Highly Selective 1,2- and 1,4-Addition of Silyl Enol Ethers to α,β-Unsaturated Carbonyl Compounds in 5 M Lithium Perchlorate−Nitromethane Medium[†]

S. Sankararaman* and R. Sudha

Department of Chemistry, Indian Institute of Technology, Madras, Chennai-600 036, India

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Introduction

Highly concentrated solutions of lithium perchlorate in various organic solvents have been used to effect several synthetic transformations,[1] and tremendous rate acceleration as well as high selectivities have been reported.[2] We have reported high chemoselectivity in the thioacetalization of carbonyl compounds,[3] substitution of acetals,[4] and the Michael reaction[5] in 5 M lithium perchlorate in diethyl ether (5 M LPDE). Although Michael addition of silyl enol ethers to nitro- and cyano-olefins is facile in 5 M LPDE at room temperature, we observed that the more commonly used Michael acceptors, namely, the α,β-unsaturated carbonyl compounds, failed to undergo any reaction in this medium. The more reactive ketene silyl acetals have been reported to undergo Michael addition to α,β-unsaturated carbonyl compounds in LPDE.[6] Recently, Ayerbe and Cossio have reported that lithium perchlorate in nitromethane (LPNM) appears to be a much better medium than LPDE in promoting certain Diels−Alder reactions.[7] The lithium ion in LPDE is a mild Lewis acid due to solvation.[8] The Lewis acidity of lithium ion is a major factor,[9] although probably not the only factor that governs the reactivity of organic substrates in these media. The Lewis acidity of lithium ion plays a major role in the activation of organic substrates by coordination to the lone pairs on the heteroatoms in these media and the consequent rate acceleration of organic transformations.[9] The donor number of nitromethane is lower than that of ether (2.7 vs 19.2 kcal mol^{-1}),[10] and hence, the Lewis acidity of lithium ion in a less coordinating solvent like nitromethane is

likely to be higher than that in ether. Also, the dielectric constant and the dipole moment of nitromethane are higher than ether, and hence, the formation of polar and ionic intermediates is more favored in nitromethane than in ether.[11] Recently we have observed that the aldol reaction of silyl enol ethers to aldehydes and ketones proceeded in 5 M LPNM at room temperature whereas the same reaction failed to proceed in 5 M LPDE.[12] Herein we report the results of our study on the addition of silyl enol ethers to α,β-unsaturated aldehydes and ketones in which high regioselectivity has been observed.

Results and Discussion

In a typical experiment to a solution of the α,β-unsaturated carbonyl compound (2 mmol) in 2 mL of 5 M LPNM under nitrogen atmosphere was added the silyl enol ether (6 mmol) and the mixture was stirred at room temperature until the disappearance of the starting materials, followed by TLC. Addition of silyl enol ethers **1** and **2** to unsaturated ketones **3a**,**b** led to the formation of the corresponding Michael addition products **4a**,**b** and **5a**,**b**, respectively (Table 1). The products were purified either by column chromatography or by preparative TLC on silica gel. Analysis of the ^{1}H NMR spectra of the crude products revealed that the addition was highly regioselective in that only the Michael adducts **4a**,**b** and **5a**,**b** were formed as nearly a 1:1 mixture of diastereoisomers and the 1,2-addition products **6a**,**b** and **7a**,**b** were not formed in these reactions. In sharp contrast, when silyl enol ethers **1** and **2** were reacted with unsaturated aldehydes **3c**,**d** it resulted in the predominant formation of the 1,2-addition products **6c**,**d** and **7c**,**d**, respectively. The Michael adducts **4c**,**d** and **5c**,**d** were formed in less than 10% as indicated by the minor peaks corresponding to these products in the ^{1}H NMR spectra of the crude products.

Addition of enol ethers **1** and **2** to cyclic α,β-unsaturated ketones **8a**,**b** gave the corresponding Michael adducts **9a**,**b** and **10a**,**b**, respectively in good yields (Table 2). However, the more hindered β-substituted ketone **8c** failed to undergo Michael reaction in LPNM with silyl enol ethers **1** and **2** as well as the more reactive ketene silyl acetal **11**. The lack of reactivity of **8c** in LPNM parallels its behavior in LPDE, reported by Grieco.[6] Addition of ketene silyl acetal **11** to **3d** resulted in the formation of **13b**[18] exclusively, whereas with **3a** it yielded predominantly **12a**.[19]

3a : R$_1$ = Ph, R$_2$ = Me	**12a** 65%	**13a** <10%
3d : R$_1$ = Ph, R$_2$ = H	**12b** 0%	**13b** 90%
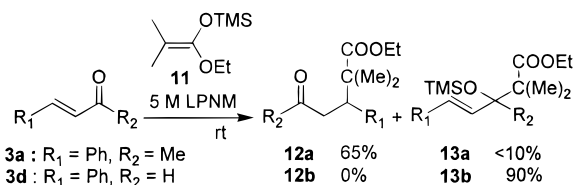
In the IR spectroscopic studies, the C=O stretching frequency of **3d** is 1724 cm^{-1} in nitromethane and it is

[†] Dedicated to Prof. Dr. M. V. George, Photochemistry Division, RRL (CSIR), Trivandrum, India, on the occasion of his 70th birthday.

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Table 1. Addition of Silyl Enol Ethers to α,β-Unsaturated Carbonyl Compounds in 5 M LPNM
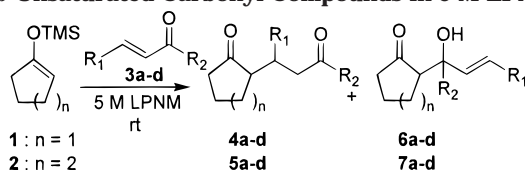
enol ether		acceptor		time (h)	yield (%)[a]				ref
		R_1	R_2		1,4-addition		1,2-addition		
1	**3a**	Ph	Me	8	**4a**	80	**6a**	0	13
2		Ph	Me	16	**5a**	85	**7a**	0	14
1	**3b**	Ph	Ph	10	**4b**	82	**6b**	0	15
2		Ph	Ph	20	**5b**	78	**7b**	0	15
1	**3c**	Me	H	17	**4c**	<10[b]	**6c**	73	
1	**3d**	Ph	H	16	**4d**	<10[b]	**6d**	75	
2		Ph	H	24	**5d**	<10[b]	**7d**	70	16

[a] Isolated yield after purification. [b] Based on ^{1}H NMR spectral integration.

Table 2. Michael Addition of Silyl Enol Ethers to Cyclic Unsaturated Ketones in 5 M LPNM
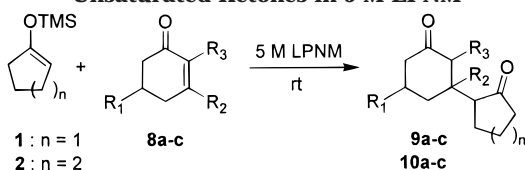
enol ether		acceptor			duration (h)	yield (%)[a]	ref
		R_1	R_2	R_3			
1	**8a**	H	H	H	12	**9a**[b] 75	17
2		H	H	H	16	**10a**[b] 70	17
1	**8b**	i-C_3H_5	H	Me	24	**9b**[c] 80	17
2		i-C_3H_5	H	Me	38	**10b**[c] 74	17
1	**8c**	H	Me	H	48	**9c** 0	
2		H	Me	H	48	**10c** 0	

[a] Isolated yield after purification. [b] 1:1 mixture of diastereoisomers. [c] mixture of four diastereoisomers.

shifted to 1705 cm^{-1} in 5 M LPNM. In the case of **3a** the C=O stretching frequency is 1712 cm^{-1} in nitromethane, which remained unaltered in 5 M LPNM. Similar results were observed with benzaldehyde and acetophenone in that the C=O stretching frequency of the former is shifted from 1724 cm^{-1} in nitromethane to 1712 cm^{-1} in LPNM whereas that of the latter remained unchanged at 1692 cm^{-1}. These results suggest that aldehydes are selectively activated in LPNM, which is primarily due to the steric factors that govern the coordination of the solvated lithium ion to the carbonyl oxygen. These changes to the lower wavenumbers in the stretching frequency of the carbonyl functional group are consistent with the coordination of the lithium ion to the carbonyl oxygen lone pair. The carbonyl stretching frequency shifts are lower in the case of LPDE in comparison with ether.[3,5] For example the carbonyl stretching frequency of benzaldehyde is shifted from 1708 cm^{-1} in ether to 1699 cm^{-1} in 5 M LPDE. The extent of the shift is a qualitative reflection of the Lewis acidity of the lithium ion which

depends on the basicity of the medium. We propose that the 1,2-addition occurs by the reaction of the silyl enol ether to the carbonyl group that is activated by the coordination of the lithium ion.[3] In the case of ketones, for the 1,4-addition to proceed it is necessary to use at least 2 equiv of the silyl enol ether which parallels the behavior observed in the Michael addition reactions in LPDE.[5] Hence we conclude that the silyl transfer mechanism proposed earlier in the case of the Michael reactions in LPDE medium[5] might operate for the 1,4-addition reactions in LPNM. The increased Lewis acidity of the lithium ion is responsible for the enhanced reactivity of α,β-unsaturated carbonyl compounds toward silyl enol ethers in LPNM in comparison to that in LPDE.

Experimental Section

General Methods. Preparation of 5 M LPDE and the instrumentation used are described earlier.[3] Nitromethane (1 L) (analytical grade) was mixed with concentrated H_2SO_4 (150 mL) and allowed to stand for 24 h at room temperature. It was separated and washed with water followed by aqueous $NaHCO_3$ and then again with water. It was dried over anhydrous $CaCl_2$, filtered, and fractionally distilled using a vigreux column. The distillate was stored over activated molecular sieve (4 Å) in an amber colored bottle. Anhydrous lithium perchlorate (53 g) was dissolved in dry nitromethane (100 mL) under N_2 atmosphere with ice bath cooling to yield a clear and free flowing solution. The dissolution was not as exothermic as in the case of the preparation of 5 M LPDE.[3] (*Caution: Solutions of lithium perchlorate in organic solvents must be handled with care!*[20])

General Procedure. In a typical experiment the carbonyl compound (2 mmol) was dissolved in 5 M LPNM (2 mL) under N_2 atmosphere. To this solution the enol silyl ether (6 mmol) was added, and the mixture was stirred at room temperature until the disappearance of the starting materials as shown by TLC. The reaction mixture was cooled in an ice bath and diluted with CH_2Cl_2 (15 mL) followed by addition of water (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4. Removal of solvent on the rotary evaporator followed by column chromatographic purification on silica gel yielded pure products. Except for compounds **6c,d**, the others are literature known compounds and were characterized by IR, NMR (^{1}H and ^{13}C), and mass spectroscopy. Compounds **6c,d** were characterized in the present study by IR, [1]H (400 MHz) and ^{13}C (100 MHz) NMR, and mass spectroscopic data by comparison with that of **7d**.

2-((*E*)-1-Hydroxy-3-phenyl-2-propenyl)cyclopentanone (6c). Yield: 73%. IR (CCl$_4$): 3484 (ν_{OH}), 1734 ($\nu_{C=O}$) cm^{-1}. Isomer I: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.2 (m, 5H), 6.61 (d, 1H, J = 16 Hz), 6.19 (dd, 1H, J = 5.8 and 16 Hz), 4.75 (m, 1H), 3.3 (s, br, OH), 2.8−1.5 (m, 7H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 220.3 (s), 136.6 (s), 130.6 (d), 129.9 (d), 128.5 (d), 127.6 (d), 126.5 (d), 70.8 (d), 54.2 (d), 39.1 (t), 23.4 (t), 20.7 (t) ppm. Isomer II: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.2 (m, 5H), 6.6 (d, 1H, J = 16 Hz), 6.15 (dd, 1H, J = 16 and 6.84 Hz), 4.4 (m, 1H), 3.3 (s, br, OH), 2.5−1.5 (m, 7H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 221.5 (s), 136.5 (s), 131.5 (d), 128.8 (d), 128.5 (d), 127.7 (d), 126.5 (d), 73.4 (d), 53.9 (d), 38.6 (t), 26.4 (t), 20.5 (t) ppm; MS (70 eV, EI) m/z 216 (M$^+$, 15), 198 (30), 133 (40), 84 (100), 77 (70), 55 (60).

2-((*E*)-1-Hydroxy-2-butenyl)cyclopentanone (6d). Yield: 75%. IR (CCl$_4$): 3504 (ν_{OH}), 1737 ($\nu_{C=O}$) cm^{-1}. Isomer I: ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.6 (m, 1H), 4.5 (m, 1H), 4.0 (br, s, OH), 2.5−1.5 (m, 7H), 1.7 (d, 3H, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 221.3 (s), 131.5 (d), 130.8 (d), 70.9 (d), 54.1 (d), 39.2 (t), 23.4 (t), 20.7 (t), 17.7 (q) ppm. Isomer II: ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.4 (m, 1H), 4.2 (m, 1H), 4.0 (br, s, OH), 2.5−1.5 (m, 7H), 1.72 (d, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 223.0 (s), 128.3 (d), 127.2 (d), 73.5 (d), 53.8 (d), 38.8

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(t), 26.5 (t), 20.6 (t), 17.5 (q) ppm; MS (70 eV, EI) *m/z* 154 (M$^+$, 5), 120 (15), 84 (100), 71 (95), 55 (80).

Supporting Information Available: IR, ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and mass spectroscopic data for compounds **6a**,**b**, **7a**,**b**, **7d**, **9a**,**b**, **10a**,**b**, **12a**, and **13b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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