COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Silazanes/catalytic bases: mild, powerful and chemoselective agents for the preparation of enol silyl ethers from ketones and aldehydes

Yoo Tanabe,* Tomonori Misaki, Minoru Kurihara, Akira Iida and Yoshinori Nishii
Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan

Received (in Cambridge, UK) 18th April 2002, Accepted 5th June 2002
First published as an Advance Article on the web 28th June 2002

We have developed an efficient method for the preparation of enol silyl ethers using novel agents, silazanes together with NaH or DBU catalyst, wherein TMS and TBDMS groups were smoothly and chemoselectively introduced into ketones and aldehydes under mild conditions.

Enol silyl ethers are widely employed as reactive precursors for carbonyl compounds in a wide range of organic syntheses, for various regio-, chemo- and stereoselective reactions.[1] Conventional preparations of enol silyl ethers use chlorosilanes with amine (*e.g.* Et_3N) and amide (*e.g.* LDA) agents.

Despite these two well-established methods, there still remains a need for an alternative method with improved efficiency, that is, for an elaborate and practical scale synthesis from a recent recognized standpoint of green chemistry.

All previously reported methods require more than equimolar amounts of the bases to generate the enolate anion and/or to capture HCl, except for the method using TMS–acetate/cat. TBAF,[2] which is not applicable to reactions with aldehydes due to the predominant aldol addition of TMS–acetate with aldehydes. In connection with the interest of mild, powerful silylations of alcohols by specific catalytic promoters,[3] we present an efficient method for preparing enol silyl (TMS and TBDMS) ethers applicable to both ketones and aldehydes using a novel agent; available silazanes **1**, **2**, **3** with catalytic NaH for ketones and with catalytic DBU for aldehydes (Scheme 1).

Table 1 lists the results for the ketones. Salient features are as follows. (a) Among the commercially available *N*-(TMS)amines screened, *N*-methyl-*N*-(TMS)acetamide (**1**) gave the best result.† (b) Unreactive α,α-disubstituted and α-chloro ketones, and labile α,β-unsaturated ketones could be converted under mild and practical conditions. (c) Both polar DMF and hydrophobic cyclohexane solvents were available. (d) Enol TBDMS-ethers were obtained by the use of available *N*,*O*-bis(TBDMS)acetamide (**2**). (e) On the regiochemistry, thermodynamic controlled products were generally obtained.

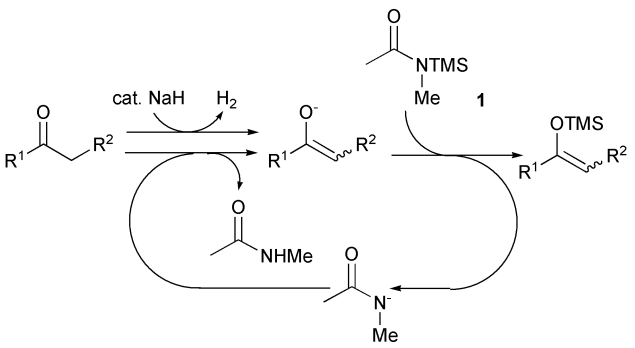
Although the silyl halide method requires a slightly tedious work-up procedure to remove HX and/or HX·amine because enol silyl ethers are susceptible to such acids, the present nearly neutral method has a practical advantage of easy isolation of enol silyl ethers.‡ Regarding the reactivity, parallel experiments of unreactive diisopropyl ketone demonstrated that the present method is considered to surpass the two methods that use conventional TMSCl–Et_3N under identical conditions (for 0.5 h; conversion yield; 100% and 0%, respectively).

A plausible reaction mechanism is proposed in Scheme 2 as exemplified by the use of **1**. First, catalytic NaH deprotonates a ketone to form the enolate, which is trapped with **1** to furnish the enol silyl ether while releasing the amidate anion. The anion, in turn, deprotonates a ketone to reform the enolate, thus completing the catalytic cycle.

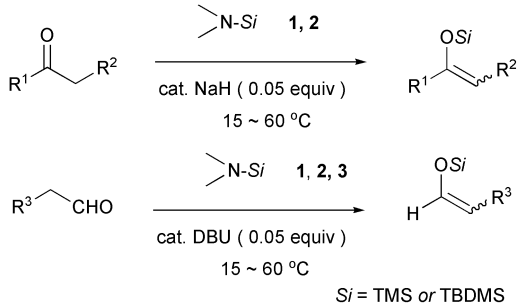
We attempted to extend this work to aldehydes, because there are few general methods that cover both ketones and aldehydes. The NaH catalysis system, however, resulted in polymerization of aldehydes. After screening milder amine–base catalysts, such as Et_3N, pyridine, TMEDA, *etc.*, only DBU successfully converted aldehydes into the desired enol silyl ethers (TMS and TBDMS) (Table 2).§ Salient features are as follows. (a) Similar to the case of ketones, among the same *N*-(TMS)amines screened, *N*-methyl-*N*-(TMS)acetamide (**1**) gave the best results. (b) For preparation of enol TBDMS ethers, *O*-(TBDMS)benzamide[3c] (**3**; *Si*-BEZA) was slightly better than *N*,*O*-bis(TBDMS)acetamide (**2**). (c) DMF solvent was better than cyclohexane. (d) Several aldehydes, including an α,β-unsaturated aldehyde, 2-methylpentenal, were applicable.

A notable aspect of the present protocol is the highly chemoselective conversion of aldehydes compared to ketones (Scheme 3).

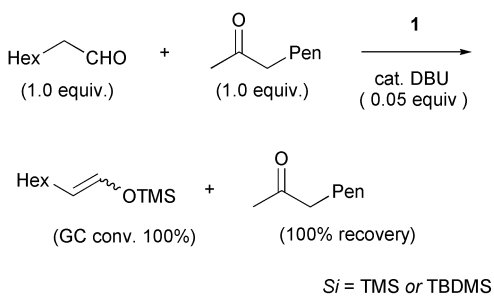
In conclusion, we have developed a new type of mild, practical, chemoselective method for preparing various enol silyl ethers using neutral silazanes and catalytic bases.



Scheme 2



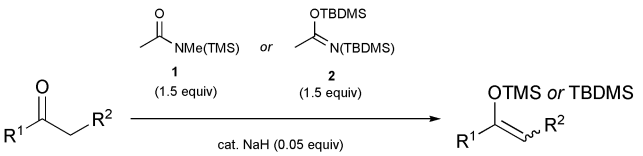
Scheme 1

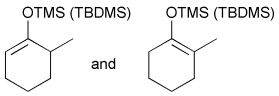
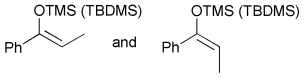
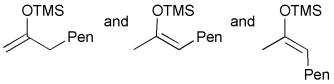
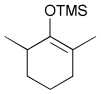
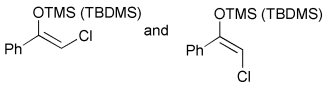
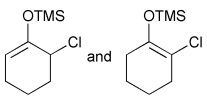
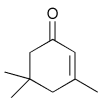
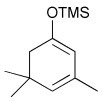
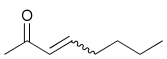
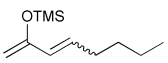


Scheme 3

DOI: 10.1039/b203783c

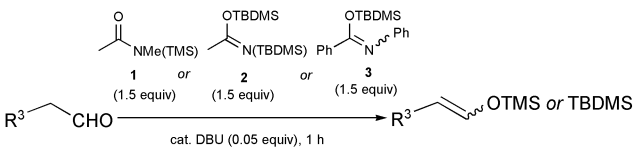
Table 1 Preparation of enol silyl ethers from ketones using silazanes **1** and **2**/cat. NaH

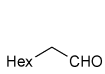
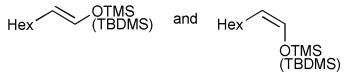
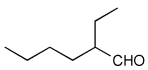
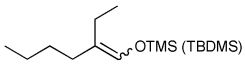
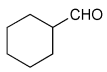
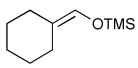
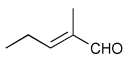
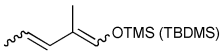


Ketone	Silazane	Conditions[a]	Product yield/%[b] (Ratio)[c]
			
	1	A	84 (18:82)
	1	B	94 (57:43)
	2	C	77 (24:76
			
	1	A	87 (98:2)
	1	B	94 (98:2)
	2	C	95 (95:5)
			
	1	A	84 (16:60:24)
	1	B	90 (15:64:21)
			
	1	D	94
			
	1	A	96 (99:1)
	1	B	trace
	2	A (8 h)	88 (99:1)
			
	1	A	84 (10:90)
			
	1	A	81
	1	B	88
			
	1	B	72

[a] A: In DMF at 15–20 °C for 0.5–1.0 h. B: In cyclohexane at 15–20 °C for 0.5–1.0 h. C: In DMF at 60 °C for 1.0–2.0 h. D: In cyclohexane at 60 °C for 0.5 h. [b] Isolated yields (100% GC conversions). [c] GLC and/or ^{1}H NMR analysis.

Table 2 Preparation of enol silyl ethers from aldehydes using silazanes **1**, **2** and **3**/cat. DBU



Aldehyde	Silazane	Conditions[a]	Product yield/%[b] (Ratio)
			
	1	A	86 (23:77)[c]
	1	B	58 (43:57)[c]
	2	C	65 (39:61)[c]
	3	C	89 (38:62)[c]
			
	1	A	96[d]
	3	C	94[d]
			
	1	A	96
			
	1	A	70[d]
	3	C	92[d]

[a] A: In DMF at 15–20 °C. B: In cyclohexane at 15–20 °C. C: In DMF at 60 °C. [b] Isolated yields (100% GC conversions). [c] GLC analysis. [d] *E*/*Z* ratios were not determined.

This research was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) ″Exploitation of Multi-Element Cyclic Molecules″ and on Basic Areas (C) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

† *N*-(TMS)imidazaole (under the identical conditions of Table 1, entry 1; 55%), *N*,*O*-bis(TMS)acetamide (78%), *N*-methyl-*N*-(TMS)trifluoroacetamide (3%), *N*-(TMS)morpholine (trace), *N*-(TMS)aniline (trace), *N*,*O*-bis(TMS)hydroxylamine (trace).

‡ Typical procedure of the gram-scale experiment for ketones: *N*-methyl-*N*-(TMS)acetamide (**1**; 8.72 g, 60.0 mmol) was added to a stirred suspension of 2,6-dimethylcyclohexane (5.05 g, 40.0 mmol) and NaH (48 mg, 2.0 mmol) in cyclohexane (40 cm^3) at 15–20 °C and the mixture was stirred for 1 h. Cool water (40 cm^3) was added to the mixture, which was extracted with hexane (20 cm^3 × 2). The combined organic phase was washed with water (40 cm^3), brine, dried (Na_2SO_4), concentrated and distilled to give the desired product (colorless oil; bp 49–50 °C, 1.8–2.2 mmHg; 7.54 g, 94%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.17 (9H, s), 1.04 (3H, d, J = 6.8 Hz), 1.32–1.39 (1H, m), 1.41–1.50 (1H, m), 1.54–1.55 (3H, m), 1.56–1.66 (1H, m), 1.74–1.81 (1H, m), 1.92–1.96 (2H, m), 2.07–2.17 (1H, m). ^{13}C NMR (100 MHz; $CDCl_3$): δ 0.60, 16.81, 18.93, 20.46, 30.78, 32.24, 34.05, 112.01, 147.02.

§ Typical procedure of gram-scale experiment for aldehydes: *N*-methyl-*N*-(TMS)acetamide (**1**; 8.72 g, 60.0 mmol) was added to a stirred solution of octanal (5.13 g, 40.0 mmol) and DBU (305 mg, 2.0 mmol) in DMF (40 cm^3) at 20–25 °C and the mixture was stirred for 1 h. The mixture was extracted with pentane and the separated pentane phase was washed with cool water, and brine, dried (Na_2SO_4), concentrated and distilled to give the desired product [colorless oil; bp 49–53 °C (oven temp. of Kügelrohr)/0.8 mmHg; 6.63 g, 83 %, *E*/*Z* = 20/80 determined by GLC and ^{1}H NMR]. ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.18 (9H, s), 0.88 (3H, t, J = 6.8 Hz), 1.22–1.36 (8H, m), 1.84–1.91 (0.43H, m), 2.01–2.12 (1.57H, m), 4.46–4.51 (0.80H, m), 4.96–5.02 (0.20H, m), 6.12–6.15 (0.80H, m), 6.17–6.20 (0.20H, m).

1 E. W. Colvin, *Silicon in Organic Synthesis*, Butterworths, London, 1981, pp. 198–287; M. B. Smith and J. March, *March's Advanced Organic Chemistry*, 5th ed., Wiley, New York, 2001, p. 793; J. K. Rasmussen, *Synthesis*, 1977, 91; P. Brownbridge, *Synthesis*, 1983, 85; I. Fleming, A. Barbero and D. Walter, *Chem. Rev.*, 1997, **97**, 2063; A. M. El-Khawaga and H. M. R. Hoffmann, *J. Pract. Chem.*, 1995, **337**, 332.

2 E. Nakamura, T. Murofushi, M. Shimizu and I. Kuwajima, *J. Am. Soc. Chem.*, 1976, **98**, 2346.

3 (*a*) Y. Tanabe, M. Murakami, K. Kitaichi and Y. Yoshida, *Tetrahedron Lett.*, 1994, **35**, 8409; (*b*) Y. Tanabe, H. Okumura, A. Maeda and M. Murakami, *Tetrahedron Lett.*, 1994, **35**, 8413; (*c*) T. Misaki, M. Kurihara and Y. Tanabe, *Chem. Commun.*, 2001, 2478.