Tetrahedron Vol. 49, No. 24, pp. 5333-5338, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Surface-mediated Solid Phase Reaction.[1] Aldol Reaction of Silyl Enol Ethers with Aldehydes on a Solid Surface of Neutral Alumina : Selectivity for Anti Aldols

Brindaban C. Ranu* and Rupak Chakraborty

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta - 700 032, India.

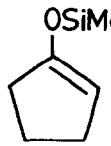
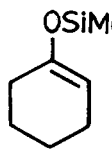
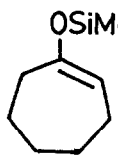
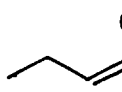
(*Received in UK* 2 *March* 1993)

Abstract : The aldol reaction of trimethyl silyl enol ethers with aldehydes on the solid surface of neutral alumina under sonication without any solvent is found to proceed providing cross aldol products with anti selectivity.

The cross aldol reaction of silyl enol ethers with aldehydes was first reported in 1973[2] and since then this is considered as one of the most important carbon-carbon bond forming reactions in organic synthesis. In recent years, the development of new reagents and methods[3,4] for the control of stereochemistry of this useful reaction has attracted much interest in relation to the challenge of acylic stereocontrol.[5] In general, syn (erythro) selectivity was conveniently achieved by a number of mild processes using lanthanide trifluoromethanesulfonate,[3a] water-promoted reaction at atmospheric[3b] and high[3c] pressure, fluoride anions,[3d] and trityl salts,[3e,3f] whereas anti (threo) selectivity was observed with acidic reagents like titanium tetrachloride,[2] clay montmorillonite,[4a] dimethylaluminium chloride,[4b] bismuth trichloride.[4c] But, the use of Lewis acids could be troublesome with acid labile substrates and in addition to that, acidic conditions led somethimes to dehydration products.[2] Moreover, the anti selectivity with these reagents[2-4] is not always uniform and is strongly influenced by several factors, e.g. structure of the silyl enol ether,[2] nature of the substituents on silicon of the enol ether,[3e,3f] choice of solvent[4a] etc. A suitable method overcoming these difficulties will thus be well-appreciated. In the course of our investigations to explore the utility of surface-mediated solid phase reaction technology for the control of regio and stereoslectivity[6] we have discovered a general anti selectivity for cross aldol products in the reaction of trimethylsilyl enol ethers with aldehydes on the solid surface of neutral alumina under sonication without any solvent.

The reaction procedure is very simple. Trimethylsilyl enol ether was added to activated neutral alumina under stirring. After 2 min. the aldehyde was added and the resulting powder was then immersed in an ultrasonic bath for a certain period of time as required for completion. The solid mass was then taken into chloroform and filtered through a short column packed with anhydrous sodium sulfate. The filtrate

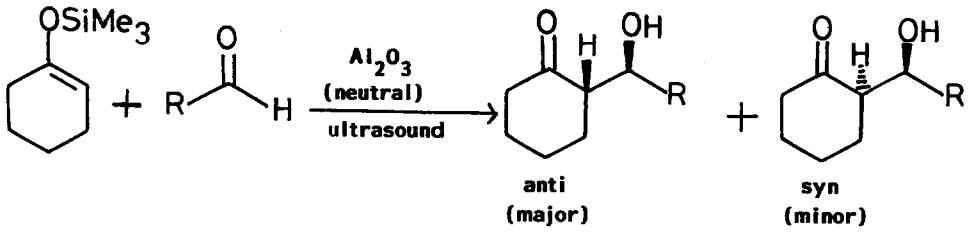
Table 1. Aldol reaction of silyl enol ethers with aldehydes on the solid surface of alumina.

entry	silyl enol ether	aldehyde	time(h)	yield(%)[a]	anti/syn[b]
1	 (1)	PhCHO	27	75	77/23
2	1	$CH_3CH_2CH_2CHO$	25	70	75/25
3	1	$(CH_3)_2CHCHO$	24	72	65/35
4	1	p-O_2N-C_6H_4CHO	30	90	60/40
5	 (2)	PhCHO	18	68	75/25
6	2	p-O_2N-C_6H_4CHO	28	70	67/33
7	2	p-MeO-C_6H_4CHO	30	70	70/30
8	2	$CH_3CH_2CH_2CHO$	25	75	60/40
9	2	p-Cl-C_6H_4CHO	30	85	75/25
10	 (3)	PhCHO	30	82	65/35
11	3	p-O_2N-C_6H_4CHO	30	88	60/40
12	 (4)	PhCHO	28	65	65/35
13	4	$CH_3CH_2CH_2CHO$	24	70	60/40

[a] all yields refer to isolated products

[b] anti/syn ratio was estimated by ^1H NMR analysis.[3,4]

was evaporated to leave the crude aldol which was further purified by column chromatography over alumina.



As shown in Table 1, a number of structurally varied silyl enol ethers reacted with a variety of aldehydes under this procedure to produce the cross aldols in high yields. Diastereoselectivities, in general, are good and a general trend for anti selectivity was observed in all the reactions irrespective of the nature of silyl enol ethers and aldehydes. No side products including the dehydrated olefin were observed. Interestingly, the presence of solvent retarded the reaction to a great extent. The progress of reaction of 1-trimethylsilyloxy cyclohexene with benzaldehyde under identical condition in dichloroethane is practically nil, while in tetrahydrofuran the reaction proceeded to the extent of only 10%, although anti/syn ratio remained the same as in solid phase reaction. This indicates that alumina surface plays the decisive role in controlling the stereochemistry of aldol in absence or presence of solvent. On the other hand the reaction was also very slow under stirring without sonication. Thus, solid alumina surface and ultrasound are two important contributors towards the progress of the reaction.

Another important feature of this reaction is that alumina can be recovered and reused after activation.

In conclusion, this procedure of aldol reaction on the solid surface of alumina under sonication provides an efficient methodology for anti selective cross aldol products. Diastereoselectivities in general, are good[7] and comparable to those obtained with existing reagents.[2-4] Although reaction time is relatively long, the procedural simplicity, mild and neutral reaction condition, and above all, suppression of undesirable side reactions compensate for it and will make this method useful with regard to acyclic stereocontrol.

Experimental

General : ^{1}H NMR spectra were recorded at 60 MHz on EM 360 spectrometer of Varian Associates in CCl_4 solutions with Me_4Si as an internal standard. IR spectra were recorded on a Perkin Elmer 298 spectrometer. Elemental analyses were performed by Mr. S. Sarkar of this laboratory. Thin layer chromatography was done on precoated silica gel plates (E. Merck). Alumina, supplied by SRL, India (Aluminium Oxide, neutral, Brockmann activity grade 1 for column chromatography) was used in all the reactions. Silica gel (60-120 mesh) used for chromatography was also from SRL, India. All commercial chemicals were distilled before use. Trimethylsilyl enol ethers were prepared following the reported procedure of House.[8] An ultrasonic bath (Julabo USR-3, manufactured by Julabo Labortechnik, Germany, 50 Hz) was used for sonication.

General Procedure for Aldol Reaction. Trimethylsilyl enol ether (1 mmol) was added to neutral alumina (1g, activated at 180°C for 4h under vacuum and cooled under nitrogen) under stirring. After 2 min the aldehyde (1 mmol) was added with stirring and an easy flowing powder was obtained. This resulting powder in a small round bottom flask was immersed in an ultrasonic bath for a certain period of time as required for completion (TLC). Chloroform (30 ml) was then poured into the reaction mixture and filtered through a short column packed with anhydrous sodium sulfate. The filtrate was evaporated to leave the crude aldol which was further purified by short column chromatography over silica gel.

The aldol products are mostly known compounds and are easily identified by comparison of ^{1}H NMR spectral data with those reported. The anti/syn ratio was estimated by ^{1}H NMR analysis of the corresponding oxymethine peaks. The spectral and analytical data of these aldol products corresponding to entries in Table 1 are presented here.

1^2 : ^{1}H NMR δ 0.92-2.59 (7H, m), 3.03 (1H, broad), 4.67 (< 1H, d, J=9 Hz, anti -OCH), 5.15 (< 1H, d, J=2Hz, syn -OCH), 7.19 (5H, s).

2^9 : ^{1}H NMR δ 1.03-2.06 (12H, m), 2.26 (2H, t, J=7 Hz), 3.49 (< 1H, m, anti -OCH), 4.14 (< 1H, m, syn -OCH).

3^{3d}: ^{1}H NMR δ 0.95 (3H, d, J=7 Hz), 1.12 (3H, d, J=7 Hz), 1.39-2.36 (8H, m), 2.57 (1H, broad), 3.19 (< 1H, m, anti -OCH), 3.52 (<1H, m, syn -OCH).

4 : ^{1}H NMR δ 1.23-2.66 (7H, m), 4.79 (< 1H, d, J=8 Hz, anti -OCH), 4.82 (1H, broad), 5.30 (< 1H, broad, syn -OCH), 7.49 (2H, d, J=9 Hz), 8.16 (2H, d, J=9 Hz). Anal. calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found : C, 61.42; H, 5.51; N, 5.83.

5^{3d}: ^{1}H NMR δ 0.75-3.0 (9H, m), 3.49 (1H, broad), 4.63 (<1H, d, J=9 Hz, anti -OCH), 5.26 (<1H, d, J=2 Hz, syn -OCH), 7.19 (5H, s).

6^{3b}: ^{1}H NMR δ 1.09-3.23 (9H, m), 3.75 (1H, broad), 4.79 (< 1H, d, J=8 Hz, anti -OCH), 5.39 (< 1H, broad s, syn -OCH), 7.42 (2H, d, J=9 Hz), 8.14 (2H, d, J=9 HZ).

7^{3b}: ^{1}H NMR δ 1.16-3.00 (9H, m), 3.26 (1H, broad), 3.79 (3H, s), 4.60 (<1H, d, J=9 Hz, anti -OCH), 5.19 (< 1H, d, J=3 Hz, syn -OCH), 6.62-7.52 (4H, m).

8 : ^{1}H MMR δ 0.66-2.60 (17H, m), 3.27 (< 1H, m, anti -OCH), 3.60 (<1H, m, syn --OCH). Anal. clacd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found. : C, 70.51; H, 10.72.

9^{3a}: ^{1}H NMR δ 0.82-3.06 (9H, m), 3.62 (1H, broad), 4.59 (<1H, d, J=4 Hz, anti -OCH), 5.27 (<1H, d, J=2 Hz, syn -OCH), 6.85-7.92 (4H, m).

10^{3d}: ^{1}H NMR δ 0.82-3.13 (11H, m), 3.66 (1H, broad), 4.72 (< 1H, d, J=8 Hz, anti --OCH), 5.02 (< 1H, d, J=3 Hz, syn -OCH), 7.23 (5H, s).

11 : ^{1}H NMR δ 0.85-3.23 (11H, m), 3.85 (1H, broad), 4.92 (< 1H, d, J=8 Hz, anti --OCH), 5.23 (<1H, broad s, syn -OCH), 7.49 (2H, d, J=9 Hz), 8.10 (2H, d, J=9 Hz). Anal. calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found : C, 63.58; H, 6.56, N, 5.45.

12 : ^{1}H NMR δ 1.14 (3H, t, J=7 Hz), 2.54 (2H, q, J=7 Hz), 2.39 (2H, m), 4.63 (<1H, m, anti -OCH), 5.31 (< 1H, m, syn -OCH), 7.46 (5H, s), 9.53 (1H, broad s). Anal. calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found : C, 74.26; H, 8.02.

13^{10}: ^{1}H NMR δ 0.65-2.62 (13H, m), 3.51 (<1H, m, anti -OCH), 4.14 (< 1H, m, syn -OCH), 5.78 (1H, broad), 9.70 (1H, broad s).

Acknowledgement. We are pleased to acknowledge financial support from CSIR, New Delhi (Grant No. 02/355) for this investigation. R.C. also thanks CSIR for his fellowship.

References and Notes

1. This is fifth in series. for previous paper, See : Ranu, B.C.; Saha, M.: Bhar, S. Tetrahedron Lett. In Press.

2. (a) Mukaiyama, T.; Narasaka, K.; Banno, K. Chem. Lett. **1973**, 1011.
(b) Mukaiyama, T.; Banno, K.; Narasaka, K. J. Am. Chem. Soc. **1974**, 96, 7503.

3. (a) Kobayashi, S.: Hachiya, I. Tetrahedron Lett. **1992**, 33, 1625.
(b) Lubineau, A.; Meyer, E. Tetrahedron **1988**, 44, 6055.
(c) Yamamoto, Y.;Maruyama, K.; Matsumoto, K. J. Am. Chem. Soc. **1983**, 105, 6963.

(d) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. J. Org. Chem. **1983**, 48, 932.
(e) Kobayashi, S.; Murakami, M.; Mukaiyama, T. Chem. Lett. **1985**, 1535.
(f) Mukaiyama, T.; Kobayashi, S.: Murakami, M. Chem. Lett. **1985**, 447.

4. (a) Kawai, M.; Onaka, M.; Izumi, Y. Bull. Chem. Soc. Jpn. **1988**, 61, 1237.
(b) Naruse, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. Chem. Lett. **1985**, 1451.
(c) Ohki, H.; Wada, M.; Akiba, K. Tetrahedron Lett. **1988**, 29, 4719.

5. (a) Masamune, S.; Choy, W. Aldrichim. Acta. **1982**, 15, 47.
(b) Barlett, P.D. Tetrahedron **1980**, 36, 3.

6. (a) Ranu, B.C.; Bhar, S.; Sarkar, D.C. Tetrahedron Lett. **1991**, 32, 2811.
(b) Ranu, B.C.; Bhar, S. Tetrahedron **1992**, 48, 1327.
(c) Ranu, B.C.; Bhar, S. J. Chem. Soc. Perkin Trans.1 **1992**, 365.
(d) Ranu, B.C.; Sarkar, D.C.; Chakraborty, R. Synth. Commun. **1992**, 22, 1095
(e) Ranu, B.C.; Bhar, S.; Chakraborti, R. J. Org. Chem. **1992**, 57, 7349.

7. Attempts for further improvement of diastereoselectivity modifying substituents on silicon of the enol ether[3e,3f] are in progress.

8. House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. J. Org. Chem. **1969**, 34, 2324.

9. Mekhtiev, S.D.; Musaev, M.R.; Alimardanov, Kh. M.; Sakhnovskaya, E.B.; Babaeva, A.R. Azerb. Khim. Zh. **1975**, 34 (Chem. Abst. **1979**, 84, 164222J)

10. Blanc, P.Y.; Perret, A.; Teppa, F. helv. Chim. Acta. **1964**, 47, 567.