



Construction of bicyclo-[2.2.2]octanone systems

by microwave-assisted solid phase Michael addition followed by Al_2O_3 -mediated intramolecular aldolisation. An eco-friendly approach

Brindaban C. Ranu,^{*a} Sankar K. Guchhait,^a Keya Ghosh^a and Amarendra Patra^b

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

^b Department of Chemistry, University College of Science, Calcutta-700 032, India

Received 22nd September 1999

Summary

Microwave irradiation of a mixture of cyclohexenones and ethyl acetoacetate adsorbed on the surface of solid lithium *S*-(−)-prolinate which is then placed on a column of basic alumina leads to the stereoselective construction of bicyclo[2.2.2]octanone systems through Michael addition and subsequent intramolecular aldolisation.

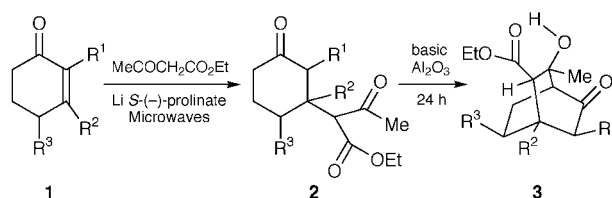
Introduction

Bicyclo[2.2.2]octane derivatives constitute an important class of synthons for natural product synthesis¹ as well as other synthetic applications.² Although there are a number of approaches for the construction of this system,³ a simpler and environment friendly approach is still required. During the course of our investigations on the surface-mediated solid phase Michael reaction,⁴ a mixture of cyclohexenone and ethyl acetoacetate adsorbed on the solid surface of lithium *S*-(−)-prolinate was microwave irradiated.⁵ During purification of the crude reaction mixture through a column of alumina, very interestingly a small amount of a crystalline compound which was eventually found to be the bicyclo[2.2.2]octanone derivative **3a**, was isolated together with the usual Michael addition product. The importance of the bicyclo[2.2.2]octane system^{1,2} prompted us to study the synthesis of this compound in a useful yield.

Results and discussion

In a typical procedure, a mixture of cyclohexenone and ethyl acetoacetate adsorbed on the solid surface of lithium *S*-(−)-prolinate was irradiated in a domestic microwave oven for 6 minutes and the reaction mixture (as a semisolid mass) was kept in a basic alumina column for 24 hours. Elution of the column (ethyl acetate) furnished the bicyclo[2.2.2]octanone derivative **3a** in 75% yield (Scheme 1).

The Michael adduct **2** undergoes intramolecular aldolisation⁶ in the alumina column to form the bicyclo[2.2.2]octanone system. The reaction is found to be effective for substituted cyclohexenones also, although the yields of **3** from 2-methyl- and 3-methylcyclohexenones are relatively low. This is possibly due to the fact that these Michael additions are never complete leaving a considerable amount (20–25%) of unreacted cyclohexenones. Microwave irradiation with higher power or longer duration also



1	Period of microwave irradiation/min	Yield of 3 (%) ^a
a $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$	6	75
b $\text{R}^1 = \text{Me}, \text{R}^2 = \text{R}^3 = \text{H}$	14	60
c $\text{R}^1 = \text{R}^3 = \text{H}, \text{R}^2 = \text{Me}$	15	55
d $\text{R}^1 = \text{R}^2 = \text{H}, \text{R}^3 = \text{Me}$	15	72

^a yields refer to pure isolated products starting from **1**

Scheme 1

did not help. However, in general, for all Michael additions microwave irradiation is essential as conventional heating in dry media (100 °C) leads to marginal addition products with

Green Context

While the search for new more efficient catalytic systems including the substitution of catalysts for reagents, and the development of more environmentally friendly reagents are important aspects of clean synthesis, an equally important goal is the discovery of alternative greener routes. This article builds on the observation that during investigations on a Michael reaction under dry conditions, an unexpected product was also observed in small quantities. By-products are commonly observed in organic synthesis and are not usually welcome but in this case it turned out to be a valuable product. Progress in Green Chemistry will require the exploitation of such serendipitous observations. Here we can read how through observation, awareness of an opportunity and subsequent studies to maximise the by-product a new cleaner synthesis route to valuable products can be developed.

JHC

considerable amounts of polymeric material. Refluxing in THF also failed to produce more than 20% of the desired adduct. The aldolisation step is also best carried out in a column of basic alumina. Irradiation in the microwave oven beyond the Michael addition period does not induce aldolisation considerably. This process of Michael addition and subsequent aldolisation is stereoselective producing the bicyclo[2.2.2]octanone derivatives as crystalline compounds and single stereoisomers as revealed from ^1H and ^{13}C NMR data. To conclude, this protocol of Michael addition and subsequent intramolecular aldolisation on the solid surface for the stereoselective synthesis of functionalised bicyclo[2.2.2]octanone derivatives is novel, simple and has high potential for useful applications in organic synthesis. In addition, this reaction has been carried out in dry media under microwave irradiation avoiding any toxic reagent and solvent and the inorganic supports used can be recycled.

Although the use of lithium *S*-(–)-prolinate as a reactive surface in the Michael addition step was to induce optical activity, under the present reaction conditions this was not successful. However, further attempts to broaden the scope of this strategy and induce asymmetry in the Michael addition step will be our next goal.

Experimental

Typical general procedure for the synthesis of bicyclo[2.2.2]octanones. Synthesis of 3a.

A mixture of cyclohexenone (288 mg, 3 mmol) and ethyl acetoacetate (390 mg, 3 mmol) was absorbed uniformly on the surface of lithium *S*-(–)-prolinate powder (454 mg, 3.75 mmol), prepared by adding an equivalent amount of an ethanolic solution of lithium ethoxide to a solution of *S*-(–)-proline in ethanol followed by evaporation of solvent and drying under vacuum, and was then irradiated in a domestic microwave oven (BPL-Sanyo, India) at 240 W in an open round-bottomed flask fitted with a CaCl_2 guard tube for 6 min (irradiation for longer duration was made with a break after every 6 min). The remaining semisolid mass was then confined in a basic alumina column for 24 h. Elution of the column (ethyl acetate) furnished the bicyclo[2.2.2]octanone **3a** (508 mg, 75%), mp 80 °C; $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 1720–1730(broad); δ_{H} (300 MHz, CDCl_3) 1.26 (3 H, t, *J* 7 Hz), 1.52 (3 H, s), 1.56–1.8 (4 H, m), 1.92–2.14 (1 H, m), 2.25 (1 H, t, *J* 3 Hz), 2.52 (2 H, br), 2.8 (1 H, dt, *J* 18 and 1.09 Hz), 3.2 (1 H, s) and 4.19 (2 H, q, *J* 7 Hz); δ_{C} (75 MHz, CDCl_3) 14.16 (CH_3), 19.59 (CH_2), 25.30 (CH_2), 27.47 (CH_3), 30.40 (CH), 40.37 (CH_2), 52.22 (CH), 55.72 (CH), 60.65 (CH_2), 72.83 (C), 171.90 (C) and 214.32 (C).

3b: mp 68 °C; $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 1720–1730 (br); δ_{H} (300 MHz, CDCl_3) 1.13 (3 H, d, *J* 7.5 Hz), 1.29 (3 H, t, *J* 7.2 Hz), 1.46–1.56 (2 H, m), 1.56 (3 H, s), 1.76–1.77 (2 H, m), 2.36 (1 H, dt, *J* 18 and 1.1 Hz), 2.66 (1 H, br), 2.69 (1 H, s), 2.83–2.84 (2 H, m) and 4.24 (2 H, q, *J* 7.2 Hz); δ_{C} (75 MHz, CDCl_3) 12.11 (CH_3), 14.18 (CH_2), 20.18 (CH_2), 20.62 (CH_2), 27.85 (CH_3), 36.90 (CH), 41.78 (CH_2), 53.47 (CH), 55.49 (CH), 60.83 (CH_2), 72.79 (C), 172.30 (C) and 216.65 (C).

3c: mp 75 °C; $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 1720–1735 (br); δ_{H} (300 MHz, CDCl_3) 1.04 (3 H, s), 1.30 (3 H, t, *J* 7.2 Hz), 1.35–1.42 (1 H, m), 1.48 (3 H, s), 1.76–1.93 (3 H, m), 2.32 (1 H, t, *J* 1.1 Hz), 2.49 (1 H, d, *J* 2.1 Hz), 2.94–3.08 (2 H, m) and 4.21 (2 H, q, *J* 7.2 Hz); δ_{C} (75 MHz, CDCl_3) 14.22 (CH_3), 19.49 (CH_2), 23.15 (CH_3), 27.69 (CH_3), 34.04 (CH_2), 35.72 (C), 45.32 (CH_2), 55.90 (CH), 57.30 (CH), 60.55 (CH_2), 72.55 (C), 171.64 (C) and 213.97 (C).

3d: mp 73 °C; $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 1720–1730 (br); δ_{H} (300 MHz, CDCl_3) 1.01 (3 H, d, *J* 7.2 Hz), 1.30 (3 H, t, *J* 7.2 Hz), 1.30–1.32

(1 H, m), 1.55 (3 H, s), 1.92–1.95 (1 H, br), 2.02–2.15 (1 H, m), 2.2–2.32 (3 H, m), 2.50 (1 H, br), 2.54–2.79 (1 H, m), 2.90 (1 H, br) and 4.23 (2 H, q, *J* 7.2 Hz); δ_{C} (75 MHz, CDCl_3) 14.21 (CH_3), 20.37 (CH_3), 28.30 (CH_3), 29.23 (CH_2), 30.07 (CH), 34.82 (CH_2), 36.31 (CH), 54.34 (CH), 56.41 (CH), 60.88 (CH_2), 72.36 (C), 171.82 (C) and 213.65 (C).

Alternatively, the initial Michael adduct can be isolated by extraction of the lithium *S*-(–)-prolinate solid support with ethyl acetate followed by evaporation of solvent and then alumina column to obtain the same final product. The lithium *S*-(–)-prolinate can be recycled after being dried.

Acknowledgements

Financial support from the CSIR, New Delhi [01/(1504)/98] for this investigation is gratefully acknowledged. S. G. and K. G. are also thankful to the CSIR for fellowships.

References

- 1 K. Mori, *Synlett*, 1995, 1097; L. A. Paquette and H. C. Tsui, *J. Org. Chem.*, 1996, **61**, 142; S. F. Martin, J. B. White and R. Wagner, *J. Org. Chem.*, 1982, **47**, 3190.
- 2 H. Waldmann, M. Weigering, C. Dreisbach and C. Wandrey, *Helv. Chim. Acta*, 1994, **77**, 2111; B. M. Trost, B. Breit, S. Peukert, J. Zambrano and J. W. Ziller, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2386; D. Seebach, G. Jaeschke and Y. M. Wang, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2395; F. Almquist and T. Frejd, *J. Org. Chem.*, 1996, **61**, 6947.
- 3 R. A. Lee, *Tetrahedron Lett.*, 1973, **35**, 3333; S. Ranganathan, D. Ranganathan and A. K. Mehrotra, *Synthesis*, 1977, 289; P. C. Belanger and C. Dufresne, *Can. J. Chem.*, 1986, **64**, 1514; G. S. R. Subba Rao and K. V. Bhaskar, *J. Chem. Soc., Perkin Trans. 1*, 1993, 333; C.-S. Chu, T.-H. Lee and C.-C. Liao, *Synlett*, 1994, 635; S. V. Ley, D. M. Mynett and W.-J. Koot, *Synlett*, 1995, 1017; L. A. Paquette and H.-C. Tsui, *J. Org. Chem.*, 1996, **61**, 142; A. Srikrishna and T. J. Reddy, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2137; M. Toyota, M. Yokota and M. Ihara, *Tetrahedron Lett.*, 1999, **40**, 1551.
- 4 B. C. Ranu, M. Saha and S. Bhar, *Synth. Commun.*, 1997, **27**, 621; B. Baruah, A. Boruah, D. Prajapati and J. S. Sandhu, *Tetrahedron Lett.*, 1997, **38**, 1449; A. Soriente, A. Spinella, M. De Rosa, M. Giordano and A. Scettri, *Tetrahedron Lett.*, 1997, **38**, 289; M. Yamaguchi, T. Shiraishi and M. Hiramata, *J. Org. Chem.*, 1996, **61**, 3520; H. Sasai, E. Emori, T. Arai and M. Shibasaki, *Tetrahedron Lett.*, 1996, **37**, 5561; U. Elder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 496.
- 5 For reviews on microwave-assisted reactions see: R. S. Varma, *Green Chem.*, 1999, **1**, 43; S. Caddick, *Tetrahedron*, 1995, **51**, 10403.
- 6 M. H. Filippini, R. Faure and J. Rodriguez, *J. Org. Chem.*, 1995, **60**, 6872; C. Agami, *Bull. Soc. Chim. Fr.*, 1988, 499.

Paper a907689a