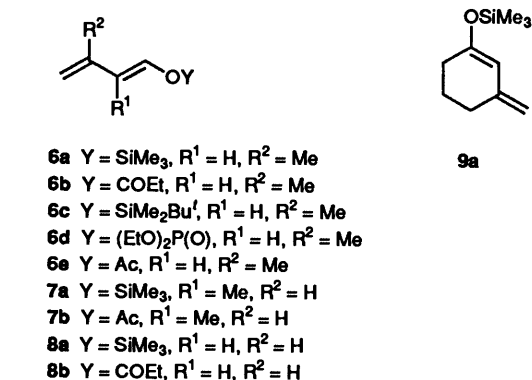
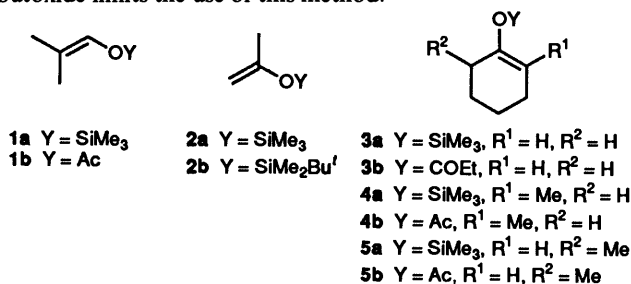


Unprecedented Route to Enolates from Silyl Enol Ethers and Enol Acetates: Reaction with Hard and Soft Electrophiles

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Reaction of silyl enol ethers with lithium, sodium or, better, potassium alkoxides resulted in a rapid formation of enolates which were trapped with hard electrophiles and benzaldehyde. Moreover, in the aldolisation reaction, only a catalytic amount of alkali alkoxide is needed. This methodology is also applied to enol acetate. During these reactions a non-basic species, ether or ester, is produced with the enolate.

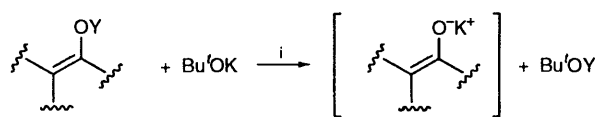
Since the pioneering work of Stork¹ and House^{2a,b} on the formation of enolates by cleavage of silyl enol ethers with methylolithium, this method has classically been used in synthetic organic chemistry. In some cases enolates can be prepared from silyl enol ethers in the presence of alkali amides (potassium, sodium and especially lithium) in a mixture THF-NH₃.³ Tetraalkylammonium fluoride such as tetrabutylammonium fluoride (TBAF) was also used in catalytic amount to prepare enolates from silyl enol ethers.⁴ Tris(diethylamino)sulfonium enolates have also been obtained from silyl enol ethers and tris(diethylamino)sulfonium difluorotrimethylsiliconate.⁵ Recently tetrabutylammonium difluorophenylstannate has been used as an anhydrous TBAF equivalent.⁶ The Stork method has been extended to the silyl dienol ether **6a** (prepared from prenal) and we have shown that the aldol reaction only takes place on the γ -site of the dienolate.⁷ Enol acetates are also considered as precursors of enolates by treating these compounds with 2 equiv. of methylolithium² but the simultaneous formation of the strongly basic lithium *tert*-butoxide limits the use of this method.



In the present communication, we report an unprecedented route to enolates from silyl enol ethers by cleavage of compounds **1a–9a** in the presence of alkali alkoxides (especially the potassium *tert*-butoxide). In the same manner, the enol acetate **6e** leads to enolate without formation of basic species

(Scheme 1). The enolates were treated with two types of electrophiles: hard electrophiles to show the effective preparation of the enolates and benzaldehyde for the aldol reaction.

The silyl enol ethers **1a–4a** and **6a–9a** were classically prepared from the corresponding carbonyl compounds by treatment of these compounds with Me₃SiCl-NEt₃ in the presence of NaI in acetonitrile.⁸ The silyl enol ether **5a** was obtained according to a



Y = SiMe₃, Ac

Scheme 1 Conditions: i, THF, -78 °C to -20 °C

literature procedure.² The silyl enol ethers **1a–8a** were treated with 1 equiv. of potassium *tert*-butoxide at low temperature in THF. For all the silyl enol ethers used, the reaction time required to obtain complete cleavage is ≤ 60 min (Table 1), as shown by the yields obtained for the reaction of the enolates so prepared with acetyl chloride (entries 1, 4, 5, 9), propionyl chloride (entries 3, 6, 10), *tert*-butyldimethylsilyl chloride (entries 2,7) or diethyl chlorophosphate (entry 8). The kinetic enol ether **5a** (regioisomeric purity 99:1) only leads to the kinetic enol acetate **5b** with the same regioisomeric ratio (entry 5).

As shown in Table 1, the silyl enol ethers **2a–5a** (entries 2–5) prepared from ketones needed a higher reaction temperature than the silyl enol ethers **1a, 6a–8a** (entries 1, 6–10) obtained from aldehydes. This result may be due to an easier attack of the silicon atom by the alkoxide anion due to a less hindered reaction site. We think that a five-coordinated silicon species is the first intermediate of the reaction pathway, this possibility is now under investigation.

To prepare the enolate, a strongly basic reagent was used but after the cleavage of the silyl enol ether the alkoxide was transformed into the silyl ether which cannot give secondary reactions.

At this stage we decided to try some other alkoxides with the silyl enol ether **6a** to see if the cleavage was dependent on the alkali metal used and/or on the nature of the alkoxide. For this purpose, benzaldehyde was used as the electrophile; results are summarized in Table 2.

The obtention of the dihydropyran **10a** is consistent with a γ -addition of the dienolate of prenal on the benzaldehyde followed by an intramolecular attack of the alkoxide on the carbonyl group leading, after subsequent hydrolysis, to compound **10a**† (Scheme 2).

† A hetero Diels-Alder reaction cannot be totally excluded despite the reaction conditions.

Table 1 Preparation of enolates from silyl enol ethers and potassium *tert*-butoxide. Reaction with hard electrophiles

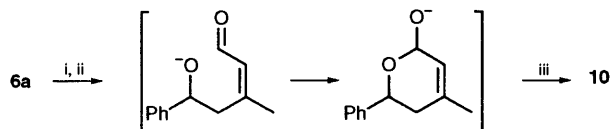
Entry	Starting silyl enol ether	Cleavage		Electrophile ^a	Reaction product	Yield (%) ^b
		Temp. (°C)	Time (min)			
1	1a	-50	45	MeCOCl	1b	72
2	2a	-30	40	Bu ^t Me ₂ SiCl	2b	74
3	3a	-20	45	EtCOCl	3b	79
4	4a	-20	45	MeCOCl	4b	85
5	5a	-20	40	MeCOCl	5b	84
6	6a	-78	60	EtCOCl	6b	94
7	6a	-78	60	Bu ^t Me ₂ SiCl	6c	90
8	6a	-78	60	(EtO) ₂ P(O)Cl	6d	86
9	7a	-78	60	MeCOCl	7b	84
10	8a	-78	60	EtCOCl	8b	91

^a 1 equiv. of electrophile was added to the enolate solution at -78 °C, and after a reaction period of 15 min the mixture was quenched with saturated aqueous NaHCO₃. ^b Yield of purified product by flash chromatography.

Table 2 Aldolisation products obtained from the silyl enol ether 6a and benzaldehyde

Entry	ROM	Equiv.	Reaction time (min)	Yield ^a (%) of			Total yield ^a (%)
				10a	10b	11	
1	Bu ^t OK ^b	1	10	86			86
2	Bu ^t ONa ^b	1	15	72			72
3	MeONa ^b	1	15	74			74
4	Bu ^t OLi ^b	1	15	42		28	70
5	MeOLi ^b	1	15	46		32	78
6	PhCH ₂ OLi ^b	1	15	41		28	69
7	Bu ^t OK ^c	0.1	30	14	68		82
8	Bu ^t OK ^c	0.01	60	33	48		81

^a Yield of isolated product, purified by flash chromatography. ^b After 1 h at -78 °C (unoptimised time) 1 equiv. of benzaldehyde was added to the reaction mixture which, after a specific time, was quenched with water. ^c The benzaldehyde was added to the reaction mixture after 15 min at -78 °C.



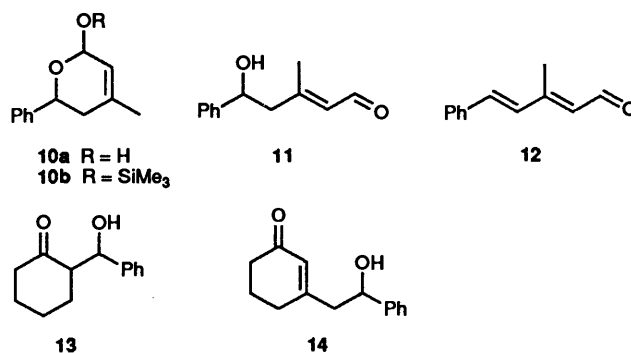
Scheme 2 Reagents and conditions: i, ROM (Table 2), THF; ii, PhCHO, -78 °C; iii, H₂O, -78 °C

All the alkoxides lead to cleavage of the silyl enol ether 6a. Comparison of the entries 1, 2 and 4 shows some differences between the three alkali metals used. Potassium and sodium *tert*-butoxide (entries 1, 2) lead to the dihydropyran 10a in a slightly higher yield for the former. Lithium *tert*-butoxide, under the same reaction conditions (entry 4) yields the dihydropyran 10a and the hydroxy enaldehyde 11.* A similar result has been obtained with the three lithium alkoxides (entries 4–6). The less basic sodium methoxide (entry 3) gave the same result as sodium *tert*-butoxide. The total yield is not significantly different between the sodium and lithium alkoxides. The result obtained with lithium alkoxide, leading partially to the enaldehyde 11, could be due to the more covalent nature of the intermediate lithium alcoholate which prevents its isomerisation. It is noteworthy that the dihydropyran 10a and the enaldehyde 11 can be transformed into the polyenaldehyde 12 by acidic treatment⁷ in 90% yield.

In some cases, traces of product 10b were detected, a result we believe of cleavage of the silyl enol ether 6a by the anion of dihydropyran 10a. Effectively, when using a catalytic amount (0.1 to 0.01 equiv.) of potassium *tert*-butoxide, the reaction time with the electrophile is a little higher but the total yield is close to that obtained for 1 equiv. (entries 1 and 7, 8). The silyl

dihydropyran 10b is present, but not in the expected yield, due to its high hydrolysis ability.†

Some other silyl enol ethers have been used for the aldolisation reaction. The enolates produced after cleavage by potassium *tert*-butoxide were allowed to react with benzaldehyde when the following aldol products were prepared: 13 (75% yield) from 3a, 14 (58% yield) from 9a. A 2:3 *erythro:threo* ratio for the aldol product 13 was determined by ¹H NMR spectroscopy, a ratio similar to that obtained by Kuwajima *et al.* with the use of TBAF.⁴



Finally, we have tried to cleave the enol acetate 6e under the same reaction conditions. With the benzaldehyde, compound 10a was obtained in 81 and 85% yield respectively with 1 equiv. of potassium *tert*-butoxide and 1 equiv. of sodium methoxide. Our results with this enol acetate have shown that this reaction is possible and that, in this case also, a non-basic species is

* The hydroxy aldehyde 11 is present as a single *E* isomer.

† To obtain compound 10b the hydrolysis must be done with basic water (pH ≥ 12).

produced (Scheme 1) contrariwise to the reaction of methyl-lithium with enol acetate.² The reaction of enol acetates and methyl-lithium is well documented² and in all cases 2 equiv. of methyl-lithium are used, one for the preparation of the enolate and the other to react with the acetone produced, leading to lithium *tert*-butoxide. Considering our result, we have supposed that the second equiv. of methyl-lithium was unnecessary since the lithium *tert*-butoxide generated was also able to cleave the enol acetate. Effectively, the use of only 1 equiv. of methyl-lithium with the enol acetate **6e** leads with benzaldehyde to a 69% yield of the dihydropyran **10a** and a 17% yield of the enaldehyde **11** (total yield: 86%).

In conclusion, we have shown that the enolates can be rapidly and quantitatively generated from either silyl enol ethers or enol acetate by treatment with an alkali alkoxide (in commercially or sublimed form). This process can be applied to a large variety of structures since the reaction was performed with silyl enol ethers of aldehyde, ketone, enaldehyde or enone. When used for aldolisation reactions, only a catalytic amount of alkali alkoxides was needed since the aldol anion was able to cleave enol ethers. The use of easy to handle reagents is also advantageous for the utilisation of this process for the generation of enolates.

Experimental

The silyl enol ethers^{2,8} and enol acetates² were obtained according to literature procedures.

General Procedure for the Generation of Enolates and Reaction with Hard Electrophiles: Synthesis of Enol Phosphate 6d (Table 1, Entry 8).—A solution of potassium *tert*-butoxide (10 mmol) in THF (10 cm³) was added to a stirred solution of the silyl enol ether **6a** (10 mmol) in THF (15 cm³) at -78°C under nitrogen and the mixture was stirred at this temperature for 60 min. After this a solution of diethyl chlorophosphate (10 mmol) in THF (5 cm³) was added to it. After 15 min the mixture was quenched at -78°C with a saturated aqueous NaHCO₃ (10 cm³) and extracted with Et₂O. The extract was dried (MgSO₄) and evaporated under reduced pressure and the crude product was purified by flash chromatography on silica gel (Et₂O–light petroleum, 10:90); δ_{H} (200 MHz, CDCl₃) 1.28 (dt, 6 H, *J* 6.7, *J*_{PH} 0.9), 1.74 (s, 3 H), 4.08 (dq, 4 H, *J* 6.7, *J*_{PH} 7.1), 4.81 (m, 2 H), 6.04 (d, 1 H, *J* 12) and 6.57 (dd, 1 H, *J* 12, *J*_{PH} 6.2); δ_{C} (50 MHz, CDCl₃) 15.9 (d, CH₃, *J*_{PC} 6.1), 18.6 (CH₃), 64.3 (d, CH₂, *J*_{PC} 4.8) and 137.8 (C=); δ_{P} (81 MHz, CDCl₃) 7.9 (m) (Found: C, 49.3; H, 7.9. C₉H₁₇O₄P. Calc. for 49.09; H, 7.78%).

General Procedure for Aldolisation Reaction.—With 1 equiv. of alkoxide: synthesis of the dihydropyran **10a** (Table 2, entry 1). A solution of potassium *tert*-butoxide (10 mmol) in THF (10 cm³) was added to a stirred solution of the enol ether **6a** (10 mmol) in THF (15 cm³) at -78°C and the mixture was stirred for 60 min. After this, benzaldehyde (10 mmol) in THF (5 cm³) was added to the mixture which was then stirred for 10 min at -78°C . It was then quenched with water (10 cm³) and extracted with Et₂O. The extract was dried (MgSO₄), concentrated and purified by flash chromatography on silica gel (Et₂O–light petroleum, 15:85); δ_{H} (200 MHz, C₆D₆) 1.76 (s, 3 H), 2.06

(dd, 1 H, *J* 3.4, 17.3), 2.26 (dd, 1 H, *J* 11.3, 17.3), 2.9 (m, OH), 4.98 (dd, 1 H, *J* 3.4, 11.3), 5.50 (m, 1 H), 5.59 (m, 1 H) and 7.34 (m, 5 H) (Found: C, 75.7; H, 7.5. Calc. for: C₁₂H₁₄O₂: C, 75.76; H, 7.42%).

With the same procedure, use of lithium alkoxide gave the dihydropyran **10a** and the hydroxy enaldehyde **11** (Table 2, entries 4–6).

Hydroxy enaldehyde **11**; ν_{max} (neat)/cm⁻¹ 1666 (C=O); δ_{H} (200 MHz, CDCl₃) 2.15 (s, 3 H), 2.50 (dd, 1 H, *J* 5.0, 14.1), 2.63 (dd, 1 H, *J* 8.5, 14.1), 2.70 (m, OH), 4.86 (dd, 1 H, *J* 5.0, 8.5), 5.86 (d, 1 H, *J* 8.1), 7.29 (m, 5 H) and 9.88 (d, 1 H, *J* 8.1) (Found: C, 75.7; H, 7.5. Calc. for: C₁₂H₁₄O₂: C, 75.89; H, 7.38%).

With a catalytic amount of alkoxide (Table 2, entries 7–8). The same procedure as described above was used except that the amount of alkoxide was less (1.0 or 0.1 mmol). After 15 min at -78°C benzaldehyde (10 mmol) was added to the mixture which was then stirred for 30 or 60 min. Subsequent work-up was carried out with aqueous NaOH (1 mol dm⁻³; 10 cm³).

Dihydropyran **10b**; δ_{H} (200 MHz, C₆D₆) 0.30 (s, 9 H), 1.46 (s, 3 H), 1.6–2.1 (m, 2 H), 4.50 (dd, 1 H), 5.48 (m, 1 H), 5.62 (m, 1 H) and 7.25 (m, 5 H) (Found: C, 68.65; H, 5.8. Calc. for C₁₅H₂₂O₂Si: C, 68.47; H, 5.87%).

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