Chemoselective aldol condensation in 5 mol dm^{-3} lithium perchlorate–nitromethane. A comparison with lithium perchlorate–diethyl ether medium

R. Sudha and S. Sankararaman *

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

Received (in Cambridge) 5th January 1999, Accepted 11th January 1999

Aldol reactions of silyl enol ethers with aldehydes proceed in 5 mol dm^{-3} lithium perchlorate–nitromethane medium at ambient temperature. The reaction is highly chemoselective such that only aldehydes and cyclic ketones reacted while acyclic and aromatic ketones failed to react. The same reaction is not promoted in 5 mol dm^{-3} lithium perchlorate–diethyl ether medium. The di erence between these two media is explained by the increased Lewis acidity of the lithium ion in nitromethane compared to that in ether.

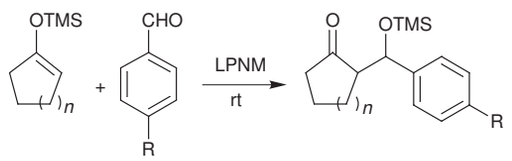
Introduction

Highly concentrated solutions of lithium perchlorate in organic solvents have been used as media to carry out several organic transformations.[1] Among these lithium perchlorate in diethyl ether (LPDE) has been widely used ever since Grieco *et al*. reported the tremendous rate acceleration and high stereoselectivity of Diels–Alder reactions in this medium.[2] We have been interested in the activation of carbonyl substrates and their acetals in this medium for synthetic transformations.[3] Recently we have reported chemoselective substitution of acetals by silyl enol ethers to yield the corresponding aldol ethers as products in 5 M LPDE.[4] During these studies we have also observed the inability of this medium to promote aldol condensation of aldehydes and ketones with silyl enol ethers, although the more reactive ketene silyl acetals have been reported to undergo this reaction.[5] The lithium ion in LPDE is a mild Lewis acid due to solvation. The Lewis acidity of the lithium ion is a major factor, although probably not the only factor that governs the reactivity of organic substrates in this medium. The use of a strong Brønsted acid in combination with LPDE has been reported by Grieco *et al*. to activate certain intramolecular Diels–Alder reactions.[6] In order to promote the aldol condensation of aldehydes and ketones with silyl enol ethers using lithium perchlorate, we have explored the possibility of changing the solvent from diethyl ether to nitromethane. Anhydrous lithium perchlorate is highly soluble in nitromethane. Recently, Ayerbe and Cossio have reported lithium perchlorate in nitromethane (LPNM) to be a more e ective medium than LPDE for certain Diels–Alder reactions.[7] Herein we present the results of our study on aldol condensation in LPNM and compare it with that in LPDE.[8]

Results and discussion

Aldol reactions of aldehydes

The trimethylsilyl ethers from cyclopentanone, cyclohexanone and tetralone (3,4-dihydronaphthalen-1(2*H*)-one) (**1**, **2** and **3**, respectively) and 1-ethoxy-2-methyl-1-trimethylsilyloxypropene (**4**) were used as nucleophiles. The aldol reactions were carried out in 2 ml of a 5 mol dm^{-3} solution of LPNM at ambient temperature (30 °C) by adding 1.2 equivalents of the silyl enol ether to the aldehyde (0.01 mol). Addition of silyl enol ethers **1** and **2** to aromatic aldehydes furnished the corresponding aldol silyl ethers as a pair of diastereoisomers in good yields and the results are summarised in Table 1 and eqn. (1).

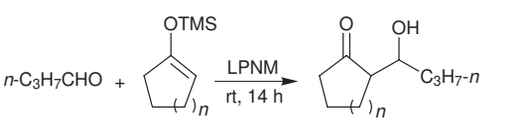


(1)

$n = 1$ **1** $n = 2$ **2** **5a-d** $n = 1$ **6a-d** $n = 2$ **7a-d**

The reaction was found to be highly sensitive to the e ect of substituents in the *para* position of the aromatic ring, along the expected trend. Thus, aldehydes bearing electron withdrawing substituents reacted faster than those bearing electron donating substituents under identical conditions. In the case of 3,4-dimethoxybenzaldehyde the reaction did not proceed even after 2 days of stirring at room temperature. In all cases the cyclopentenyl enol ether **1** reacted faster than the cyclohexenyl enol ether **2**.

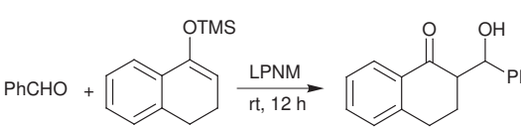
Addition of enol ethers **1** and **2** to butyraldehyde **8** yielded the corresponding aldol products,[11] **9** and **10** respectively, in good yields as a 1:1.5 mixture of diastereoisomers. The reactivity of butyraldehyde was found to be much lower in comparison with benzaldehyde under identical reaction conditions [eqn. (2)].



(2)

8 $n = 1$ **1** $n = 2$ **2** $n = 1$ **9** 72% $n = 2$ **10** 75%

Addition of enol ether **3** to benzaldehyde yielded the corresponding aldol product **11**[12] as a 1:1 mixture of diastereoisomers in 70% yield [eqn. (3)].



(3)

5b **3** **11** 70%

Aldol reactions of ketones

The addition reactions of enol silyl ethers with aliphatic (butan-2-one) and aromatic ketones (acetophenone, benzophenone

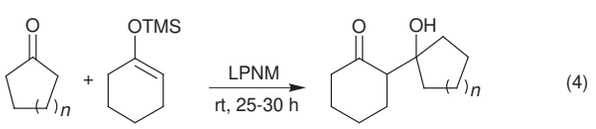
Table 1 Aldol reactions of aromatic aldehydes in LPNM

Enol ether	Aldehyde	R	Product	Duration	Yield (%)[a]	Ratio of diastereomers[b]	Ref.
1	**5a**	NO_2	**6a**	15 min	90	3:1	9
1	**5b**	H	**6b**	4 h	85	17:1	10
1	**5c**	Me	**6c**	7 h	83	1.5:1	11
1	**5d**	OMe	**6d**	20 h	80	7:1	10
2	**5a**		**7a**	45 min	85	1.1:1	9
2	**5b**		**7b**	6 h	82	2:1	10
2	**5c**		**7c**	12 h	80	4:1	11
2	**5d**		**7d**	48 h	30[c]	—	10

[a] Isolated yields after puri cation. [b] From the peak integration of the 400 MHz ^{1}H-NMR spectra of the products. [c] Remainder was starting material.

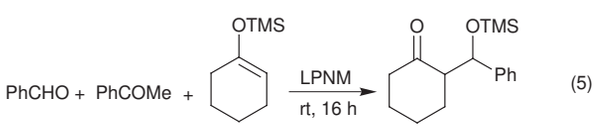
and tetralone) were carried out by adding two equivalents of silyl enol ether to the ketone (0.05 mol) in 2 ml of 5 mol dm^{-3} LPNM. In all cases after prolonged stirring at ambient temperature no reaction was observed. After workup the starting materials were recovered quantitatively. The enol ether **3** also failed to react with acetophenone in LPNM. After workup only unreacted acetophenone and tetralone were recovered.

Unlike the acyclic ketones, the aliphatic cyclic ketones **12** and **13** underwent the expected aldol condensation to yield **14** (35%)[13] and **15** (73%),[13] respectively, albeit at a much slower rate than the aldehydes [eqn. (4)].



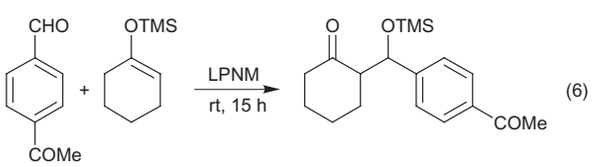
n = 1 **12** **2** n = 1 **14** 35%
n = 2 **13** n = 2 **15** 73%

From these experiments it is evident that the aldol condensation is highly chemoselective in LPNM. In order to demonstrate the chemoselectivity more clearly the following competitive reactions were carried out. A 1:1 mixture of benzaldehyde and acetophenone was treated with 4 equivalents of silyl enol ether **2** in LPNM. After 16 h of stirring at ambient temperature followed by aqueous workup, the crude product was analysed by 400 MHz ^{1}H-NMR spectroscopy. It consisted of a 1:1 mixture of unreacted acetophenone and the aldol product from benzaldehyde **7b** along with cyclohexanone from the hydrolysis of the excess silyl enol ether [eqn. (5)].



5b **2** **7b** + PhCOMe

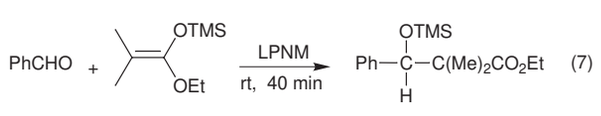
It should be emphasised here that in the same competitive reaction when performed in 5 mol dm^{-3} LPDE, both benzaldehyde and acetophenone failed to react. When the ketoaldehyde **16** was treated with 5 equivalents of enol ether **2** for 18 h it resulted in the formation of a single product **17** as a pair of diastereoisomers, which clearly demonstrated that only the aldehyde functionality of the starting material had reacted while the keto group remained intact [eqn. (6)].



16 **2** **17** 90%
1:1 diastereomer ratio

Aldol reactions of ketene silyl acetal 4

Ketene silyl acetals are generally more reactive nucleophiles than silyl enol ethers and hence they have been reported to undergo aldol reactions with carbonyl compounds in 5 mol dm^{-3} LPDE.[5] Our interest in this study was to investigate the chemoselectivity of the aldol reaction of the ketene silyl acetal **4** in LPNM. While treatment of 1.2 equivalents of **4** with benzaldehyde (1 equivalent) in 5 M LPNM resulted in the formation of the corresponding aldol product within 40 min in 85% yield [eqn. (7)] the reaction of **4** with acetophenone gave only 10%



5b **4** **18** 85%

conversion to give the corresponding aldol product under identical conditions.

Comparison of LPDE and LPNM as reaction media for aldol condensation

Aldol reactions of silyl enol ethers **1** and **2** with aldehydes and ketones failed to proceed in 5 mol dm^{-3} LPDE medium. In 5 mol dm^{-3} LPNM chemoselective aldol reactions of aldehydes and cyclic ketones with silyl enol ethers **1** and **2** occurred. Acyclic and aromatic ketones failed to undergo aldol reactions in LPNM. The di erence between these two media could arise from the following factors. In comparison to diethyl ether, nitromethane is a poor cation coordinating solvent as re ected by the donor numbers[14] (19.2 *versus* 2.7 respectively for ether and nitromethane). Due to its higher relative permittivity and dipole moment nitromethane is a more polar solvent than ether. Due to these factors the Lewis acidity of the lithium ion in nitromethane is expected to be higher than that in diethyl ether. Formation of polar and ionic intermediates would also be facilitated in nitromethane.[15] Activation of the carbonyl group by the coordination of a lithium ion with the carbonyl oxygen lone pair has been studied by infrared spectroscopy. In the case of benzaldehyde the carbonyl stretching frequency is shifted from 1708 cm^{-1} in ether to 1699 cm^{-1} in 5 mol dm^{-3} LPDE and from 1724 cm^{-1} in nitromethane to 1708 cm^{-1} in 5 mol dm^{-3} LPNM. These changes to the lower wavenumbers in the stretching frequency of the carbonyl functional group arise as a result of the coordination of the lithium ion to the carbonyl oxygen lone pair and the extent of the shift is a qualitative re ection of the Lewis acidity of the lithium ion. In comparison, the carbonyl stretching frequency of acetophenone remained unchanged in nitromethane and in LPNM indicating the absence of activation of the carbonyl functional group by the lithium ion and hence the lack of reactivity towards aldol condensation in LPNM.

Conclusions

The present study when compared with our earlier report,[4] clearly indicates that LPNM is a better medium than LPDE for aldol condensation of silyl enol ethers and ketene silyl acetals with aldehydes. The enhanced reactivity towards aldol condensation of aldehydes in LPNM in comparison with LPDE is attributed to the higher Lewis acidity of lithium ions in nitromethane than in ether and hence better activation of the carbonyl group. High chemoselectivity has been observed in these reactions in that only aldehydes and aliphatic cyclic ketones reacted while aliphatic and aromatic ketones remained inert.

Experimental

Materials

Analytical grade nitromethane (1 litre) was stirred with concentrated sulfuric acid (150 cm^3) overnight at room temperature and subsequently washed with 10% aqueous sodium carbonate solution followed by water. It was dried over anhydrous calcium chloride and fractionally distilled. It was stored over activated molecular sieves (4 Å type) under nitrogen in an amber coloured bottle. Anhydrous lithium perchlorate was dissolved in dry nitromethane under nitrogen atmosphere with adequate cooling to obtain a 5 mol dm^{-3} solution. Preparation of 5 mol dm^{-3} LPDE has been reported earlier.[3] **CAUTION**: *Although lithium perchlorate is stable up to its melting point, preparation of the anhydrous salt and the solutions in organic solvents should be done carefully, preferably in the fume cupboard behind a shield.* Starting materials **1**–**3**[16] and **4**[17] were prepared according to literature methods. Except for compound **17** all the other products from the aldol reactions are literature known compounds and they were characterised by IR, high resolution ^{1}H- and ^{13}C-NMR and mass spectroscopic data.

General procedure for aldol reaction in 5 mol dm^{-3} LPNM

The carbonyl compound (2 mmol) taken up in 2 cm^3 of 5 mol dm^{-3} LPNM under nitrogen was treated with 2.4 mmol of the silyl enol ether and the mixture was stirred at room temperature until the disappearance of the starting materials as indicated by TLC. The mixture was diluted with dichloromethane (25 cm^3) and washed with water (10 cm^3). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed to obtain the crude product which was puri ed by column chromatography over silica gel to obtain the pure products. The products were generally obtained as a pair of diastereoisomers and the ratio of the isomers was calculated from the peak integration of high resolution (400 MHz) ^{1}H-NMR spectra.

Spectroscopic characterisation of products

2-[(4-Acetylphenyl)trimethylsilyloxymethyl]cyclohexanone 17. Yield 90%, ratio of diastereoisomers 1 : 1.1; $\nu_{max}(CCl_4)/cm^{-1}$ 2944, 1712 s (C=O), 1680 s (C=O), 1603 s; δ_H ($CDCl_3$) isomer I: 7.9 (2H, d, *J* 6.3), 7.4 (2H, d, *J* 6.3), 5.36 (1H, d, *J* 4.4), 2.6–1.4 (12H, m), 0.04 (9H, s); isomer II: 7.9 (2H, d, *J* 6.3), 7.42 (2H, d, *J* 6.3), 5.16 (1H, d, *J* 7.32), 2.6–1.4 (12H, m), 0.03 (9H, s); δ_C($CDCl_3$) isomer I: 210.3 (s), 197.6 (s), 148.2 (s), 135.8 (s), 128.0 (d), 126.4 (d), 71.3 (d), 58.1 (d), 41.8 (t), 29.9 (t), 26.9 (t), 26.5 (q), 24.4 (t), 0.0 (q); isomer II: 210.7 (s), 197.6 (s), 149.9 (s), 136.2 (s), 128.0 (d), 127.1 (d), 72.5 (d), 58.9 (d), 42.2 (t), 28.0 (t), 26.8 (t), 26.5 (q), 24.3 (t), 0.03 (q); *m/z* (EI, 70 eV) 318 (M^+, 25%), 221 (75), 170 (25), 155 (30), 115 (15), 84 (20), 73 (100); HRMS: calculated for $C_{18}H_{26}SiO_3$ 318.16511, found 318.1649. (Figs. 1, 2 and 3)

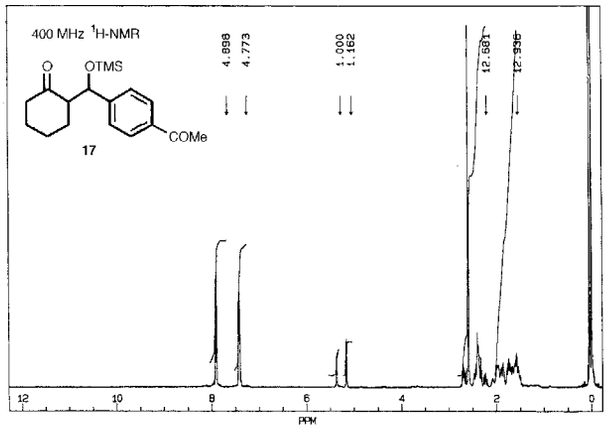


Fig. 1 400 MHz ^{1}H NMR Spectrum of compound **17**.

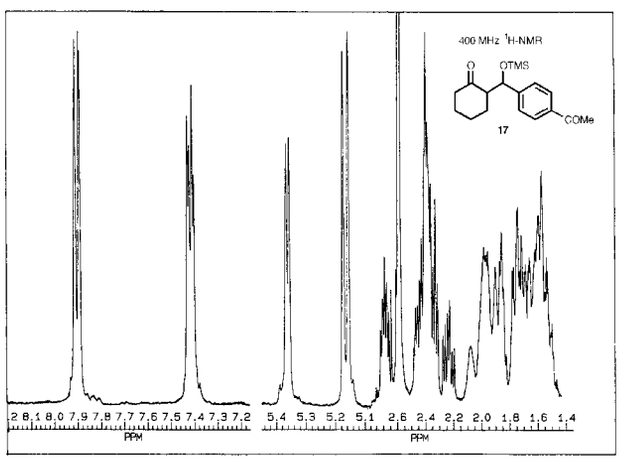


Fig. 2 400 MHz ^{1}H NMR Spectrum (expanded) of compound **17**.

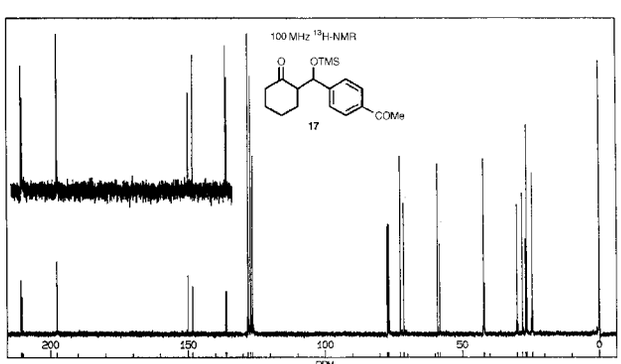


Fig. 3 100 MHz ^{13}C NMR Spectrum of compound **17**.

Acknowledgements

Financial support from CSIR, New Delhi, in the form of a Senior Research Fellowship (R. S.) and a Sponsored Research Project (S. S.) is gratefully acknowledged. We thank the Regional Sophisticated Instrumentation Centre, IIT, Madras, for the high resolution NMR and mass spectral data.

References

1 (*a*) P. A. Grieco, *Aldrichimica Acta*, 1991, **24**, 61; (*b*) H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, 1991, 30, 1306; (*c*) P. A. Grieco, in *Organic Chemistry; Its Language and its State of Art*, ed. V. Kisakürek, VCH, Basel, 1993, p. 133; (*d*) A. Flohr and H. Waldmann, *J. Prakt. Chem.*, 1995, **337**, 609.
2 P. A. Grieco, J. J. Nunes and M. D. Gaul, *J. Am. Chem. Soc.*, 1990, **112**, 4595.
3 V. Geetha Saraswathy and S. Sankararaman, *J. Org. Chem.*, 1994, **59**, 4665.
4 V. Geetha Saraswathy and S. Sankararaman, *J. Chem. Soc., Perkin Trans. 2*, 1996, 29.
5 (*a*) M. T. Reetz, B. Raguse, C. F. Marth, H. M. Hügel, T. Bach and D. N. A. Fox, *Tetrahedron*, 1992, **48**, 5731; (*b*) J. Ipaktschi and A. Heydari, *Chem. Ber.*, 1993, **126**, 1905.

6 (*a*) P. A. Grieco, S. T. Handy and J. P. Beck, *Tetrahedron Lett.*, 1994, **35**, 2663; (*b*) P. A. Grieco, J. P. Beck, S. T. Handy, N. Saito and J. F. Daeube, *Tetrahedron Lett.*, 1994, **35**, 6783.
7 M. Ayerbe and F. P. Cossio, *Tetrahedron Lett.*, 1995, **36**, 4447.
8 From the PhD dissertation of R. Sudha, Indian Institute of Technology, Madras, 1998.
9 R. Noyori, I. Nishida and J. Sakata, *J. Am. Chem. Soc.*, 1983, **105**, 1598.
10 S. Torii, T. Inokuchi, S. Takagisti, H. Horike, H. Kurode and K. Uneyama, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 2173.
11 C. L. Roux, H. G. Iluoghmane, J. Dubac, J. Jaud and P. Vignaux, *J. Org. Chem.*, 1993, **58**, 1835.
12 A. Ando, T. Miura, T. Tatematsu and T. Shioiri, *Tetrahedron Lett.*, 1993, **34**, 1507.
13 B. J. J. van de Heisteeg, G. Schat, M. A. G. M. Tinga, O. S. Akkerman and F. Bickelhaupt, *Tetrahedron Lett.*, 1986, **27**, 6123.
14 J. E. Gordon, *The Organic Chemistry of Electrolyte Solutions*, John Wiley, New York, 1975.
15 T. V. Rajan Babu, *J. Org. Chem.*, 1984, **49**, 2083.
16 H. O. House, L. J. Czuba, M. Gall and H. D. Olmstead, *J. Org. Chem.*, 1969, **34**, 2324.
17 K. S. Mikami, A. Matsumoto, A. Ishida, S. Takamuku, T. Suenobu and S. Fukuzumi, *J. Am. Chem. Soc.*, 1995, **117**, 11134.

Paper 9/00095J