Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Catalysis A: Chemical 274 (2007) 105–108
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Microwave accelerated S_N2' substitution of Baylis–Hillman acetates: A comparative study of conventional heating versus microwave irradiation

J.S. Yadav *, B.V. Subba Reddy, A.K. Basak, A. Venkat Narsaiah

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India

Received 19 March 2007; accepted 27 March 2007
Available online 31 March 2007

Abstract

Baylis–Hillman acetates undergo a rapid S_N2' allylic substitution with ethyl (triphenyl phosphoranylidene) acetate under microwave irradiation to afford ethyl 5-aryl or alkyl-(*E*)-pent-4-enoates in high yields with high (*E*)-stereoselectivity. The reaction rates and yields are significantly improved by employing microwave irradiation. A comparative study under thermal conditions and microwave irradiation is also described.

Keywords: Phosphonium ylide; S_N2' substitution; Allylic acetates; Microwave

1. Introduction

Baylis–Hillman reaction is one of the most important carbon–carbon bond forming reactions in organic synthesis [1]. The coupling of activated vinylic systems with aldehydes or imines in the presence of 1,4-diazabicyclo [2,2,2] octane (DABCO), known as Baylis–Hillman reaction [2], is widely used for the direct synthesis of α-hydroxy or α-amino alkyl- or aryl-vinyl systems. The resulting densely functionalized products allow numerous transformations and have made these Baylis–Hillman adducts a valuable synthetic intermediates [3]. Baylis–Hillman adducts and their acetates are known to undergo S_N2' allylic substitution with various nucleophiles such as metal hydrides, halides, azides, cyanides, alcohols, amines, arenes and active methylene compounds to give a wide range of synthetic intermediates [4–19]. Consequently, there have been some precedents on the allylic substitution of Baylis–Hillman acetates with a stabilized ylide [20–21]. However, these methods typically require the use of basic conditions, expensive reagents and longer reaction times. Recently, microwave-assisted organic reactions have attracted considerable importance in organic synthesis because of the simplicity in operation, greater selectivity and rapid synthesis of a variety of organic compounds [22–23]. The notable features of the microwave approach are enhanced reaction rates, formation of pure products in high yields and ease of manipulation. Furthermore, solvent-free microwave assisted reactions have gained more popularity as they provide an opportunity to work with open vessels. This avoids the risk of development of high pressure and provides a possibility of upscaling the reaction and helps the induction of the reaction under dry conditions. Thus, microwave irradiation has become a powerful tool for the rapid synthesis of a variety of organic molecules under solvent-free conditions [24–25].

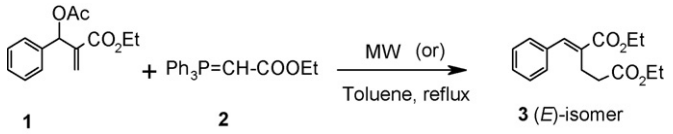
2. Results and discussion

In this article, we describe a rapid and catalyst-free method for the derivatization of Baylis–Hillman acetates using ethyl (triphenyl phosphoranylidene) acetate under microwave irradiation in solvent-free conditions. Thus, treatment of Baylis–Hillman acetate derived from benzaldehyde and ethyl acrylate, ethyl 3-acetoxy-2-methylene-3-phenylpropanoate (**1**) with a stabilized ylide (**2**) under microwave irradiation for 3 min afforded diethyl 2-(1-phenyl-(*E*)-methylidene)pentanedioate (**3a**) in 87% yield (Scheme 1).

Similarly, various aryl substituted Baylis–Hillman acetates reacted smoothly with two carbon stable ylide to give the corresponding 5-aryl-(*E*)-pentenoates in high yields with high (*E*)-stereoselectivity. The (*E*)-stereochemistry of the products was assigned on the basis of the chemical shift values of vinyl and allylic protons in the ^{1}H NMR spectrum of the products

* Corresponding author. Tel.: +91 40 27193030; fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (J.S. Yadav).

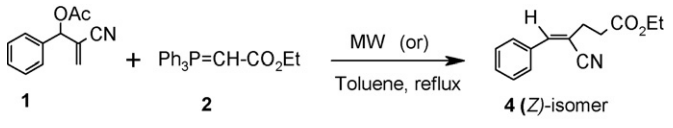
1381-1169/$ – see front matter © 2007 Published by Elsevier B.V.
doi:10.1016/j.molcata.2007.03.073



Scheme 1.

and also by the comparison of the spectral data with authentic compounds [10]. In the ^{13}C NMR spectra of trisubstituted olefins, allyic carbon *cis* to aryl group appears up field while the same carbon *trans* to aryl group appears down field. In case of thiophene-2-carboxaldehyde and furfural the products were obtained as a mixture of (*E*) and (*Z*) isomers (entries e and f, Table 1). The ratio of (*E*) and (*Z*) isomers was determined on the basis of integration ratios of isomeric olefinic proton and allylic methylene protons in ^{1}H NMR spectrum of products. Interestingly, cinnamaldehyde gave diethyl 2-[3-phenyl-(*E*,2*E*)-2-propenylidene] pentanedioate with (*E*,*E*)-stereoselectivity (entry g). Further the reactions of Baylis–Hillman acetates derived from acrylonitrile, i.e. 3-acetoxy-2-methylene-3-phenyl propionitrile with ethyl (triphenyl phosphoranylidene) acetate produced the corresponding trisubstituted alkenes in high yields (Scheme 2).

In case of 3-acetoxy-2-methylene-3-aryl propionitriles, the products were obtained with (*Z*)-stereoselectivity. The (*Z*)-stereochemistry of the products was assigned by comparing the chemical shift values of allylic methylene protons and vinyl protons with authentic compounds [10]. The reactions were clean and highly stereoselective affording the products in high yields with high degree of stereoselectivity. All the products were characterized by ^{1}H NMR, IR and mass spectroscopy and also by comparison with authentic compounds [10]. The reactions were carried out both under microwave as well as thermal conditions. The reaction proceeded rapidly under microwave irradiation in solvent-free conditions. Microwave irradiations were performed using BPL, BMO-700T domestic microwave oven operated at 2450 MHz (450 W). The reaction temperature was controlled by using a pulsed irradiation technique (1 min with 20 s intervals). The temperature was measured after each pulse. The lowest observed temperature was 80 °C after irradiation for 1-min at 450 W and the highest temperature was 110 °C after 3 min irradiation at the same power. The reaction rates and yields were dramatically enhanced by microwave irradiation. The rate enhancement under microwave irradiation may be attributed to the absorption of more microwave energy by the polar media (neutral alumina), which generates sufficient heat energy to promote the reaction. The same reaction, under thermal conditions, at 110 °C, took 6–36 h to afford comparable yields those that are obtained by microwave irradiation and the comparative results are summarized in Table 1. Furthermore, the reactions were carried out with Baylis–Hillman adducts (hydroxy compounds) instead of acetates. Even though, the reactions succeeded with hydroxy compounds, low conversions were obtained even after long reaction times. Best results were obtained only with Baylis–Hillman acetates. The scope of this method was investigated with respect to various allylic acetates including aliphatic (entry l, m) systems and the results are presented in the Table 1.



Scheme 2.

3. Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 and Varian Bruker-300 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

3.1. Typical procedure

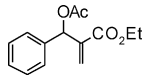
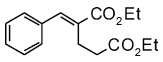
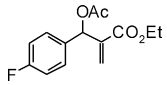
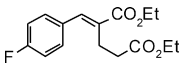
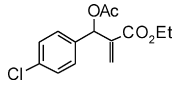
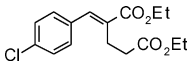
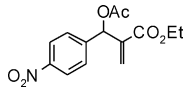
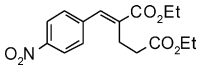
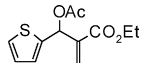
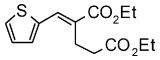
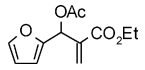
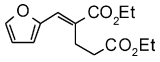
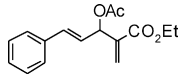
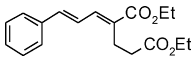
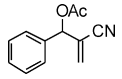
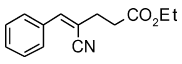
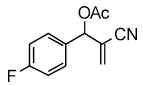
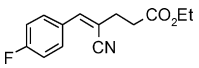
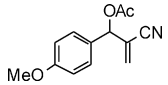
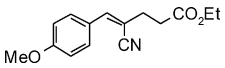
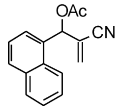
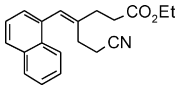
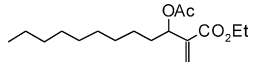
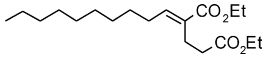
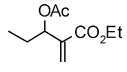
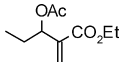
Method A (*Microwave irradiation*): a mixture of Baylis–Hillman acetate (1 mmol), and ethyl 2-triphenyl-λ^5-phosphoranylideneacetate (1.5 mmol) was adsorbed on neutral alumina and subjected to microwave irradiation, operating at 450 W using BPL, BMO-800 T microwave oven, for the appropriate time (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was treated with ethyl acetate (5 mL) under vigorous stirring conditions over 10 min. The resulting mixture was filtered and the cake was washed with ethyl acetate (2 mL × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the resulting crude product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure substituted alkenoates.

Method B (*Conventional method*): a mixture of Baylis–Hillman acetate (1 mmol), and ethyl 2-triphenyl-λ^5-phosphoranylideneacetate (1.5 mmol) was stirred in refluxing toluene (10 mL) for the appropriate time (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3 mL × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure substituted alkenoate.

3.1.1. Spectroscopic data for selected compounds

(**3a**) IR (KBr): υ 3085, 2982, 1734, 1708, 1634, 1574, 1449, 1370, 1251, 1202, 1177, 1094, 1028, 935, 855, 769, 700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J = 6.9 Hz, 3H), 1.38 (t, J = 7.0 Hz, 3H), 2.48 (t, J = 6.8 Hz, 2H), 2.85 (t, J = 6.8 Hz, 2H), 4.10 (q, J = 6.9 Hz, 2H), 4.29 (q, J = 7.0 Hz, 2H), 7.29–7.40 (m, 5H), 7.70 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 14.2, 23.0, 29.6, 33.5, 60.3, 60.8, 124.3, 128.5, 129.0, 129.6, 130.3, 136.6, 140.0. EIMS *m*/*z* (%): 276 (M^+, 10), 230 (40), 202 (37), 174 (30), 129 (100), 115 (35), 91 (20). (**3g**): IR (KBr): υ 2983, 2930, 1731, 1706, 1622, 1451, 1372, 1234, 1180, 1082,

Table 1
Nucleophilic substitution of Baylis–Hillman acetates with ethyl triphenyl phosphoranyldene acetate

Entry	Allylic acetates	Product[a]	Configuration	Conventional heating[b]		Microwave irradiation[c]	
				Time (h)	Yield (%)[d]	Time (min)	Yield (%)[d]
a			*E*	12	85	3.0	87
b			*E*	6	87	2.5	90
c			*E*	10	81	3.0	83
d			*E*	10	86	4.0	89
e			75:25(*E*/*Z*)	14	79	3.0	81
f			80:20(*E*/*Z*)	16	82	3.5	85
g			*E*,*E*	10	80	3.0	82
h			80:20(*Z*/*E*)	10	86	2.5	89
i			75:25(*Z*/*E*)	8	89	3.5	91
j			85:15(*Z*/*E*)	18	90	2.5	93
k			*Z*	14	85	3.0	88
l			*E*	36	88	3.5	90
m			80:20(*E*/*Z*)	36	85	3.0	87

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Conventional heating in refluxing toluene.
[c] Microwave irradiation was carried out using BPL, BMO-800T domestic oven operating at 450 W.
[d] Isolated and unoptimized yields.

1026, 974, 858, 792 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 2.50 (t, J = 6.9 Hz, 2H), 2.80 (t, J = 6.9 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 6.90 (d, J = 17.1 Hz, 1H), 7.10–7.50 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 22.2, 29.7, 33.2, 59.7, 71.3, 95.6, 122.9, 124.9, 126.0, 126.6, 127.4, 127.9, 133.0, 138.8, 139.3. EIMS *m*/*z* (%): 302 (M^+, 80) 257 (20), 228 (90), 200 (35), 155 (100), 141 (95), 115 (60), 91 (50), 43 (40). (**4h**). IR (neat): υ 3021, 2925, 2212, 1731, 1626, 1447, 1374, 1218, 1173, 1033, 771, 692 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, 3H, J = 6.9 Hz), 2.55–2.75 (m, 4H), 4.15 (q, 2H, J = 6.9 Hz), 6.92 (s, 1H), 7.30–7.45 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2,

31.4, 32.8, 60.7, 74.3, 126.9, 128.8, 128.7, 128.9, 129.2, 130.1, 140.6. EIMS *m/z* (%): 229 (M^+, 36), 156 (100), 130 (41), 91 (23), 51 (62).

4. Conclusion

In conclusion, we have described a rapid and efficient protocol for the preparation of 5-aryl-pentenoates from Baylis–Hillman acetates and a stable ylide via S_N2' type allylic substitution. The present method avoids high temperature reaction conditions, the use of solvent and extended reaction times. The time saving ability together with very short response times and the minimization of thermal decomposition of products are the main advantages of microwave heating over classical methods.

Acknowledgement

AKB thanks to UGC New Delhi for the award of fellowships.

References

[1] S.E. Drewes, G.H.P. Roos, Tetrahedron 44 (1988) 4653.
[2] (a) A.B. Baylis, M.E.D. Hillman, German patent, 2155113 (1972); (b) A.B. Baylis, M.E.D. Hillman, Chem. Abstr. 77 (1972) 34174q.
[3] D. Basavaiah, P. Dharma Rao, H.R. Suguna, Tetrahedron 52 (1996) 8001.
[4] K.Y. Lee, J.M. Kim, J.N. Kim, Tetrahedron Lett. 44 (2003) 6737.
[5] K.Y. Lee, J.M. Kim, J.N. Kim, Tetrahedron 59 (2003) 385.
[6] Y.J. Im, K.Y. Lee, T.H. Kim, J.N. Kim, Tetrahedron Lett. 43 (2002) 4675.
[7] J.N. Kim, J.M. Kim, K.Y. Lee, Synlett (2003) 821.
[8] J.N. Kim, H.S. Kim, J.H. Gong, Y.M. Chung, Tetrahedron Lett. 42 (2001) 8341.
[9] S.E. Drewes, N.D. Emslie, J. Chem. Soc. Perkin Trans. 1 (1982) 2079.
[10] H.M.R. Hoffmann, J. Rabe, Helv. Chem. Acta 67 (1984) 413.
[11] H.M.R. Hoffmann, J. Rabe, J. Org. Chem. 50 (1985) 3849.
[12] J.S. Yadav, B.V.S. Reddy, A.K. Basak, A.V. Narsaiah, A. Prabhakar, B Jagadesh, Tetrahedron Lett. 46 (2005) 639.
[13] A. Patra, A.K. Roy, S. Batra, A.P. Bhaduri, Synlett 11 (2002) 1819.
[14] H.M.R. Hoffmann, J. Rabe, Angew. Chem. Int. Ed. Engl. 24 (1985) 94.
[15] R. Buchholz, H.M.R. Hoffmann, Helv. Chim. Acta 74 (1991) 1213.
[16] F. Ameer, S.E. Drewes, R.F.A. Hoole, P.T. Kaye, A.T. Pitchford, J. Chem. Soc. Perkin Trans. 1 (1985) 2713.
[17] D. Basavaiah, A. Jaganmohan Rao, T. Satyanarayana, Chem. Rev. 103 (2003) 811.
[18] D.K. O'Dell, K.M. Nicholas, J. Org. Chem. 68 (2003) 6427.
[19] D. Basavaiah, R.M. Reddy, N. Kumaraguruban, D.S. Sharada, Tetrahedron 58 (2002) 3693.
[20] Y.J. Im, J.E. Na, J.N. Kim, Bull. Korean Chem. Soc. 24 (2003) 511.
[21] A.S.K. Murthy, C. Rambabu, K. Vijeender, P.B. Bhusan, S. Chandrasekhar, Synlett (2007) 494.
[22] R.A. Abramovitch, Org. Prep. Proced. Int. 23 (1991) 685.
[23] S. Caddick, Tetrahedron 51 (1995) 10403.
[24] A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault, D. Mathe, Synthesis (1998) 1213.
[25] R.S. Varma, Green Chem. (1999) 43.