JOC Article

Convenient Preparation of Cyclic Acetals, Using Diols, TMS-Source, and a Catalytic Amount of TMSOTf

Masaaki Kurihara* and Wataru Hakamata

Division of Organic Chemistry, National Institute of Health Sciences, Setagaya-ku, Tokyo 158-8501, Japan

masaaki@nihs.go.jp

Received July 15, 2002

With use of diol, alkoxysilane, and a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf), carbonyl compounds are converted to acetals in good yields under mild conditions. This procedure, which was carried out without synthesizing the silylated diols, is a more convenient adaptation of Noyori's method. This acetalization applies to not only simple but also conjugated carbonyl compounds. Moreover, various TMS compounds, including solid supported compounds, are effective for this method instead of alkoxylsilane.

Introduction

The utility of acetalization in organic synthesis is well-recognized for protection of carbonyl compounds[1] and the generation of chiral auxiliaries for asymmetric induction.[2] The introduction of new methods and modification of existing methogology for making acetals is thus an important challenge. Among acetalization methods,[3] Noyori's procedure[4] with silylated alcohols and a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as Lewis acid is useful for the synthesis of acetals, under mild conditions. We reported a facile procedure of acetalization using diols, alkoxysilanes, and a catalytic amount of TMSOTf.[5] This modification of the Noyori procedure uses an alkoxysilane and avoids preparation of the silylated diols. Recently, Ikegami and co-workers have succeeded in synthesis of glycosidic spiro-ortho esters under similar conditions.[6] We describe now application of this method with various "TMS-sources" as silylating agents.

Results and Discussion

Carbonyl compounds were treated with various chiral and achiral diols, alkoxysilanes, and a catalytic amount of TMSOTf in CH_2Cl_2 at −20 °C to prepare the corresponding acetals in high yields under mild conditions (Table 1). α,β-Unsaturated carbonyl compounds (**1f** and **1g**) were converted to acetals without double bond migration. Sterically hindered ketones (**1d** and **1e)** were also converted to acetals in good yield (entries 1 and 2 in Table 1). Carbamate and ester groups were well-tolerated under these conditions. Several TMS compounds were examined as replacements for the alkoxysilane in the synthesis of acetal **4a**. 3-Trimethylsilyl-2-oxazolidinone (**3c**), *N*-(trimethylsilyl)acetamide (**3d**), and 2-(trimethylsilyloxy)furan (**3f**) proved effective as TMS-sources for this acetalization; however, 1-(trimethylsilyl)imidazole (**3e**) failed to affect this reaction (Table 2), suggesting that amines may inactivate the Lewis acid in this reaction. A solid-supported TMS-source **3h**, which was prepared by trimethylsilylation of Wang resin, also proved effective (entry 8 in Table 2).

When diol **2a** was treated with isopropoxytrimethylsilane **3a** in the presence of a catalytic amount of TMSOTf in dichloromethane at −20 °C, disilylated diol was shown to be formed by GLC analysis[7] (Scheme 1). Silylation of the diol in situ may thus proceed in the presence of a catalytic amount of TMSOTf prior to the acetalization.

Because these conditions were effective for the preparation of acetals, they may serve in other reactions such

(1) Greene, T. W.; Wuts, P. G. M. *Protective Group in Organic Synthesis*; John Wiley & Sons: New York, 1999.

(2) For reviews, see: (a) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477. (b) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. For recent examples, see: (c) Corey, E. J.; Wu, L. I. *J. Am. Chem. Soc.* **1993**, *115*, 9327. (d) Sugimura, T.; Goto, S.; Koguro, K.; Futagawa, T.; Misaki, S.; Morimoto, Y.; Yasuoka, N.; Tai, A. *Tetrahedron Lett.* **1993**, *34*, 505. (e) Konopelski, J. P.; Kasar, R. A. *Tetrahedron Lett.* **1993**, *34*, 4587. (f) Chitkul, B.; Pinyopronpanich, Y.; Thebtaranonth, C.; Thebtaranonth, Y.; Taylor, W. C. *Tetrahedron Lett.* **1994**, *35*, 1099. (g) Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron Lett.* **1994**, *35*, 1913. (h) Kato, K.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1994**, *35*, 3103. (i) Sugimura, T.; Fujiwara, Y.; Tai, A. *Tetrahedron Lett.* **1997**, *38*, 6019. (j) Konepelski, J. P.; Deng, H.; Schiemann, K.; Keane, J. M.; Olmstead, M. M. *Synlett*, **1988**, 1105. (k) Wunsch, B.; Nerdinger, S. *Eur. J. Org. Chem.* **1999**, *64*, 503. (l) Tanaka, M.; Oba, M.; Tamai, K.; Suemune, H. *J. Org. Chem.* **2001**, *66*, 2667.

(3) For recent examples, see: (a) Dauben, W. G.; Gerdes, J. M.; Look, G. C. *J. Org. Chem.* **1986**, *51*, 4964. (b) Torok, D. S.; Figueroa, J. J.; Scott., W. J. *J. Org. Chem.* **1993**, *58*, 7274. (c) Yuan, T.-M.; Yeh, S.-M.; Hsieh, Y.-T.; Luh, T.-Y. *J. Org. Chem.* **1994**, *59*, 8192. (d) Tateiwa, J.; Horiuchi, H.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 4039. (e) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synlett* **1999**, 321. (f) Basu, K. M.; Samajdar, S.; Becker, F. F.; Banik, K. B. *Synlett* **2002**, 319.

(4) (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. (b) Hwu, J. R.; Leu, L.-C.; Robl, J. A.; Anderson, D. A.; Wetzel, J. M. *J. Org. Chem.* **1987**, *52*, 188.

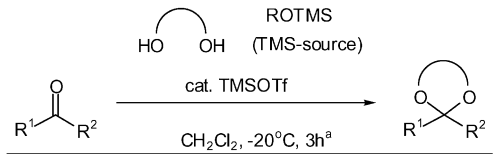
(5) Kurihara, M.; Miyata, N. *Chem. Lett.* **1995**, 263.

(6) Ohtake, H.; Iimori, T.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 3413−3414.

(7) Gas chromatographic analyses were performed with a CBP-1 column (50 m, ϕ 0.25 mm, carrier gas He, column temperature 100 °C, flow 0.6 mL/min). The retention times of diol **2a** and disilylated diol were 1.97 and 3.29 min, respectively.

10.1021/jo020471z CCC: $25.00
Published on Web 03/28/2003

TABLE 1.



Entry	Carbonyl compound	Diol	TMS-source	Acetal	Isolated yield(%)
1	**1a**	**2a**	**3a**	**4a**	98
2	**1a**	**2a**	**3b**	**4a**	96
3	**1b**	**2b**	**3a**	**4b**	99
4	**1b**	**2b**	**3b**	**4b**	98
5	**1a**	**2c**	**3b**	**4c**	92
6	**1b**	**2d**	**3a**	**4d**	89
7	**1a**	**2e**	**3a**	**4e**	85
8	**1c**	**2a**	**3b**	**4f**	95
9	**1c**	**2b**	**3b**	**4g**	96
10	**1c**	**2c**	**3b**	**4h**	94
11	**1c**	**2d**	**3b**	**4i**	96
12	**1d**	**2a**	**3a**	**4j**	88
13	**1e**	**2a**	**3b**	**4k**	70
14	**1f**	**2a**	**3a**	**4l**	84
15	**1g**	**2a**	**3b**	**4m**	82
16	**1h**	**2a**	**3b**	**4n**	92
17	**1i**	**2a**	**3b**	**4p**	93

[a] Entry 13: rt, 16 h.

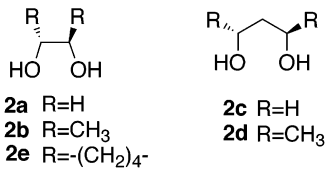


FIGURE 1.

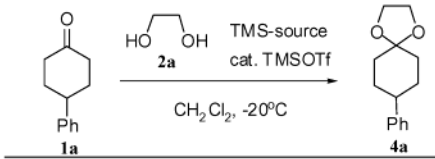
as esterifications,[8] lactonizations,[9] and glycosidations[10] which employ similar silylated compounds.

Experimental Section

NMR spectra were recorded on a 300-MHz spectrometer. Alkoxysilanes **3a**−**c** were synthesized with the respective alcohol, TMSCl, and triethylamine in solvent.[11] Other TMS compounds were obtained from commercial sources. Dry CH_2Cl_2 was purchased from a commercial supplier.

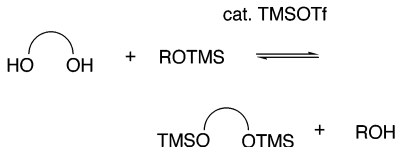
General Procedure for Acetalization. To a mixture of ketone (0.672 mmol), diol (0.862 mmol), and TMS-source (2.68 mmol) in dry CH_2Cl_2 (10 mL) was added TMSOTf (0.007 mmol) at −20 °C under argon atmosphere. The reaction mixture was stirred for 3 h, treated with pyridine (0.5 mL) and evaporated under reduced pressure to a residue that was purified by silica gel chromatography to afford acetal.

TABLE 2.



Entry	TMS-source	Time	Isolated yield (%)
1	**3a**	3h	98
2	**3b**	3h	96
3	**3c**	3h	97
4	**3d**	3h	93
5	**3e**	16h	88
6	**3f**	6h	trace
7	**3g**	3h	98
8	**3h**	3h	98

SCHEME 1



The acetals **4b**,[12] **4d**,[13] **4f**,[14] **4g**,[15] **4h**,[16] **4i**,[15] **4j**,[17] **4k**,[3a] **4l**,[3b] **4m**,[4b] and **4p**[18] were identified by comparison with the literature known NMR data.

(8) (a) Mukaiyama, T.; Shiina, I.; Miyashita, M. *Chem. Lett.* **1992**, 625−628. (b) Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1992**, 2319−2320.
(9) Mukaiyama, T.; Izumi, J.; Miyashita, M.; Shiina, I. *Chem. Lett.* **1993**, 907−910.
(10) (a) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379−1382. (b) Tietze, L.-F.; Fischer, R.; Guder, H.-J. *Tetrahedron Lett.* **1982**, *23*, 4661−4664.
(11) Trimethylisopropoxysilane is commercially available from Shin-etsu silicon Chemicals.
(12) Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1991**, *47*, 5877.
(13) Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955.
(14) Davies, S. G.; Goodfellow, C. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 393.
(15) Normant, J. F.; Alexakis, A.; Ghribi, A.; Mangeney, P. *Tetrahedron* **1989**, *45*, 507.

6-Phenyl-1,4-dioxaspiro[4,5]decane (4a). ^{1}H NMR ($CDCl_3$) δ 1.62−1.88 (8 H, m), 2.51−2.60 (1 H, m), 3.98 (4 H, s), 7.15−7.31 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 31.50, 35.10, 43.29, 64.24, 64.28, 108.46, 126.82, 128.29, 146.52. HRMS (FAB) calcd for $C_{14}H_{19}O_2$ (M^+ + H) 219.1385, found 219.1378.

9-Phenyl-1,5-dioxaspiro[5,5]undecane (4c). ^{1}H NMR ($CDCl_3$) δ 1.48 (2 H, m), 1.62−1.81 (6 H, m), 2.40 (2 H, m), 2.56 (1 H, m), 3.92 (2 H, t, J = 5.6 Hz), 3.97 (2 H, t, J = 5.6 Hz), 7.15−7.32 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 25.70, 29.95, 32.98, 43.90, 59.12, 59.41, 97.36, 125.99, 126.85, 128.29, 146.63. HRMS (FAB) calcd for $C_{15}H_{21}O_2$ (M^+ + H) 233.1542, found 233.1542.

Hexahydro-4′-phenyl-*trans*-spiro[1,3-benzodioxole-2,1′-cyclohexane] (4e). ^{1}H NMR($CDCl_3$) δ 1.29 (2 H, m), 1.44 (2 H, m), 1.66−1.99 (10 H, m), 2.15 (2 H, m), 2.57 (1 H, m), 3.31 (2 H, m), 7.15−7.31 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 23.75, 29.02, 31.05, 31.80, 35.90, 37.11, 43.38, 79.74, 80.08, 108.46, 125.97, 126.91, 128.28, 146.67. HRMS (FAB) calcd for $C_{18}H_{25}O_2$ (M^+ + H) 273.1855, found 273.1858.

Benzyl 1,4-Dioxa-7-azaspiro[4,5]decane-7-carboxylate (4n). ^{1}H NMR ($CDCl_3$) δ 1.74 (4 H, s), 3.43 (4 H, m), 3.95 (4 H, m), 5.43 (2 H, s), 7.34 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 22.85, 33.96, 43.68, 49.61, 49.79, 64.52, 66.99, 105.31, 127.72, 127.82, 128.15, 136.76, 155.46. HRMS (FAB) calcd for $C_{15}H_{20}O_4$ (M^+ + H) 278.1392, found 278.1393.

Acetalization with Solid Surported TMS-Source. Wang resin (0.6−1.0 mmol/g) 5 g was treated with TMSCl (6 mmol) and Et_3N (6.5 mmol) in CH_2Cl_2 (40 mL), and then washed with CH_2Cl_2 and dried. 3-Phenylcyclohexanone (0.1 mmol) was treated with ethylene glycol (0.12 mmol), silylated resin **3h** (500 mg), and a catalytic amount of TMSOTf in CH_2Cl_2 at −20 °C for 3 h. The reaction mixture was filtered and purified by silica gel chromatography.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **4d**, **4f**, **4g**, **4h**, **4i**, **4j**, **4k**, **4l**, **4m**, and **4p**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO020471Z

(16) Suginome, H.; Wang, J. B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2825.
(17) Arnold, D. R.; Lamout, L. J.; Perrott, A. L. *Can. J. Chem*. **1991**, *69*, 225.
(18) Hernandez, A.; Marcos, M.; Rapoport, H. *J. Org. Chem*. **1995**, *60*, 2683.