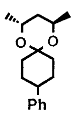
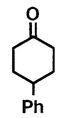
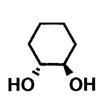
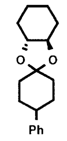
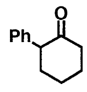
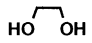
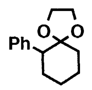
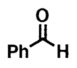
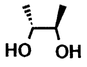
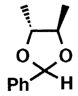
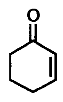
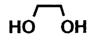
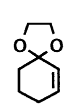
Entry	ROTMS	Isolated yield / %
1	 3a	98
2	 3b	96
3	 3c	97

Table 2.



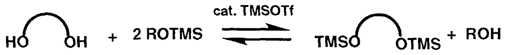
Entry	Ketone	Diol	ROTMS	Acetal[a]	Yield / %[b]
1	 1 a	 2b	3a		99
2			3b		98
3		 2c	3b		92
4		 2d	3a		89
5		 2e	3a		85
6	 1b	 2a	3a		88
7	 1c	 2b	3b		96
8	 1d	 2a	3a		84[c]

[a] Acetals were indentified by ^{1}HNMR, ^{13}CNMR, and MS.
[b] Isolated yield. [c] GLC yield.

without double-bond migration (entry 8).[5]

A typical procedure is as follows: to a mixture of the ketone **1a** (117 mg, 0.672 mmol), the diol **2a** (50 mg, 0.862 mmol) and isopropoxytrimethylsilane (355 mg, 2.68 mmol) in dry dichloromethane was added TMSOTf (1.7 mg, 0.007 mmol, 1 mol%) at -20 °C under argon atmosphere. The reaction mixture was stirred at the same temperature for 3 h, quenched by addition of pyridine and the solvent was evaporated under reduced pressure. The residue was purified by silica-gel chromatography to afford acetal **4a** (144 mg, 0.659 mmol, 98 %).

When diol **2a** was treated with isopropoxytrimethylsilane in the presence of a catalytic amount of TMSOTf in dichloromethane at -20 °C, disilylated diol was shown to be formed by GLC analysis. (eq. III) This observation suggest that the alkoxysilane of the diol was generated in situ and reacted with the carbonyl compound in the presence of a catalytic amount of TMSOTf to afford the acetal.



(III)

References and Notes

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2 For review, see: A. Alexakis and P. Mangeney, *Tetrahedron : Asymmetry*, **1**, 477 (1990); J. K. Whitesell, *Chem. Rev.*, **89**, 1581 (1989): For recent example, see: Y. Kondo, J. R. Green, and J. Ho, *J. Org. Chem.*, **56**, 7199 (1991); C. Giordano and L. Coppi, *J. Org. Chem.*, **57**, 2765 (1992); J. Aube, J. A. Heppert, M. L. Milligan, M. J. Smith, and P. Zenk, *J. Org. Chem.*, **57**, 3563 (1992); T. L. Underiner and L. A. Paquette, *J. Org. Chem.*, **57**, 5438 (1992); H. Fujioka, T. Yamanaka, N. Matsunaga, M. Fuji, and Y. Kita, *Synlett*, **1992**, 35; T. Fujisawa, Y. Ukaji, T. Noro, K. Date, and M. Shimizu, *Tetrahedron*, **48**, 5629 (1992); P. Maglioli, O. D. Lucchi, G. Deiogu, and G. Valle, *Tetrahedron: Asymmetry*, **3**, 365 (1992); P. A. Rose, S. R. Abrams, and A. C. Shaw, *Tetrahedron: Asymmetry*, **3**, 443 (1992); S. Tang and R. M. Kennedy, *Tetrahedron Lett.*, **33**, 7823 (1992); E. J. Corey and L. I. Wu, *J. Am. Chem. Soc.*, **115**, 9327 (1993); T. Sugimura, S. Goto, K. Koguro, T. Futagawa, S. Misaki, Y. Morimoto, N. Yasuoka, and A. Tai, *Tetrahedron Lett.*, **34**, 505 (1993); J. P. Konopelski and R. A. Kasar, *Tetrahedron Lett.*, **34** 4587 (1993); B. Chitkul, Y. Pinyopronpanich, C. Thebtaranonth, Y. Thebtaranonth, and W. C. Taylor, *Tetrahedron Lett.*, **35**, 1099 (1994); K. Tomooka, T. Igarashi, and T. Nakai, *Tetrahedron Lett.*, **35**, 1913 (1994); K. Kato, H. Suemune, and K. Sakai, *Tetraherdon Lett.*, **35**, 3103 (1994).

3 T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, **21**, 1357 (1980).

4 Alkoxysilanes were prepared by silylating the corresponding alcohols with chlorotrimethylsilane and Et_3N.

5 Acetal with double-bond migration was not detected by GLC analysis.