The Baylis–Hillman Reaction: One-Pot Stereoselective Synthesis of Methyl (2*E*)-3-Aryl-2-hydroxymethylprop-2-enoates

Deevi Basavaiah,* Kisari Padmaja, Tummanapalli Satyanarayana

School of Chemistry, University of Hyderabad, Hyderabad-500 046, India

E-mail: dbsc@uohyd.ernet.in

Received 1 June 2000; revised 20 June 2000

Abstract: A facile, simple and one-pot conversion of methyl 3-aryl-3-hydroxy-2-methylenepropanoates into methyl (2*E*)-3-aryl-2-hydroxymethylprop-2-enoates via the sequential treatment with acetic anhydride/trimethylsilyl trifluoromethanesulfonate (TMSOTf) and potassium carbonate/methanol is described.

Key words: Baylis–Hillman reaction, trimethylsilyl trifluoromethanesulfonate (TMSOTf), methyl (2*E*)-3-aryl-2-hydroxymethylprop-2-enoates, one-pot stereoselective synthesis

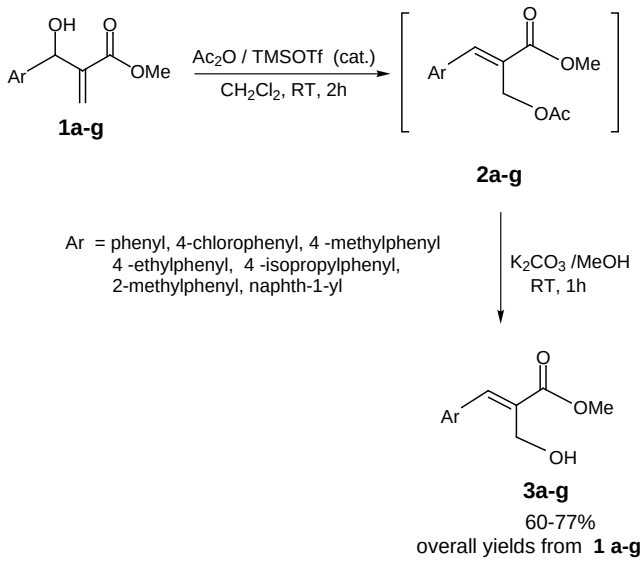
The Baylis–Hillman reaction has been and continues to be an interesting carbon-carbon bond forming reaction providing a useful class of densely functionalized molecules whose applications in a variety of stereoselective transformations have been well documented in the literature.[1-14] In continuation of our interest in the development of the Baylis–Hillman reaction as a potential source for stereoselective processes,[9-14] we herein report simple, convenient and one-pot stereoselective transformation of methyl 3-aryl-3-hydroxy-2-methylenepropanoates, the Baylis–Hillman adducts obtained from the activated alkene, methyl acrylate, into methyl (2*E*)-3-aryl-2-hydroxymethylprop-2-enoates via the successive treatment with acetic anhydride/trimethylsilyl trifluoromethanesulfonate (TMSOTf), and potassium carbonate/methanol in very good yields.

(2*E*)-2-Hydroxymethylalk-2-enoic acids and their esters are useful synthons for synthesis of various biologically active molecules.[15-22] However, there are only a few methods available in the literature for synthesis of these important molecules.[18-22] It is interesting to note that (m)ethyl 3-hydroxy-2-methylenealkanoates, the Baylis–Hillman adducts obtained from (m)ethyl acrylate, have been a major source for obtaining these (2*E*)-2-hydroxymethylalk-2-enoic acid derivatives. Thus, (m)ethyl 3-hydroxy-2-methylenealkanoates have been transformed into the desired (m)ethyl (2*E*)-2-hydroxymethylalk-2-enoates in three different elegant ways. The first involves a three step sequence, bromination-formylation-hydrolysis,[20] the second deals with bromination-acetylation-hydrolysis,[18] while the third method uses DEAD/PPh_3 (Mitsunobu conditions) reagent to first obtain the O-protected alcohol, which on hydrolysis provides the desired (*E*)-allylic alcohols.[19,22] All these methods, though simple, involve at least two steps. In view of the importance of these molecules we felt that it would be desirable and more useful if methyl 3-hydroxy-2-methylenealkanoates can be converted in an operationally simple one-pot procedure directly into methyl (2*E*)-2-hydroxymethylalk-2-enoates.

We have recently reported a convenient aqueous sulfuric acid mediated isomerization of 3-hydroxy-3-aryl-2-methylenepropanenitriles into (*E*)-α-cyanocinnamyl alcohols.[13] Our attempts to extend a similar aqueous sulfuric acid mediated isomerization reaction to methyl 3-hydroxy-2-methylenealkanoates were not successful. Based on our recent report on the trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalyzed isomerization of methyl 3-aryl-3-acetoxy-2-methylenepropanoates into methyl (2*E*)-3-aryl-2-acetoxymethylprop-2-enoates,[14] we envisioned that we can first prepare the required acetates of methyl 3-hydroxy-2-methylenealkanoates, then these molecules can be subjected to TMSOTf catalyzed isomerization to provide (2*E*)-2-acetoxymethylalk-2-enoates. Subsequent hydrolysis of the acetate group with potassium carbonate/methanol can in principle provide the desired (*E*)-allylic alcohols. Also we felt that all these three operations can be very conveniently carried out in one pot without isolating any compound in any step.

Accordingly, we have first selected methyl 3-phenyl-3-hydroxy-2-methylenepropanoate (**1a**) as a substrate for this purpose and various conditions were tried for one-pot transformation. The best results were obtained when methyl 3-phenyl-3-hydroxy-2-methylenepropanoate (**1a**) (10 mM) was treated with acetic anhydride (12 mM) and TMSOTf (cat. 11 mol%) at room temperature for two hours in dichloromethane as a solvent, followed by the treatment with potassium carbonate/methanol, after the removal of the solvent dichloromethane, for one hour at room temperature thus providing the desired methyl (2*E*)-3-phenyl-2-hydroxymethylprop-2-enoate (**3a**)[23] in 61% yield (Scheme). Encouraged by this successful result, we have prepared a representative class of methyl (2*E*)-3-aryl-2-hydroxymethylprop-2-enoates (**3b**–**g**) in high yields using the corresponding Baylis–Hillman adducts (Scheme and Tables 1, 2).

However, our attempts to extend this methodology to methyl 3-hydroxy-2-methylenenonanoate under the similar reaction conditions were unsuccessful. And also our attempts to directly transform methyl 3-phenyl-3-hydroxy-2-methylenepropanoate (**1a**) into methyl (2*E*)-3-phenyl-2-hydroxymethylprop-2-enoate via the treatment with trimethylsilyl trifluoromethanesulfonate (TMSOTf) (without using acetic anhydride) were not successful.



Scheme

Table 1 Syntheses of Methyl (2*E*)-3-Aryl-2-hydroxymethylprop-2-enoates (**3a–g**)[a]

Alcohol	Ar	Product	Yield (%)
1a	Phenyl	**3a**[b]	61
1b	*p*-chlorophenyl	**3b**[b]	69
1c	*p*-tolyl	**3c**	60
1d	*p*-ethylphenyl	**3d**	77
1e	*p*-isopropylphenyl	**3e**	74
1f	*o*-tolyl	**3f**	70
1g	naphth-1-yl	**3g**	64

[a] All reactions were carried out in 10 mM scale of alcohols (**1a–g**) and yields refer to the isolated yields based on the alcohols (**1a–g**).
[b] We observed that there is formation of small amounts (≈ 5%) of presumably the (*Z*)-isomer as indicated by a singlet δ ≈ 6.9 with low intensity in the ^{1}H NMR of the crude products (**3a, 3b**). However, the pure (*E*)-isomers were obtained after silica gel column chromatography.[24]

During preparation of this manuscript, a similar type of work was reported by Kim and co-workers.[25] They have described an interesting synthesis of ethyl (2*E*)-3-aryl-2-hydroxymethylprop-2-enoates via the treatment of ethyl 3-aryl-3-hydroxy-2-methylenepropanoates (2 mM) with trifluoroacetic acid (2 mL) at 60–70 °C for 20 hours. A quick comparison of our work with Kim's elegant work clearly indicates that Kim's method is a one step reaction requiring 20 hours, while our procedure is a two step one-

Table 2 Data for Products (**3a–g**)[a]

Product	R_f[b]	IR (neat)[c] ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS, 200 MHz); δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS, 50 MHz); δ
3a	0.49	3476, 1689, 1630	2.60 (t, 1 H, *J* = 6.5), 3.86 (s, 3 H), 4.49 (d, 2 H, *J* = 6.5),7.32–7.53 (m, 5 H), 7.83 (s, 1 H)	51.94, 57.42, 128.41, 129.06, 129.51, 130.94, 134.45, 142.56, 168.29
3b	0.50	3489, 1685, 1627	2.61 (t, 1 H, *J* = 6.5), 3.86 (s, 3 H), 4.45 (d, 2 H, *J* = 6.5), 7.40 (m, 4 H), 7.77 (s, 1 H)	51.99, 57.08, 128.62, 130.85, 131.29, 132.80, 135.14, 141.26, 167.99
3c	0.53	3470, 1709, 1631	2.38 (s, 3 H), 2.54 (t, 1 H, *J* = 6.6), 3.86 (s, 3 H), 4.51 (d, 2 H, *J* = 6.6), 7.22 (d, 2 H, *J* = 7.8), 7.37 (d, 2 H, *J* = 7.8), 7.81 (s, 1 H)	21.26, 51.99 57.70, 129.26, 129.70, 130.11, 131.68, 139.47, 142.76, 168.52
3d	0.54	3470, 1709, 1630	1.24 (t, 3 H, *J* = 7.6), 2.50–2.78 (m, 3 H), 3.85 (s, 3 H), 4.50 (d, 2 H, *J* = 6.7), 7.23 (d, 2 H, *J* = 7.4), 7.39 (d, 2 H, *J* = 7.4), 7.81 (s, 1 H)	15.26, 28.70, 52.04, 57.79, 128.11, 129.83, 130.16, 131.96, 142.82, 145.82, 168.59
3e	0.54	3477, 1709, 1630	1.26 (d, 6 H, *J* = 6.8), 2.53 (t, 1 H, *J* = 6.7), 2.93 (sept, 1 H, *J* = 6.8), 3.85 (s, 3 H), 4.51 (d, 2 H, *J* = 6.7), 7.26 (d, 2 H, *J* = 8.8), 7.40 (d, 2 H, *J*= 8.8), 7.81 (s, 1 H)	23.72, 33.95, 52.00, 57.74, 126.65, 129.84, 130.17, 132.08, 142.76, 150.37, 168.55
3f	0.51	3420, 1701, 1631	2.31 (s, 3 H), 2.66 (t, 1 H, *J* = 6.8), 3.87 (s, 3 H), 4.39 (d, 2 H, *J* = 6.8), 7.14–7.34 (m, 4 H), 7.89 (s, 1 H)	19.89, 52.11, 58.08, 125.87, 129.09, 129.20, 130.09, 131.47, 133.77, 136.94, 141.46, 168.29
3g	0.52	3503, 1705, 1635	2.67 (t, 1 H, *J* = 6.8), 3.93 (s, 3 H), 4.43 (d, 2 H, *J* = 6.8), 7.44–7.61 (m, 4 H), 7.81–7.98 (m, 3 H), 8.37 (s, 1 H)	52.17, 58.33, 124.38, 125.25, 126.21, 126.61, 127.26, 128.54, 129.49, 131.45, 131.60, 132.81, 133.35, 140.56, 168.13

[a] Satisfactory elemental analyses were obtained for **3a–g** (C ± 0. 47%, H ± 0. 58%).
[b] Eluent = 25% EtOAc in hexanes.
[c] Molecules **3a, 3b**, **3g** were obtained as crystalline solids (mp for **3a** = 57-58 °C, **3b** = 55-56°C, **3g** = 63-65 °C, and IR spectra were recorded as KBr plates), and the remaining ones as colorless liquids.

comparable in both cases (our procedure and the Kim's method).

In conclusion, we have developed a convenient operationally simple one-pot procedure for the stereoselective transformation of methyl 3-aryl-3-hydroxy-2-methyleneprop anoates into methyl (2*E*)-3-aryl-2-hydroxymethylprop-2-enoates.

Mps were recorded on a Superfit (India) capillary melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO-FT-IR model 5300 or Perkin−Elmer model 1310 spectrometer using samples as neat liquids or in KBr. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in $CDCl_3$ on a Bruker-AC-200 spectrometer using TMS (δ = 0 ppm) as internal standard. Elemental analyses were recorded on a Perkin−Elmer 240C-CHN analyzer. All the required Baylis−Hillman adducts (starting materials) were prepared by reaction of the corresponding aldehydes with methyl acrylate in the presence of a catalytic amount of DABCO according to the literature procedure.[2,3]

Isomerization of Baylis−Hillman Adducts; General Procedure

To a stirred solution of the Baylis−Hillman adduct (**1a**−**g**, 10 mM) and acetic anhydride (12 mM) in CH_2Cl_2 (20 mL), was added TMSOTf (0.2 mL, 11mol%, 0.245 g) at r.t. After 2 h, CH_2Cl_2 was removed, MeOH (20 mL) and K_2CO_3 (30 mM, 4.14 g) were added and the reaction mixture was stirred for 1 h at r.t. Then the solvent, MeOH was removed under reduced pressure and the residue was diluted with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layer was dried (Na_2SO_4). The solvent was evaporated and the crude product, thus obtained, was purified by column chromatography (8% EtOAc in hexanes) to provide the desired product (**3a**−**g**). The isolated yields of the products **(3a**−**g)** are given in Table 1 and the spectral data along with elemental analyses and R_f values are given in Table 2.

Acknowledgement

We thank DST (New Delhi) for funding this project. We thank the UGC (New Delhi) for Special Assistance Program in organic chemistry in the School of Chemistry, University of Hyderabad. KP and TSN thank UGC (New Delhi) for their research fellowships.

References

(1) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.
(2) Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001.
(3) Ciganek, E. In *Organic Reactions*, Vol. 51; Paquette, L. A., Ed.; Wiley: New York, 1997; pp 201−350.
(4) Matsumoto, S.; Okubo, Y.; Mikami, K. *J. Am. Chem. Soc.* **1998**, *120*, 4015.
(5) Chamakh, A.; Amri, H. *Tetrahedron Lett.* **1998**, *39*, 375.
(6) Hoffmann, H. M. R.; Eggert, U.; Poly, W. *Angew. Chem., Int. Ed. Engl*. **1987**, *26*, 1015.
(7) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.
(8) Sugahara, T.; Ogasawara, K. *Synlett* **1999**, 419.
(9) Basavaiah, D.; Krishnamacharyulu, M.; Suguna Hyma, R.; Pandiaraju, S. *Tetrahedron Lett.* 1**997**, *38*, 2141.
(10) Basavaiah, D.; Krishnamacharyulu, M.; Suguna Hyma, R.; Sarma, P. K. S.; Kumaragurubaran, N. *J. Org. Chem.* **1999**, *64*, 1197.
(11) Basavaiah, D.; Suguna Hyma, R.; Padmaja, K.; Krishnamacharyulu, M. *Tetrahedron* **1999**, *55*, 6971.
(12) Basavaiah, D.; Bakthadoss, M.; Pandiaraju, S. *Chem. Commun*. **1998**, 1639.
(13) Basavaiah, D.; Kumaragurubaran, N.; Padmaja, K. *Synlett* **1999**, 1630.
(14) Basavaiah, D.; Muthukumaran, K.; Sreenivasulu, B. *Synthesis* **2000**, 545.
(15) Edwards, J. D.; Matsumoto, T.; Hase, T. *J. Org. Chem.* **1967**, *32*, 244.
(16) Campi, E. V.; Dyall, K.; Fallon, G.; Jackson, W. R.; Perlmutter, P.; Smallridge, A. J. *Synthesis* **1990**, 855.
(17) Kupchan, S. M.; Davies, V. H.; Fujita, T.; Cox, M. R.; Bryan, R. F. *J. Am. Chem. Soc*. **1971**, *93*, 4916.
(18) Roush, W. R.; Brown, B. B. *J. Org. Chem*. **1993**, *58*, 2151.
(19) Charette, A. B.; Cote, B. *Tetrahedron Lett*. **1993**, *34*, 6833.
(20) Beltaief, I.; Hbaieb, S.; Besbes, R.; Amri, H.; Villieras, M.; Villieras, J. *Synthesis* **1998**, 1765.
(21) Beltaief, I.; Besbes, R.; Amri, H.; Villieras, J. *Tetrahedron Lett.* **1997**, *37*, 813.
(22) Charette, A. B.; Cote, B.; Monroc, S.; Prescott, S. *J. Org. Chem*. **1995**, *60*, 6888.
(23) ^{1}H NMR spectrum of the crude product shows a peak of very low intensity at δ ≈ 6.9 presumably indicating the presence of minor amounts (≈ 5%) of the (*Z*)-isomer. However, pure (*E*)-isomer was obtained after column chromatography. The *E* stereochemistry was assigned by comparison of the ^{1}H NMR chemical shift value of the vinylic proton (δ = 7.83) with that of the corresponding ethyl ester (δ = 7.76).[20,25]
(24) In ^{1}H NMR spectrum of the 3-aryl-(2-substituted)-prop-2-enoates, the β-vinylic proton *cis* to the ester group [(*E*)-isomer] appears at δ ≈ 7.70, while the β-vinylic proton *trans* to the ester group [(*Z*)-isomer] appears at δ ≈ 6.80.[26,27,28]
(25) Kim, H. S.; Kim, T. Y.; Lee, K. Y.; Chung, Y. M.; Lee, H. J.; Kim, J. N. *Tetrahedron Lett*. **2000**, *41*, 2613.
(26) Tanaka, K.; Yamagishi, N.; Tanikaga, R.; Kaji, A. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 3619.
(27) Basavaiah, D.; Pandiaraju, S.; Krishnamacharyulu, M.; *Synlett* **1996**, 747.
(28) Basavaiah, D.; Pandiaraju, S. *Tetrahedron* **1996**, *52*, 2261.

Article Identifier:
1437-210X,E;2000,0,12,1662,1664,ftx,en;Z05100SS.pdf