Chemoselective aldol type condensation of silyl enol ethers and acetals in 5 mol dm^{-3} lithium perchlorate–diethyl ether

V. Geetha Saraswathy and S. Sankararaman *
Department of Chemistry, Indian Institute of Technology, Madras–600036, India

Acetals are efficiently and chemoselectively converted into the corresponding aldol ethers upon treatment with 1-trimethylsilyloxycyclohexene 2 in 5 mol dm^{-3} lithium perchlorate–diethyl ether (LPDE) at ambient temperature with moderate diastereoselectivity, whereas under the same conditions aldehydes and ketals fail to react with 2. The present method allows the acetal substitution to be carried out under neutral reaction and work up conditions. A mechanism involving the formation of an oxocarbenium ion intermediate from the acetal followed by nucleophilic addition of the silyl enol ether is proposed. The observed chemoselectivity is attributed to the mild Lewis acidity of the lithium ion in diethyl ether.

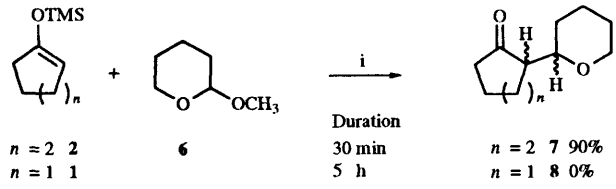
Nucleophilic substitution of acetals by silyl enol ethers to give aldol ethers is a useful C–C bond-forming reaction.[1] The reaction is generally carried out under strong Lewis-acidic conditions.[2] Although very high diastereoselectivities have been reported, the reactions seldom show any chemoselectivity.[2,3] For example, acetals from aldehydes as well as ketones react with equal facility to give the corresponding aldol ethers.

Recently, we have reported high chemoselectivity in the dithioacetalization of aldehydes and acetals over ketones and ketals in 5 mol dm^{-3} lithium perchlorate–diethyl ether (LPDE).[4] We have also reported the chemoselective Michael addition of silyl enol ethers to β-nitro- and β,β-dicyano-styrenes over α,β-unsaturated carbonyl compounds in this medium.[5] In the recent past the LPDE medium has been widely used to carry out a variety of reactions for which unusual rate enhancements and selectivities have been reported compared with the conventional methods.[6,7] Herein, we report our findings on the chemo- and stereo-selectivities of aldol-type condensations of silyl enol ethers with acetals in 5 mol dm^{-3} LPDE.

Results and discussion

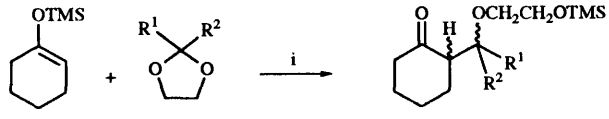
When an equimolar mixture of benzaldehyde dimethyl acetal **3a** and 1-trimethylsilyloxycyclohexene **2** was stirred in 5 mol dm^{-3} LPDE at ambient temperature for 10 min, the starting materials disappeared and the corresponding aldol ether **5a** was formed exclusively as a pair of diastereoisomers in the ratio 1.75:1. The results obtained from the substitution reaction of other acetals by silyl ethers **1** and **2** are summarized in Table 1, of which the following points are noteworthy. Silyl ether **2** was found to be more reactive than **1** towards various acetals. While the reactions of silyl ether **2** with aromatic and aliphatic acetals were equally facile, silyl ether **1** did not react with aromatic acetals even after a prolonged period. This is in sharp contrast to the conventional Lewis acid mediated aldol type condensation of acetals and silyl enol ethers in which such fine tuning of reactivity could not be observed.[2] The difference in the reactivity of **1** and **2** is also reflected in their reactions with 2-methoxytetrahydropyran **6**. While silyl ether **2** reacted with **6** to give the aldol ether **7** in 90% yield within 30 min, silyl ether **1** failed to react even after 5 h (Scheme 1). The difference in reactivity between **1** and **2** can be explained by invoking larger I strain associated with the 5-membered ring on going from sp^2 to sp^3 hybridization which is favourable in the case of a six-membered ring.[8] From the results presented in Table 1 and Scheme 1 it is evident that the 5 mol dm^{-3} LPDE medium offers a method for the chemoselective substitution of acetals by silyl enol ether **2** over silyl enol ether **1**.

Silyl ether **2** reacted with the cyclic acetal of benzaldehyde **9a**



Scheme 1 *Reagents and conditions:* i, 5 mol dm^{-3} LPDE, room temp.

in 5 mol dm^{-3} LPDE to give aldol ether **10a** in 60% yield as a pair of diastereoisomers in the ratio 1.3:1. In sharp contrast, cyclic acetals **9b** and **9c** obtained from the corresponding ketones failed to react with **2** under identical conditions even after a prolonged period (Scheme 2). These results suggest that



		R^1	R^2	Duration		
2	9a	Ph	H	30 min	10a	60%
	9b	Ph	Me	24 h	10b	0%
	9c	$PhCH_2$	$PhCH_2$	24 h	10c	0%

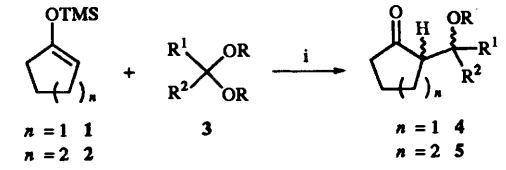
Scheme 2 *Reagents and conditions:* i, 5 mol dm^{-3} LPDE, room temp.

the chemoselective substitution of acetals in preference to ketals is possible in 5 mol dm^{-3} LPDE medium. In fact, a competitive experiment involving an equimolar mixture of **9a** and **9b** with excess of **2** in the LPDE medium led to the formation of only **10a**, while **9b** was recovered unreacted.

Though acetals are highly reactive receptors of silyl enol ether **2**, remarkably, the parent aldehydes do not react with **2** in 5 mol dm^{-3} LPDE. Attempted reaction of **2** with benzaldehyde, 4-methoxy-, 4-nitro- and 3,4-dimethoxy-benzaldehyde, -isobutyraldehyde and -cinnamaldehyde in 5 mol dm^{-3} LPDE resulted in the recovery of the starting materials. This is in sharp contrast to the dithioacetalization reactions reported[4] earlier wherein both aldehydes and acetals could be activated in 5 mol dm^{-3} LPDE in the presence of more powerful thiol nucleophiles.

The mechanism of the Lewis acid mediated nucleophilic substitution of acetals has been the subject of intensive investigation.[9] The substitution could proceed either directly by an S_N2 mechanism or through the initial formation of an oxocarbenium ion intermediate by an S_N1 mechanism, after the initial coordination of Lewis acid to the acetal. Recently, we have presented evidence for the formation of oxocarbenium ion

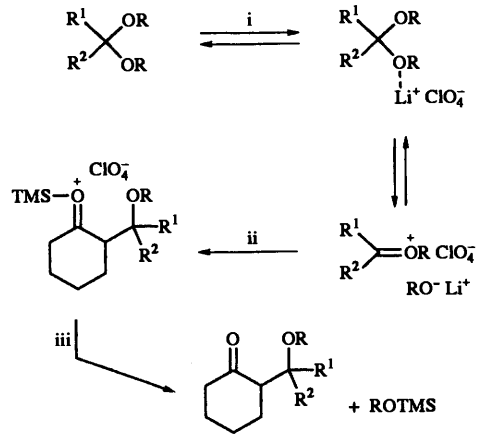
Table 1 Substitution of acetals by silyl enol ethers in 5 mol dm^{-3} LPDE



Reagents and conditions: i, 5 mol dm^{-3} LPDE, room temp.

Enol ether	Acetal				Product	Duration	Yield (%)[a]	Ratio of diastereoisomers[b]
		R^1	R^2	R				
2	3a	Ph	H	Me	5a	10 min	81	1.75:1
2	3b	4-$MeOC_6H_4$	H	Et	5b	10 min	70	2.3:1
2	3c	PhCH=CH	H	Et	5c	15 min	85	2.0:1
2	3d	Me_2CH	H	Et	5d	10 min	95	1.5:1
2	3e	$Me(CH_2)_2$	H	Me	5e	30 min	85	—
2	3f	Me	Me	Me	5f	1 h	90	—
1	3a				4a	24 h	0	—
1	3b				4b	24 h	0	—
1	3d				4d	1 h	90	2.0:1
1	3e				4e	1 h	90	—
1	3f				4f	24 h	30[c]	—

[a] Isolated yield after purification. [b] From the peak integration of 400 MHz ^1H NMR spectra of the product. [c] Remainder was starting material.



Scheme 3 *Reagents and conditions:* i, 5 mol dm^{-3} LPDE; ii, 1-trimethylsilyloxycyclohexene; iii, $RO^- Li^+$

intermediates from acetals in 5 mol dm^{-3} LPDE[4] and on that basis we propose the mechanism depicted in Scheme 3 for the acetal substitution. The Lewis acidity of the lithium ion combined with the high ionic strength of the 5 mol dm^{-3} LPDE medium would favour the ionization of the acetal and formation of an oxocarbenium ion intermediate.

The chemoselectivity observed in the substitution of acetals over ketals by silyl enol ethers could be attributed to the moderate Lewis acidity of the lithium ion combined with the steric factors associated with the substitution of ketals. Compared with conventional Lewis acids such as BF_3, $TiCl_4$, *etc.*, a lithium ion in ether is a mild Lewis acid even though the gas phase Lewis acidity of the lithium ion is much higher.[10] Finally, the acetal substitution in 5 mol dm^{-3} LPDE led to only moderate diastereoselectivity compared with high diastereoselectivity reported using strong Lewis acids.

Experimental

Materials

Acetals **3a**,[9a] **3b–e**,[11] **9a–c**[12] and silyl enol ethers **1** and **2**[13] were prepared according to literature methods and were characterized by IR, ^1H NMR and mass spectral data. Preparation of 5 mol dm^{-3} LPDE has been described previously.[4] The products **4e–f**,[2b] **5a**[2a,b] and **5d–f**[2a] have been reported previously and they were characterized by IR, ^1H NMR and ^{13}C NMR spectroscopy, MS and HRMS data in the present study. The instrumentation used has been described previously.[14] Coupling constants (J) are quoted in Hz.

Typical procedure for the substitution of acetals by silyl enol ether

Silyl enol ether **2** (0.34 g, 2 mmol) was taken up in LPDE (5 mol dm^{-3}; 3 cm^3) and acetal **3a** (0.3 g, 2 mmol) was added from a syringe under nitrogen atmosphere at ambient temperature. The mixture was stirred at room temperature and the reaction followed by TLC. After the starting materials disappeared (Table 1), the reaction mixture was diluted with CH_2Cl_2 (15 cm^3) and then water was added. The aqueous and organic layers were separated and the aqueous layer was repeatedly extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated to give the crude product. This was purified by preparative TLC over silica gel using benzene as the eluent to furnish the aldol ether **5a** in 81% yield as a pair of diastereoisomers in the ratio 1.75:1.

Spectroscopic characterization of products

2-[Ethoxy(4-methoxyphenyl)methyl]cyclohexanone 5b. Yield 70%, ratio of diastereoisomers 2.3:1; ν_{max}(neat)/cm^{-1} 2912s, 1708s (C=O), 1612s, 1510s; δ_H($CDCl_3$) isomer I: 7.22 (2 H, d, J 6.8), 6.85 (2 H, d, J 6.8), 4.75 (1 H, d, J 5.4), 3.78 (3 H, s), 3.35 (2 H, m), 2.7–1.5 (9 H, m), 1.14 (3 H, t, J 6.3); isomer II: 7.22 (2 H, d, J 6.8), 6.87 (2 H, d, J 6.8), 4.62 (1 H, d, J 8.3), 3.79 (3 H, s), 3.35 (2 H, m), 2.7–1.5 (9 H, m), 1.11 (3 H, t, J 6.8); δ_C($CDCl_3$) isomer I: 210.8 (s), 158.8 (s), 133.6 (s), 128.0 (d), 113.6 (d), 78.0 (d), 64.4 (t), 57.6 (d), 55.1 (q), 42.3 (t), 30.5 (t), 27.3 (t), 24.4 (t), 15.2 (q); isomer II: 211.4 (s), 159.2 (s), 132.2 (s), 128.7 (d), 113.5 (d), 79.5 (d), 64.0 (t), 57.4 (d), 55.1 (q), 42.0 (t), 31.8 (t), 28.5 (t), 24.2 (t), 15.2 (q); m/z (EI, 70 eV) 262 (M^+, 27%), 233 (12), 166 (34), 165 (100), 137 (98), 135 (61), 121 (27), 159 (47) (Found: M, 262.15798. $C_{16}H_{22}O_3$ requires M, 262.15696).

2-(1-Ethoxy-3-phenylprop-2-enyl)cyclohexanone 5c. Yield 85%, ratio of diastereoisomers 2:1; ν_{max}(neat)/cm^{-1} 2912s, 1728s (C=O), 1625s, 1449s, 1308s, 1059s; δ_H($CDCl_3$) isomer I: 7.3 (5 H, m), 6.57 (1 H, d, J 16.2), 6.18 (1 H, dd, J 15.6 and 6.8),

4.3 (1 H, apparent triplet, *J* 6.3), 3.6 (1 H, m), 3.4 (1 H, m), 2.8–1.5 (9 H, m), 1.18 (3 H, t, *J* 6.8); isomer II: 7.3 (5 H, m), 6.57 (1 H, d, *J* 16.2), 6.07 (1 H, dd, *J* 15.9 and 7.6), 4.3 (1 H, apparent triplet, *J* 6.3), 3.6 (1 H, m), 3.4 (1 H, m), 2.8–1.5 (9 H, m), 1.17 (3 H, t, *J* 7.3); $\delta_C(CDCl_3)$ isomer I: 210.7 (s), 136.7 (s), 131.3 (d), 129.2 (d), 128.5 (d), 128.4 (d), 126.5 (d), 77.5 (d), 64.6 (t), 55.9 (d), 42.3 (t), 28.0 (t), 27.3 (t), 24.4 (t), 15.3 (q); isomer II: 210.9 (s), 136.6 (s), 132.7 (d), 128.1 (d), 127.5 (d), 127.4 (d), 126.4 (d), 78.6 (d), 64.2 (t), 55.6 (d), 42.1 (t), 29.5 (t), 27.8 (t), 24.2 (t), 15.2 (q); *m/z* (EI, 70 eV) 258 (M^+, 22%), 229 (85), 208 (18), 162 (27), 161 (100), 135 (52), 133 (71), 131 (74), 115 (39), 104 (41), 92 (33), 77 (28) (Found M, 258.15865. $C_{17}H_{22}O_2$ requires *M*, 258.16198).

2-(1-Ethoxy-2-methylpropyl)cyclopentanone 4d. Yield 90%, ratio of diastereoisomers 2:1; ν_{max}(neat)/cm^{-1} 2944s, 1744s (C=O), 1644m, 1472m, 1260s, 960s; $\delta_H(CDCl_3)$ (mixture of isomers) 3.6–3.2 (3 H, m), 2.4–1.7 (7 H, m), 1.2–0.8 (10 H, m); $\delta_C(CDCl_3)$ isomer I: 221.6 (s), 83.7 (d), 67.7 (t), 51.3 (d), 39.2 (t), 32.2 (d), 23.5 (t), 21.2 (t), 19.2 (q), 15.7 (q); isomer II: 219.1 (s), 85.1 (d), 67.0 (t), 51.5 (d), 38.9 (t), 30.9 (d), 25.9 (t), 21.0 (t), 19.5 (q), 15.6 (q); *m/z* (EI, 70 eV) 141 ($M^+ - Me_2CH$, 100%), 138 (97), 123 (40), 113 (68), 85 (66), 82 (34).

2-[Phenyl(2-trimethylsilyloxyethoxy)methyl]cyclohexanone 10a. Yield 60%, ratio of diastereoisomers 1.3:1; ν_{max}(neat)/cm^{-1} 2928s, 1708s (C=O), 1452s, 1059s, 704m; $\delta_H(CDCl_3)$ isomer I: 7.3 (5 H, m), 5.11 (1 H, d, *J* 2.4), 3.8–3.3 (4 H, m), 2.8–1.5 (9 H, m), 0.008 (9 H, s); isomer II: 7.3 (5 H, m), 4.64 (1 H, d, *J* 9.2), 3.8–3.3 (4 H, m), 2.8–1.5 (9 H, m), 0.08 (9 H, s); $\delta_C(CDCl_3)$ isomer I: 212.3 (s), 139.3 (s), 128.3 (d), 127.5 (d), 126.7 (s), 77.7 (d), 70.4 (t), 61.6 (t), 57.1 (d), 42.4 (t), 31.4 (t), 25.7 (t), 24.8 (t), 0.0 (q); isomer II: 213.3 (s), 140.4 (s), 128.5 (d), 128.2 (d), 127.4 (d), 80.0 (d), 69.6 (t), 61.2 (t), 56.9 (d), 42.8 (t), 28.7 (t), 27.1 (t), 24.9 (t), 1.0 (q); *m/z* (EI, 70 eV) 230 ($M^+ - OSiMe_3$, 6%), 203 (12), 186 (45), 185 (58), 151 (19), 84 (100).

2-(Tetrahydropyran-2-yl)cyclohexanone 7. Yield 90%, ratio of diastereoisomers 2:1; ν_{max}(neat)/cm^{-1} 2941s, 2864s, 1708s (C=O), 1449s, 1084s, 1049s; $\delta_H(CDCl_3)$ (mixture of isomers) 3.9 (1 H, m), 3.8–3.3 (2 H, m), 2.3 (3 H, m), 2.0–1.2 (12 H, m); $\delta_C(CDCl_3)$ isomer I: 211.6 (s), 75.4 (d), 68.7 (t), 56.1 (d), 42.5 (t), 30.2 (t), 29.0 (t), 27.9 (t), 26.2 (t), 24.4 (t), 23.5 (t); isomer II: 211.6 (s), 76.2 (d), 68.8 (t), 55.9 (d), 41.9 (t), 28.7 (t), 28.0 (t), 27.8 (t), 27.0 (t), 26.1 (t), 24.1 (t); *m/z* (EI, 70 eV) 182 (M^+, 47%), 153 (35), 138 (42), 125 (43), 111 (30), 97 (58), 85 (100), 67 (70) (Found M, 182.12925. $C_{11}H_{18}O_2$ requires *M* 182.13068).

Conclusions

High chemoselectivity has been observed for the substitution of acetals in preference to ketals by silyl enol ethers in 5 mol dm^{-3} LPDE to give aldol ethers in good yields. The LPDE medium offers a method for the synthesis of aldol ethers under essentially neutral reaction and work up conditions. The difference in the reactivity of cyclohexenyl and cyclopentenyl enol ethers **2** and **1** is exemplified in the present study in that the former is more reactive than the latter, which allows the chemoselective substitution of acetals by **2** in preference to **1** as the nucleophile. Such fine tuning of reactivity is possible in 5 mol dm^{-3} LPDE which is otherwise difficult to achieve using conventional Lewis acids. The observed chemoselectivity is attributed to the moderate Lewis acidity of the lithium ion in diethyl ether.

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