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Surface-Mediated Solid Phase Reaction : Dramatic Improvement of Michael Reaction on the Surface of Alumina

Brindaban C. Ranu* and Sanjay Bhar

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

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Key Words : Michael reaction; Al_2O_3; dramatic improvement

Abstract : The Michael reaction of several 1,3-dicarbonyl compounds, nitroalkanes, and thiols as donors with methyl vinyl ketone, acrolein, methyl acrylate, methyl methacrylate, and mesityl oxide as acceptors on the surface of alumina without any solvent proceed very effeciently and furnish high yield of adducts.

The technique of surface-mediated solid phase reaction is of growing interest[1] because of their advantages of ease of set-up, mild conditions, rapid reactions, selectivity, increased yields and low cost compared with their homogeneous counterparts. As a part of our continuing efforts to explore the novel utilities of surface-mediated reactions[2] we have disclosed a dramatic acceleration of Michael reaction on the surface of alumina in a recent communication[3] and wish to report here the details of these results and further scope and generality of this procedure.

The Michael reaction is one of the most efficient methods for effecting carbon-carbon bond formation[4] and has wide synthetic applications.[5] These reactions are usually carried out in a suitable solvent in presence of strong bases. Side reactions, frequently encountered in presence of a base, are secondary condensations, bis additions, polymerisations, retrogressions and rearrangements. Use of transition-metal complex,[6] alumina- and clay-supported catalysts,[7] and phase-transfer catalysts[8] have made considerable improvements in the Michael addition, yet, these procedures have one or more limitations as regards the scope and generality of the reaction, the use of toxic and expensive materials, long reaction procedures, and/or relatively low yields of products. The need to accomplish this important synthetic transformation more efficiently has led us to develop this procedure of Michael reaction on the solid surface of Al_2O_3.

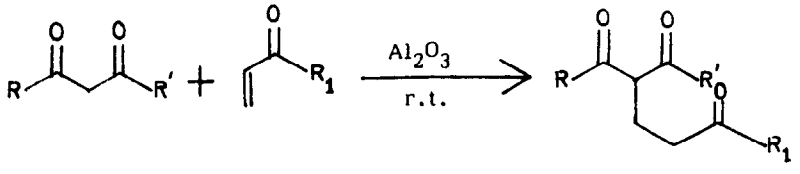


Table 1 : Al_2O_3-mediated Michael Addition

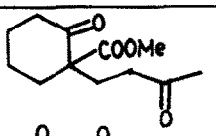
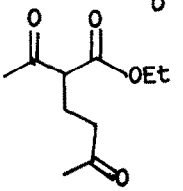
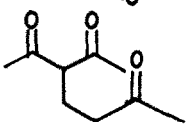
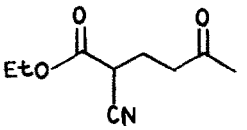
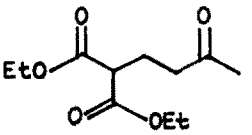
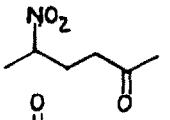
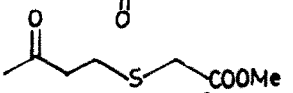
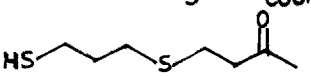
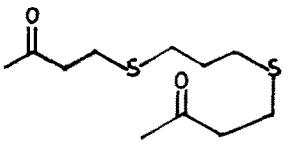
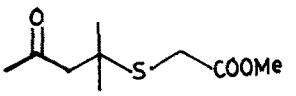
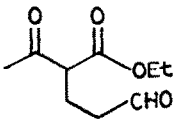
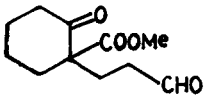
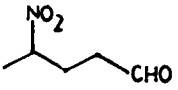
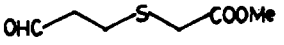
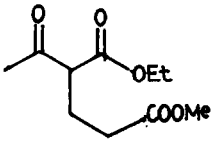
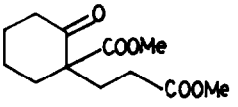
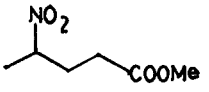
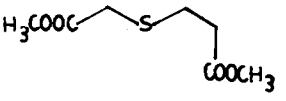
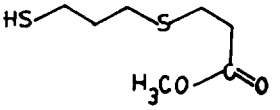
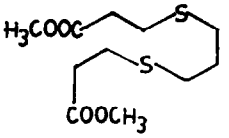
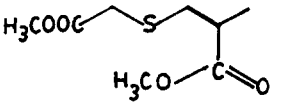
Entry	Donor	Acceptor	Time	Adduct	Yield,%[a]
1	Methyl 2-oxocyclo-hexanecarboxylate	MVK[b]	5 min		91
2	Ethyl acetoacetate	MVK	5 min		95
3	Acetylacetone	MVK	30 min		84
4	Ethyl cyanoacetate	MVK	4 h		90
5	Diethyl malonate	MVK	4 h		90
6[c]	Nitroethane	MVK	2 h		60
7	Methyl thioglycolate	MVK	5 min		85
8	1,3-Propanedithiol	MVK (1 eqiv)	5 min		75
9	1,3-Propanedithiol	MVK (2 equiv)	5 min		82
10	Methyl thioglycolate	Mesityl oxide	30 min		80
11[c]	Ethyl acetoacetate	Acrolein	5 min		90

Table 1 (Contd....)

Entry	Donor	Acceptor	Time	Adduct	Yield,%[a]
12[c]	Methyl 2-oxycyclo-hexanecarboxylate	Acrolein	5 min		91
13[d]	Nitroethane	Acrolein	1 h		60
14[d]	Methylthioglycolate	Acrolein	10 min		90
15	Ethyl acetoacetate	MA[b]	4 h		80
16	Methyl 2-oxocyclo-hexane carboxylate	MA	4 h		88
17[c]	Nitroethane	MA	4 h		55
18	Methyl thioglycolate	MA	2 h		85
19	1,3-propanedithiol	MA (1 equiv)	30 min		76
20	1,3-propanedithiol	MA (2 equiv)	30 min		90
21	Methyl thioglycolate	MMA[b]	2 h		75

[a]Yield of isolated pure products, fully characterized by their IR, NMR data; [b]MVK, MA and MMA are abbreviations for methyl vinyl ketone, methyl acrylate and methyl methacrylate respectively; [c]Reactions were carried out at 0°C; [d]Reactions were carried out at -10 to -15°C (ice-salt bath).

In a typical general procedure, the Michael donor (1 mmol) was stirred on the surface of activated alumina at room temperature for 10 min after which the Michael acceptor (1 mmol) was added and stirring was continued under nitrogen till completion of the reaction, as monitored by TLC/or GC. The product was isolated in a pure state by simple filtration chromatography of the solid mass through a short plug of silica gel. The results are reported in Table 1.

As shown in Table 1, several structurally varied donors including 1,3-dicarbonyl compounds, ethyl cyanoacetate, diethyl malonate, nitroethane, methyl thioglycolate and 1,3-propanedithiol underwent clean and remarkably fast Michael additions with a variety of acceptors like methyl vinyl ketone, acrolein, methyl acrylate, mesityl oxide and methyl methacrylate under this procedure. The dramatic improvement observed is with regard to reaction time. Many reactions are complete within a period of 5 minutes. Interestingly, it was found that presence of solvent (THF) slowered the reaction. The reasons for the efficiency of the process on the solid phase are yet to explore. The yields, in general, are very high except in the additions of nitroethane where the isolated yields are relatively low presumably due to decomposition of adduct during isolation process. The reactions were usually carried out at room temperature, although in few cases (entries 6,11-14,17) where acrolein or nitroethane are involved, lower temperature furnished better yields. All the additions were carried out with 1:1 donor-acceptor proportions. 1,3-Propanedithiol having two reactive sites produced a small amount (to the extent of 10%) of di-adducts when one equivalent of acceptors were used (entries 8,20), although the mono adducts were easily separated by column chromatography. The additions with mesityl oxide and methyl methacrylate are not general; these acceptors, though, went very well with relatively more reactive methyl thioglycolate (entries 10,22), additions with 1,3-dicarbonyl compounds and nitroethane are not very successful.

To sum up, the important features of this methodology are: (a) no requirement of base; (b) no undesirable side reaction; (c) remarkably fast addition; (d) mild reaction condition; (e) ease of set-up and work-up; (f) involvement of no toxic and expensive material; and (g) high yield.

In conclusion, this procedure of Michael addition on the solid surface of Al_2O_3 without any solvent offers significant improvements over the existing methods and would thus help facile entry into a host of new Michael adducts of potentially high synthetic utility. Nevertheless, this procedure clearly illustrates a finer application of surface-mediated solid phase reaction technology.

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Experimental

General : ^{1}H NMR spectra were recorded at 60 MHz on Em 360 spectrometers of Varian Associates in CCl_4 solutions with Me_4Si as an internal standard. IR spectra were recorded on a Perkin Elmer 298 spectometer as a thin film (neat). GLC was done on a Shimadzu GC-9A instrument using a SE-30 column (2 m) and nitrogen as carrier gas. 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 filtration chromatography was also from SRL, India. All the chemicals are commercial products and distilled before use.

General procedure for Michael addition : The Michael donor (1 mmol) was added onto the surface of alumina (500 mg, activated at 180°C for 4 h under vacuum) and stirred for 10 min at room temperature. The Michael acceptor (1 mmol) was then added and stirring was continued at room temperature unless otherwise mentioned in Table 1 under nitrogen till completion of the reaction as monitored by TLC or GC. The solid mass was then taken in a column with a short plug of silica gel and eluted with methylene chloride. Evaporation of solvent furnished practically pure product which was further purified by column chromatography over silica gel or short path distillation.

Although the results shown in Table 1 were obtained from milligram scale reactions, gram-scale reactions afforded the corresponding products in analogously excellent yields.

The Michael adducts were easily identified by their spectral (IR and ^{1}H NMR) data which are presented here for ready reference (adducts correspond to entries in Table 1).

1 : IR 1710, 1735 cm^{-1}; ^{1}H NMR δ 1.5-2.53 (12H, m), 2.03 (3H, s), 3.66 (3H, s).

2 : IR 1710, 1735 cm^{-1}; ^{1}H NMR δ 1.30 (3H, t, J = 7 Hz), 2.06 (3H, s), 2.16 (3H, s), 1.93-2.56 (4H, m), 3.36 (1H, t, J = 6 Hz), 4.16 (2H, q, J = 7 Hz).

3 : IR 1695, 1710 cm^{-1}; ^{1}H NMR δ 1.76-2.46 (4H, m), 2.06 (3H, s), 2.1 (3H, s) 2.13 (3H, s), 3.5 (1H, t, J = 7 Hz) (enol present).

4 : IR 1715, 1745, 2250(w) cm^{-1}; ^{1}H NMR δ 1.33 (3H, t, J = 7 Hz), 1.73-2.66 (4H, m), 2.13 (3H, s), 3.6 (1H, t, J = 7Hz), 4.23 (2H, q, J = 7 Hz).

5 : IR 1710, 1740 cm^{-1}; ^{1}H NMR δ 1.3 (6H, t, J = 7 Hz), 1.83-2.5 (4H, m), 2.13 (3H, s), 3.3 (1H, t, J = 8 Hz), 4.2 (4H, q, J = 7 Hz).

6 : IR 1360, 1545, 1715 cm^{-1}; ^{1}H NMR δ 1.55 (3H, d, J = 7 Hz), 2.13 (3H, s), 2.0-2.63 (4H, m), 4.57 (1H, sextet, J = 7 Hz).

7 : IR 1710, 1735 cm^{-1}; ^{1}H NMR δ 2.06 (3H, s), 2.7 (4H, broad s), 3.1 (2H, s), 3.63 (3H s).

8 : IR 1710 cm^{-1}; ^{1}H NMR δ 1.27 (1H, t, J = 8 Hz), 1.7-2.0 (2H, m), 2.13 (3H, s), 2.47-2.73 (8H, m with 2.66 (s)).

9 : IR 1710 cm^{-1}; ^{1}H NMR δ 1.7-2.0 (2H, m), 2.1 (6H, s), 2.46-2.66 (12H, m).

10 : IR 1715, 1735 cm^{-1}; ^{1}H NMR δ 1.36 (6H, s), 2.1 (3H, s), 2.6 (2H, s), 3.2 (2H, s), 3.7 (3H, s).

11 : IR 1710, 1720, 1735, 2730(w) cm^{-1}; ^{1}H NMR δ 1.28 (3H, t, J = 7 Hz), 2.0-2.46 (7H, m with 2.2 (s)), 3.4 (1H, m), 4.16 (2H, q, J = 7 Hz), 9.66 (1H, s).

12 : IR 1710, 1720, 1730, 2730(w) cm^{-1}; ^{1}H NMR δ 1.60-2.56 (12H, m), 3.73 (3H, s), 9.66 (1H, s).

13 : IR 1350, 1550, 1720, 2720(w) cm^{-1}; ^{1}H NMR δ 1.57 (3H, d, J = 7 Hz), 1.90-2.6 (4H, m), 4.53 (1H, sextet, J = 7 Hz), 9.8 (1H, s).

14 : IR 1720, 1735 cm^{-1}; ^{1}H NMR δ 2.70-2.86 (4H, m), 3.16 (2H, s), 3.73 (3H, s), 9.8 (1H, s).

15 : IR 1715, 1745 cm^{-1}; ^{1}H NMR δ 1.3 (3H, t, J = 7 Hz), 2.00-2.33 (7H, m with 2.13 (s) and 2.2(s)), 3.46 (1H, t, J = 8 Hz), 3.63 (3H, s), 4.16 (2H, q, J = 7 Hz).

16 : IR 1710, 1735 cm^{-1}; ^{1}H NMR δ 1.43-2.56 (12H, m), 3.6 (3H, s), 3.70 (3H, s).

17 : IR 1360, 1550, 1735 cm^{-1}; ^{1}H NMR δ 1.60 (3H, d, J = 7 Hz), 2.00-2.53 (4H, m), 3.66 (3H, s), 4.33-4.90 (1H, m).

18 : IR 1735 cm^{-1}; ^{1}H NMR δ 2.33-3.00 (4H, m), 3.13 (2H, s), 3.63 (3H, s), 3.66 (3H, s).

19 : IR 1735 cm^{-1}; ^{1}H NMR δ 1.23 (1H t, J = 8 Hz), 1.73-2.06 (2H, m), 2.33-2.83 (8H, m), 3.67 (3H, s).

20 : IR 1735 cm^{-1}; ^{1}H NMR δ 1.60-2.13 (2H, m), 2.36-2.90 (12H, m), 3.66 (6H, s).

21 : IR 1735 cm^{-1}; ^1H NMR δ 1.21 (3H, d, J = 7 Hz), 2.30-2.96 (3H, m), 3.1 (2H, s), 3.6 (3H, s), 3.66 (3H, s).

References

1. (a) Fadel, A.; Yefash, R.; Salaun, J. Synthesis **1987**, 37. (b) Rosini, G.; Galarini, R.; Marotta, E.; Righi, R. J. Org. Chem. **1990**, 55, 781. (c) Kodomari, M.; Sakamoto, T.; Yoshitomi, S. J. Chem. Soc. Chem. Commun. **1990**, 701. (d) Kropp, P.J.; Daus, K.A.; Crawford, S.D.; Tubergren, M.W.; Kepler, K.D.; Craig, S.L.; Wilson, V.P. J. Am. Chem. Soc. **1990**, 112, 7433. (e) Hondrogiannis, G.; Pagni, R.M.; Kabalka, G.W.; Anosike, P.; Kurt, R. Tetrahedron Lett. **1990**, 31, 5433. (f) Patney, H.K. Tetrahedron Lett. **1991**, 32, 2259. (g) Pautet, F.; Daudon, M. Tetrahedron Lett. **1991**, 32, 1457.
2. (a) Ranu, B.C.; Das, A.R. J. Chem. Soc. Chem. Commun. **1990**, 1334. (b) Ranu, B.C.; Das, A.R. J. Org. Chem. **1991**, 56, 4796. (c) Ranu, B.C.; Bhar, S. J. Chem. Soc. Perkin Trans. 1, In press.
3. Ranu, B.C.; Bhar, S.; Sarkar, D.C. Tetrahedron Lett. **1991**, 32, 2811.
4. (a) Bergman, E.D.; Ginsburg, D.; Pappo, R. Organic Reactions, **1959**, 10, 179. (b) Hermann, K.; Wynburg, H. J. Org. Chem. **1979**, 44, 2238. (c) Oare, D.A.; Heathcock, C.H. J. Org. Chem. **1990**, 55, 157 and references cited therein. (d) Ganesh, S.; Sarkar, A. Tetrahedron Lett. **1991**, 32, 1085. (e) Machida, S.; Hashimoto, Y.; Saigo, K.; Inoue, J.; Hasegawa, M. Tetrahedron **1991**, 47, 3737.
5. (a) Oare, D.A.; Heathcock, C.H. in 'Topics in Stereochemistry' Eds. Eliel, E.L.; Willen, S.H. vol. 19, p. 277, John Wiley and sons, New York, **1989**. (b) Angelo, J. ; Revial, G.; Costa, P.R.R.; Castro, R.N.; Antunes, O.A.C. Tetrahedron Asymmetry **1991**, 2, 199. (c) Jansen, J.F.G.A.; Feringa, B.L. Tetrahedron Asymmetry **1991**, 1, 719.
6. (a) Saegusa, T.; Ito, Y.; Tomita, S.; Kinoshita, H. Bull. Chem. Soc. Jpn. **1972**, 45, 496. (b) Trost, B.M.; Strege, P.E.; Webber, L.; Fullerton, T.J.; Dietsche, T.J. J. Am. Chem. Soc. **1978**, 100, 3407. (c) Nelson, J.H.; Howells, P.H.; Delullo, G.C.; Landen, G.L.; Henry, R.A. J. Org. Chem. **1980**, 45, 1246. (d) Watanabe, K.; Miyazu, K.; Irie, K. Bull. Chem. Soc. Jpn. **1982**, 55, 3212. (e) Coda, A.C.; Desimoni, G.; Righetti, P.; Tacconi, G. Gazz. Chim. Ital. **1984**, 114, 417. (f) Kocousky, P.; Dvorak, D. Tetrahedron Lett. **1986**, 27, 5015. (g) Maota, T.; Taki, H.; Mizuno, M.; Murahashi, S.I. J. Am. Chem. Soc. **1989**, 111, 5954. (h) Paganelli, S.; Schionato, A.; Botteghi, C. Tetrahedron Lett. **1991**, 32, 2807.
7. (a) Clark, J.H.; Cork, D.G.; Robertson, M.S. Chem. Lett. **1983**, 1145. (b) Yamawaki, J.; Kawate, T.; Ando, T.; Hanafusa, T. Bull. Chem. Soc. Jpn. **1983**, 56, 1885. (c) Laszlo, P.; Pennetreau, P. Tetrahedron Lett. **1985**, 26, 2645. (d) Laszlo, P.; Montaufier, M.-T.; Randriamahefa, S.L. Tetrahedron Lett. **1990**, 31, 4867.
8. (a) Kryshtal, G.V.; Kulganek, V.V.; Kucherov, V.F.; Yanovskaya, L.A. Synthesis **1979**, 107. (b) Cram, D.J.; Sogah, G.D.Y. J. Chem. Soc. Chem. Commun. **1981**, 625. (c) Aoki, S.; Sasaki, S.; Koga, K. Tetrahedron Lett. **1989**, 30, 7229.