Efficient Baylis−Hillman Reaction Using Stoichiometric Base Catalyst and an Aqueous Medium

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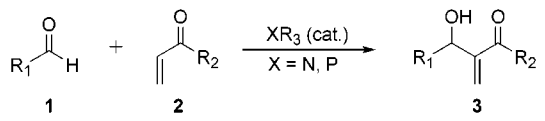
Received March 12, 2001

A practical and efficient set of conditions were developed using stoichiometric base catalyst, 1,4-diazabicyclo[2,2,2]octane (DABCO), and an aqueous medium to overcome problems commonly associated with the Baylis−Hillman reaction, such as low reaction yields and long reaction time. These simple modifications to the classical conditions, using more base catalyst and an aqueous medium, proved to be successful in converting a variety of aliphatic and aromatic aldehydes to their corresponding Baylis−Hillman products. The inclusion of environmentally friendly water in the reaction solvent was critical for achieving the high yield of Baylis−Hillman adducts. Our deuterium-exchange experiments suggest that the Michael addition adduct formed between DABCO and methyl acrylate is the active intermediate for the Baylis−Hillman reaction in aqueous conditions, and its hydrolysis, a nonproductive side reaction facilitated by the quaternary ammonium ion, leading to the formation of a stable betaine product, consumes both the catalyst and methyl acrylate, making it necessary to add more base catalyst and methyl acrylate.

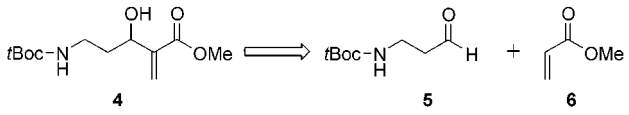
Introduction

The Baylis−Hillman reaction, a tertiary amine- or phosphine-catalyzed coupling of an aldehyde **1** with an α,β-unsaturated carbonyl compound **2** (Scheme 1), is among the most useful C−C bond-forming reactions in organic synthesis.[1] The Baylis−Hillman adduct, 3-hydroxy-2-methylenepropionate (**3**), is an important structural motif that is often present in natural and unnatural products of biological and medicinal interest.[2] Advances in combinatorial chemistry and the need to generate diverse polyfunctionalized molecules make such easily functionalized motifs highly desirable.[3] However, there are a number of problems commonly associated with this reaction, most notably, its slow reaction rate, especially for acrylates. Reaction times of one week or more are common, and some reactions have been reported to take more than one month to complete. Efforts to accelerate the reaction include low-temperature techniques, the addition of a Lewis acid such as $La(OTf)_3$ or $LiClO_4$, the use of other bases such as the non-nucleophilic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and the use of high pressure or microwave techniques.[4] Few modifications, however, were successful in improving the rate of the Baylis−Hillman reaction, and when they do, they often are applicable to a limited number of substrates. Herein, we report the development of a practical and efficient set of conditions for the Baylis−Hillman reaction using stoichiometric base catalyst and an aqueous medium.

Scheme 1



Scheme 2



Results and Discussion

In our efforts to synthesize potential protein kinase inhibitors, we needed to prepare compound **4** and thought that the Baylis−Hillman reaction as outlined in Scheme 2 would be the most economical. However, the typical conditions reported in the literature failed to couple *N-tert*-butyloxycarbonyl-3-aminopropionaldehyde (**5**) with methyl acrylate (**6**). The report that water as a solvent accelerated 1,4-diazabicyclo[2,2,2]octane (DABCO)-cat-

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(1) For reviews, see: (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062. (b) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653−4670. (c) Ciganek, E. *Org. React.* **1997**, *51*, 201−350. (d) Langer, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3049−3052.

(2) For examples, see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370. (b) Atkinson, R. S.; Fawcett, J.; Russell, D. R.; Williams, P. *Chem. Commun.* **1994**, 2031−2032. (c) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2151−2161. (d) Yu, L. C.; Helquist, P. *J. Org. Chem.* **1981**, *46*, 4536−4541. (e) Smith, A. B.; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M.; Korn, A. *Organic Syntheses*; Wiley & Sons: New York, 1990; Collect. Vol. VII, pp 271−275.

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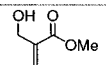
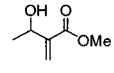
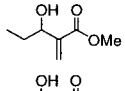
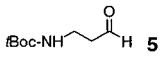
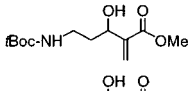
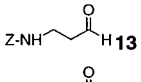
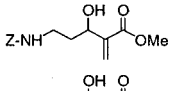
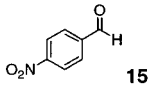
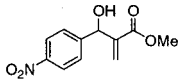
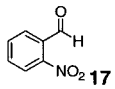
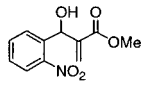
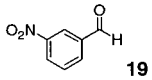
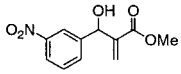
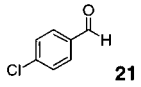
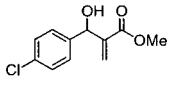
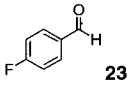
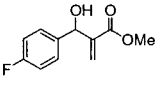
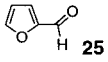
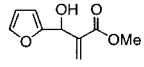
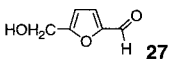
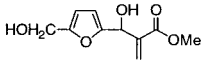
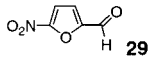
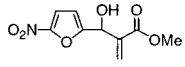
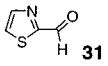
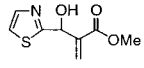
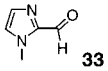
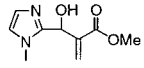
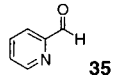
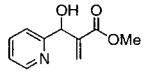
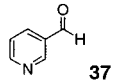
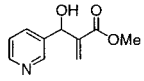
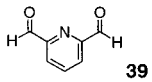
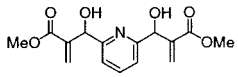
(4) (a) Rafel, S.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 1521−1522. (b) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. J. *J. Org. Chem.* **1998**, *63*, 7183−7189. (c) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311−2312. (d) Hayase, T.; Shibata, T.; Soai, K.; Wakatsuki, Y. *Chem. Commun.* **1998**, 1271−1272. (e) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533−2534. (f) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539−1542. (g) Jenner, G. *High-Pressure Res.* **1999**, *16*, 243−252.

10.1021/jo015628m CCC: $20.00
Published on Web 07/17/2001

Table 1. Baylis−Hillman Reaction of Aldehydes with Methyl Acrylate[a]

entry	substrate	product	time (h)	yield %[b]
1	 **7**	 **8**	9	90
2	 **9**	 **10**	10	86
3	 **11**	 **12**	14	83
4	 **5**	 **4**	4	99
5	 **13**	 **14**	8	80
6	 **15**	 **16**	3	83
7	 **17**	 **18**	16	95
8	 **19**	 **20**	16	87
9	 **21**	 **22**	36	53[c]
10	 **23**	 **24**	36	41[c]
11	 **25**	 **26**	20	85
12	 **27**	 **28**	36	62[c]
13	 **29**	 **30**	0.5	100
14	 **31**	 **32**	0.5	100
15	 **33**	 **34**	8	100[d]
16	 **35**	 **36**	1	100
17	 **37**	 **38**	8	100
18	 **39**	 **40**	2.5	100

[a] General conditions: methyl acrylate (3 mmol), DABCO (100 mol %), 1,4-dioxane−H_2O (1:1, v/v), rt. [b] Isolated yields, except entries 13−18 where products were pure after workup. [c] Percentages of recovered starting material were 31%, 49%, and 23% for entries 9, 10, and 12, respectively. [d] The product is too water-soluble to be extracted with *tert*-butyl methyl ether. Chloroform (150 mL) and brine (60 mL) were added to partition the reaction mixture. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

alyzed coupling of benzaldehyde with acrylonitrile[5] prompted us to look at the effect of water on our Baylis−Hillman coupling of aldehyde **5** with methyl acrylate **6**. To our surprise, when a solution of **5** (1 mmol) and methyl acrylate **6** (1 mmol) in a 1:1 (v/v) mixture of 1,4-dioxane and water was treated with 50 mol % DABCO at room temperature for 36 h, the desired product **4** was isolated in 76% yield. In subsequent experiments, we found that the reaction was complete in less than 4 h and gave the desired product **4** in 99% isolated yield when 100 mol % DABCO and 3 equiv of methyl acrylate were used. This condition worked well even when the reaction was scaled up 50-fold.

Substrate Scope. As shown in Table 1, both aliphatic aldehydes (entries 1−5) and aromatic aldehydes (entries 6−18) were converted to their corresponding Baylis−

(5) Augé, J.; Lubin, N.; Lubineau, A. *Tetrahedron Lett.* **1994**, *58*, 7947−7948.

Table 2. Effect of Solvent on the Baylis−Hillman Reaction[a]

entry	solvent (v/v)	time (h)	yield[b] (%)
1	THF−MeOH (1:1)	48	0
2	1,4-dioxane	48	0
3	THF−H_2O (1:1)	36	21
4	DMF−H_2O (1:1)	48	12
5	1,4-dioxane−THF−H_2O (1:1:2)	36	35
6	CH_3CN−H_2O (1:1)	36	56
7	1,4-dioxane−H_2O (1:1)	36	68
8	THF−MeOH−H_2O (1:1:2)	36	65
9	*i*-PrOH−H_2O (1:1)	36	15
10	EtOH−H_2O (1:1)	48	8
11	H_2O	60	0

[a] General conditions: *p*-nitrobenzaldehyde **15** (1 mmol, 0.1 M), methyl acrylate (1 mmol), DABCO (50 mol %), rt. [b] Isolated yields.

Table 3. Effect of the Ratio of 1,4-Dioxane to Water on the Baylis−Hillman Reaction[a]

entry	1,4-dioxane (mL)	H_2O (mL)	yield[b] (%)
1	8	2	21
2	6	4	57
3	5.5	4.5	61
4	5	5	68
5	4.5	5.5	65
6	4	6	27
7	2	8	10

[a] General conditions: *p*-nitrobenzaldehyde **15** (1 mmol, 0.1 M), methyl acrylate (1 mmol), DABCO (50 mol %), rt, 36 h. [b] Isolated yields.

Hillman products in 41−100% yield in reaction times as short as 0.5 h. No side reactions of aldehydes such as aldol condensation were observed under our conditions. It should also be noted that both aldehyde groups of pyridine-2,6-dicarbaldehyde (**39)** underwent the coupling reaction forming the corresponding bis(3-hydroxy-2-methylene)propionate (**40)** in quantitative yield within 2.5 h.

Solvent Effects. We studied the effects of solvent, substrate aldehyde concentration, and amount of methyl acrylate and base on the Baylis−Hillman reaction using a common substrate aldehyde, *p*-nitrobenzaldehyde (**15)**. After evaluating a number of solvent systems as listed in Table 2, we found that the binary medium consisting of 1,4-dioxane and water was the solvent of choice. It was clear that water was one of the desiderata responsible for the successful Baylis−Hillman reaction of *p*-nitrobenzaldehyde with methyl acrylate; the use of neat organic solvent or just water as the solvent failed to produce any desired product.

The ratio of 1,4-dioxane to water was also important under our conditions. As shown in Table 3, the preferred composition for our binary solvent system was found to be 50% 1,4-dioxane and 50% water. The 1:1 (v/v) ratio of the mixed solvents was the best for the coupling reaction in terms of both the reaction rate and the product yield. The selection of the environmentally friendly water as a cosolvent was critical for achieving the fast rate of reaction and the high yield of product, suggesting that water might help stabilize the transition states or intermediates in the coupling reaction. This effect of water in promoting the Baylis−Hillman reaction has been reported by others but is not completely understood.[5] As illustrated in Scheme 3, the widely accepted mechanism of the Baylis−Hillman reaction consists of three steps: (1) nucleophilic Michael addition of base DABCO to methyl acrylate, forming the zwitterionic

Scheme 3

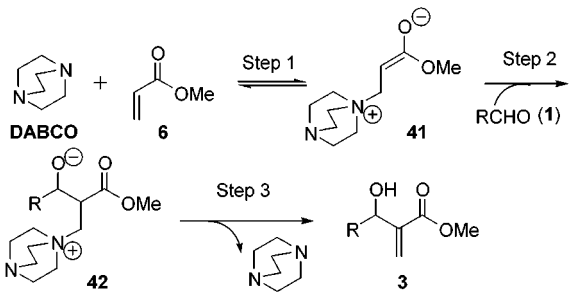


Table 4. Effect of Reactants on the Baylis−Hillman Reaction

reactant		yield[c] (%)
p-nitrobenzaldehyde (**15**)[a]	0.5 M	46
	0.2 M	56
	0.1 M	68
	0.05 M	5
	0.02 M	0
methyl acrylate[b]	1 equiv	46
	5 equiv	56
	10 equiv	68
	20 equiv	5
	40 equiv	0[d]

[a] General conditions: *p*-nitrobenzaldehyde (**15**) (1 mmol), methyl acrylate (1 equiv), DABCO (50 mol %), 1,4-dioxane−H_2O (1:1, v/v), rt, 36 h. [b] General conditions: *p*-nitrobenzaldehyde (**15**) (1 mmol, 0.1 M), methyl acrylate (varying equiv), DABCO (50 mol %), 1,4-dioxane−H_2O (1:1, v/v), rt, 36 h. [c] Isolated yields. [d] The reaction mixture under this condition became turbid upon the addition of methyl acrylate.

intermediate **41**, (2) an aldol-type reaction of **41** with the aldehyde, forming a second zwitterionic intermediate **42**, and (3) the subsequent release of the base via *β*-elimination, leading to the formation of the Baylis−Hillman reaction product **3**. The reaction sequence is believed to involve charged transition states and intermediates that could be stabilized by polar solvents such as water through intermolecular charge−dipole interactions as well as hydrogen-bonding interactions. These stabilizing interactions, in part, contributed to the observed effect of water in promoting the Baylis−Hillman reaction under our conditions and those reported by others.

Reactant Concentrations. In principle, intermolecular reactions are promoted by increasing the concentrations of the reactants. However, when we increased substrate aldehyde concentration to greater than 0.1 M or the amount of methyl acrylate to more than 10 equiv, the yield of the Baylis−Hillman product was adversely affected (Table 4). This deleterious effect of higher reactant concentrations could be the result of decreased relative water content. The optimum concentration for substrate aldehyde was found to be around 0.1 M, and the optimum amount of methyl acrylate was 3 equiv.

Kinetic Studies and the Effect of Base. According to the mechanism outlined in Scheme 3, the base is a catalyst for the Baylis−Hillman reaction. However, we found that the reaction in an aqueous medium could not be completed and seemed to reach "equilibrium" in the presence of DABCO, as shown in Figure 1. Extending the reaction time did not increase the product yield, and no further conversion to product was observed after a few hours of incubation. Interestingly, when the amount of DABCO was increased from 9 to 100 mol %, the initial rate of product formation was increased by nearly 10-fold and the final yield of product by over 5-fold as shown

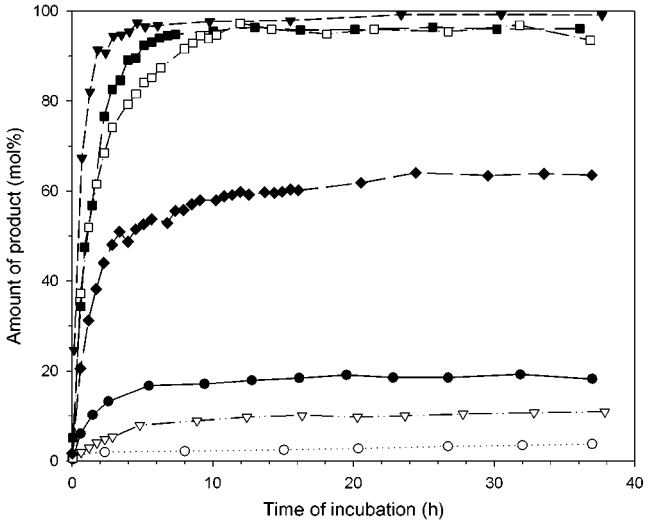


Figure 1. Effect of base, DABCO, on the time-dependent formation of Baylis−Hillman product as monitored by HPLC. *p*-Nitrobenzaldehyde (1 mmol, 0.1 M) and methyl acrylate (3 mmol) were incubated in a 1:1 (v/v) mixture of 1,4-dioxane−water in the presence of 9 mol % (entry 1, ●), 50 mol % (entry 2, ◆), 100 mol % (entry 3, ■), and 200 mol % (entry 4, ▼) of DABCO. Also shown are three control experiments: reaction in neat 1,4-dioxane (100 mol % DABCO, entry 5, ○), reaction with 8 h preincubation of 100 mol % DABCO and 3 equiv of methyl acrylate in a 1:1 (v/v) mixture of 1,4-dioxane and water (entry 6, ▽), and reaction with preincubation of 100 mol % DABCO and 3 equiv of methyl acrylate in a 1:1 (v/v) mixture of 1,4-dioxane and water with the addition of another 100 mol % DABCO at the time *p*-nitrobenzaldehyde was added (entry 7, □). Entries refer to Table 5.

Table 5. Effect of Catalyst DABCO on the Baylis−Hillman Reaction[a]

entry	catalyst loading	initial rate (mol %/h)	final product yield[b] (%)
1	9 mol % DABCO	5.7	18
2	50 mol % DABCO	24.5	62
3	100 mol % DABCO	45.2	96
4	200 mol % DABCO	59.1	99
5	100 mol % DABCO in neat 1,4-dioxane	1.1	4
6	100 mol % DABCO preincubated	1.8	11
7	100 mol % DABCO + 100 mol % DABCO preincubated	40.1	94

[a] All incubations were performed at room temperature in 1,4-dioxane−water (1:1, v/v) except as noted in entry 5. [b] After 36 h.

in Table 5. This result suggests that the use of greater loading of DABCO than usual is necessary to increase the reaction rate and the product yield. Preincubation of 100 mol % DABCO with 3 equiv of methyl acrylate in a 1:1 (v/v) mixture of 1,4-dioxane and water before the addition of aldehyde reduced the initial rate of reaction by 25-fold and the final product yield by 9-fold, suggesting that there might be a side reaction occurring between DABCO and methyl acrylate that reduced the effective concentration of DABCO. Indeed, this deleterious effect of preincubation could be rectified by the addition of another 100 mol % of DABCO at the time the substrate aldehyde was added.

To characterize the nonproductive side reaction, we incubated DABCO (1 mmol) and methyl acrylate (3 mmol) in a mixed solvent of 1,4-dioxane-d_8 (5 mL) and D_2O (5 mL) and monitored the mixture using ^1H NMR.

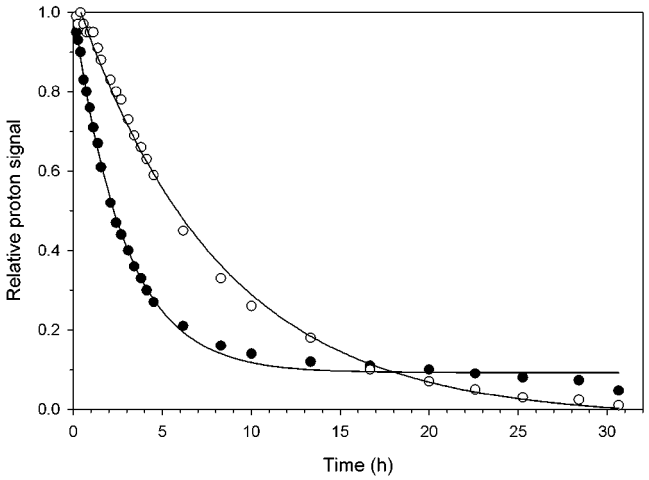
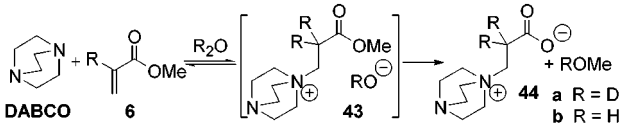


Figure 2. Time-dependent deuterium exchange of methyl acrylate (●) and disappearance of DABCO (○) in D_2O and 1,4-dioxane-d_8 as monitored by ^1H NMR. Methyl acrylate (3 mmol) and DABCO (1 mmol) were incubated in a 1:1 (v/v) mixture of 1,4-dioxane-d_8 and D_2O.

Scheme 4



We found that the coupling pattern of the alkenyl protons of methyl acrylate was simplified as a result of deuterium exchange with a half-life of 2 h as shown in Figure 2. Also, we found that the sharp singlet at 2.91 ppm for DABCO disappeared as a new group of signals (a triplet at 3.33 ppm, a triplet at 3.54 ppm, and a singlet at 3.48 ppm) appeared, all with a half-life of 5.6 h. At the same time, the apparent pH of the incubation mixture dropped from 12.2 to 7.5 after 36 h of incubation, suggesting that there was a hydrolysis of an ester bond leading to the formation of a carboxylic acid, which neutralized the basicity of DABCO. Indeed, we were able to isolate and characterize a betaine product **44a**[6] from the incubation mixture. The formation of betaine **44** is shown in Scheme 4.

The first step of Michael addition is fast and reversible, as shown by the deuterium exchange of C_α−H of acrylate. The hydrolysis of the methyl ester intermediate **43** leads to the formation of betaine **44**. The ester hydrolysis is facilitated by the ammonium ion in **43**, as direct incubation of acrylic acid with DABCO under the same condition failed to produce a significant amount of betaine **44** after 36 h and no ester hydrolysis was observed when the Baylis−Hillman product was incubated with DABCO under the same condition.[7] These experiments suggest that the Michael addition adduct **43** formed between DABCO and methyl acrylate is the active intermediate for the Baylis−Hillman reaction under aqueous conditions. The hydrolysis of the Michael adduct **43**, a non-

(6) Incubation of methyl acrylate (3 mmol) with DABCO (100 mol %) under the same conditions in 1,4-dioxane−water (1:1, v/v) gave the betaine product **44b**. Betaine **44b** was reported to be the product of a reaction between DABCO and acrylic acid in the presence of the polymerization inhibitor hydroquinone in DMF. See: (a) Le Berre, P. A.; Delacroix, A. *Bull. Soc. Chim. Fr.* **1973**, 2404−2407. (b) Kazantsev, A. O.; Kazakov, S. A.; Shirshin, K. V.; Danov, S. M.; Krasnov, V. L. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1998**, *34*, 484−487.

productive side reaction facilitated by the quaternary ammonium ion leading to the formation of a stable betaine product **44**, consumes both the catalyst and methyl acrylate, making it necessary to add more base catalyst and methyl acrylate.

Conclusions

A set of practical and efficient conditions were developed using a greater loading of DABCO catalyst than usual in an aqueous medium to overcome problems commonly associated with the Baylis−Hillman reaction. These simple modifications to the classical condition using more base and an aqueous medium proved to be successful in converting a variety of aliphatic and aromatic aldehydes to their corresponding Baylis−Hillman products.

Experimental Section

General Methods. All reactions were performed without the protection of an inert atmosphere. Solvents were either ACS reagent grade or HPLC grade. $CDCl_3$ was stored over magnesium turnings and filtered through a short column packed with basic aluminum oxide. Water for HPLC was purified using a Millipore water purification system. Unless otherwise stated, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman precoated silica gel plates. TLC plates were visualized using either 7% (w/w) ethanolic phosphomolybdic acid or 1% (w/w) aqueous potassium permagnate containing 1% (w/w) $NaHCO_3$. Flash column chromatography was performed using silica gel (Merck 230−400 mesh). Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. All reagents were purchased at the highest commercial quality and used without further purification, unless otherwise noted.

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer model 1600 series FTIR spectrometer using polystyrene as an external standard. Infrared absorbance is reported in reciprocal centimeters (cm^{-1}). All ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer at ambient temperature and calibrated using residual undeuterated solvents as an internal reference. Chemical shifts (200 MHz for ^{1}H and 50 MHz for ^{13}C) are reported in parts per million (δ) relative to $CDCl_3$ (δ 7.24 for ^{1}H and 77.0 for ^{13}C) or DMSO-d_6 (δ 2.49 for ^{1}H and 39.5 for ^{13}C). Coupling constants (J values) are given in hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, br = broad. Mass spectral data were obtained from the University of Kansas Mass Spectrometry Laboratory (Lawrence, KS).

General Conditions. A solution of substrate aldehyde (1 mmol) and methyl acrylate (3 mmol) in 10 mL of 1,4-dioxane−water (1:1, v/v) was stirred at room temperature in the presence of 100 mol % DABCO, and the reaction progress was monitored by TLC. Upon completion, the reaction mixture was partitioned with *tert*-butyl methyl ether (150 mL) and water (80 mL). The organic phase was washed with brine (2 × 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, using ethyl acetate and hexane as the eluting solvents to give the desired product. Compounds **8**,[8] **10**,[9] **12**,[10] **16**,[11] **18**,[4c] and **22**[10] are known compounds, and their spectroscopic data matched those reported in the literature.

Kinetic Analysis of the Baylis−Hillman Reaction Using HPLC. *p*-Nitrobenzaldehyde **15** (1 mmol, 0.1 M) and methyl acrylate (3 mmol) were incubated in a 1:1 (v/v) mixture of 1,4-dioxane−water in the presence of various amounts of DABCO. At different time intervals, 3 μL aliquots were withdrawn and analyzed by reversed phase HPLC, using a Phenomenex AQUA 5 μm C-18 column (4.6 mm × 250 mm). The elution started with an isocratic elution of 2% acetonitrile for 5 min, followed by a gradient elution from 2% acetonitrile to 70% acetonitrile over 15 min and a final isocratic elution of 70% acetonitrile for 5 min at a flow rate of 1 mL/min and detection wavelengths of 220 and 280 nm. The peak area corresponding to the product was plotted against the time of incubation and the initial rate estimated using the first few time points in the linear region of the curve.

Kinetic Analysis of the Reaction between DABCO and Methyl Acrylate Using ^{1}H NMR. DABCO was incubated with 3 equiv of methyl acrylate in a 1:1 (v/v) mixture of 1,4-dioxane-d_8 and deuterium oxide at room temperature. ^{1}H NMR spectra were taken at various time intervals. The integrations of various signals were normalized on the basis of the 1,4-dixoane proton signals at 3.84. The pseudo-first-order rate constants were then calculated for the disappearance of the C_α−H signal of methyl acrylate because of deuterium exchange and for the disappearance of proton signals corresponding to free DABCO.

3-Hydroxy-2-methylene-heptanedioic Acid, 7-*tert*-Butyl Ester, 1-Methyl Ester (4). ^{1}H NMR ($CDCl_3$): δ 6.28 (s, 1H), 5.94 (s, 1H), 4.95 (br s, 1H, OH), 4.58−4.51 (m, 1H), 3.78 (s, 3H), 3.66−3.63 (m, 1H), 3.47−3.41 (m, 1H), 3.25−3.13 (m, 1H), 1.94−1.81 (m, 1H), 1.71−1.59 (m, 1H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 167.0, 157.0, 142.4, 125.2, 79.8, 68.5, 52.1, 37.6, 36.8, 28.6. IR (neat): ν 3390, 2978, 1713, 1694, 1520 cm^{-1}. ESIMS *m/z* (relative intensity): 282.14 ($M + Na^+$, 63), 260.16 (MH^+, 78). HRMS (ESI) *m/z*: calcd for $C_{12}H_{22}NO_5$ (MH^+), 260.1498; found, 260.1499.

3-Hydroxy-2-methylene-heptanedioic Acid, 7-Benzyl Ester, 1-Methyl Ester (14). ^{1}H NMR ($CDCl_3$): δ 7.39−7.29 (m, 6H), 6.28 (s, 1H), 5.91 (s, 1H), 5.23 (br s, 1H, OH), 5.12 (s, 2H), 4.59−4.50 (m, 1H), 3.78 (s, 3H), 3.51−3.45 (m, 1H), 3.36−3.23 (m, 1H), 1.97−1.71 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 167.0, 157.2, 142.2, 136.7, 128.7, 128.3, 125.4, 69.1, 67.0, 52.2, 38.3, 36.4. IR (neat): ν 3381, 2953, 1713, 1531, 1265 cm^{-1}. ESIMS *m/z* (relative intensity): 316.14 ($M + Na^+$, 40), 294.16 (MH^+, 100). HRMS (ESI) *m/z*: calcd for $C_{15}H_{20}NO_5$ (MH^+), 294.1341; found, 294.1323.

2-[Hydroxy-(3-nitro-phenyl)-methyl]-acrylic Acid, 1-Methyl Ester (20). ^{1}H NMR ($CDCl_3$): δ 8.21 (t, J = 1.0 Hz, 1H), 8.10 (ddd, J = 8.0, 1.2, 1.1 Hz, 1H), 7.73−7.69 (m, 1H), 7.50 (t, J = 7.8 Hz, 1H), 6.38 (s, 1H), 5.94 (s, 1H), 5.62 (d, J = 5.6 Hz, 1H), 3.70 (s, 3H), 3.58 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 166.5, 148.4, 143.9, 141.2, 133.0, 129.5, 127.2, 122.9, 121.8, 72.4, 52.4. IR (neat): ν 3488, 1716, 1531, 1351 cm^{-1}. ESIMS *m/z* (relative intensity): 260.06 ($M + Na^+$, 100), 238.8 (MH^+, 60). HRMS (ESI) *m/z*: calcd for $C_{11}H_{15}N_2O_5$ ($M + NH_4^+$), 255.0981; found, 255.0990.

2-[(4-Fluoro-phenyl)-hydroxy-methyl]-acrylic Acid, 1-Methyl Ester (24). ^{1}H NMR ($CDCl_3$): δ 7.39−7.30 (m, 2H), 7.10−7.00 (m, 2H), 6.35 (s, 1H), 5.85 (t, J = 1.8 Hz, 1H), 5.56 (d, J = 5.2 Hz, 1H), 3.74 (s, 3H), 3.13 (d, J = 5.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 166.9, 165.0, 160.1, 142.0, 137.2, 128.6, 126.3, 115.7, 115.3, 72.8, 52.2. IR (neat): ν 3446, 1718, 1508 cm^{-1}. ESIMS *m/z* (relative intensity): 233.07 ($M + Na^+$, 100), 210.99 (MH^+, 14). HRMS (ESI) *m/z*: calcd for $C_{11}H_{11}O_3F$ ($M + Na^+$), 233.0596; found, 233.0617.

(7) ^{1}H NMR monitoring of the incubation of Baylis−Hillman product **16** under the same conditions showed that **16** was stable after 72 h with no detectable hydrolysis. A small amount of *p*-nitrobenzaldehyde **15** was detected by ^{1}H NMR after 72 h, and its molar ratio to product after 2 weeks was 1:14 after column purification, suggesting that the Baylis−Hillman reaction is reversible but the retro-Baylis−Hillman reaction is very slow.

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2-(Furan-2-yl-hydroxy-methyl)-acrylic Acid, 1-Methyl Ester (26). ^{1}H NMR ($CDCl_3$): δ 7.37−7.35 (m, 1H), 6.39−6.37 (m, 1H), 6.34−6.31 (m, 1H), 6.25−6.23 (m, 1H), 5.96 (t, J = 1.1 Hz, 1H), 5.59 (d, J = 5.2 Hz, 1H), 3.75 (s, 3H), 3.43 (d, J = 5.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 166.6, 154.3, 142.5, 139.7, 126.9, 110.6, 107.4, 67.2, 52.2. IR (neat): ν 3436, 1713, 1631, 1436, 1282, 1149 cm^{-1}. ESIMS *m/z* (relative intensity): 164.96 (M − OH, 100). HRMS (ESI) *m/z*: calcd for $C_9H_9O_3$ (M − OH), 165.0552; found, 165.0560.

2-[Hydroxy-(5-hydroxymethyl-furan-2-yl)-methyl]-acrylic Acid, 1-Methyl Ester (28). ^{1}H NMR ($CDCl_3$): δ 6.39 (s, 1H), 6.19 (d, J = 3.4 Hz, 1H), 6.14 (d, J = 3.0 Hz, 1H), 6.02 (s, 1H), 5.57 (br s, 1H), 4.50 (s, 2H), 3.99 (d, J = 4.8 Hz, 1H, OH), 3.74 (s, 3H), 3.21 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 166.7, 154.3, 154.1, 139.5, 127.0, 108.8, 108.2, 66.7, 57.3, 52.3. IR (neat): ν 3385, 1708, 1631, 1436 cm^{-1}. ESIMS *m/z* (relative intensity): 235.07 (M + Na$^+$, 63), 195.04 (M − OH, 100). HRMS (ESI) *m/z*: calcd for $C_{10}H_{16}NO_5$ (M + NH_4^+), 230.1028; found, 230.1036.

2-[Hydroxy-(5-nitro-furan-2-yl)-methyl]-acrylic Acid, 1-Methyl Ester (30). ^{1}H NMR ($CDCl_3$): δ 7.27 (d, J = 4.4 Hz, 1H), 6.53 (d, J = 3.6 Hz, 1H), 6.48 (s, 1H), 6.09 (s, 1H), 5.60 (s, 1H), 4.05−3.80 (br s, 1H, OH), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 166.1, 158.1, 151.8, 137.8, 128.9, 112.8, 110.6, 67.4, 52.6. IR (neat): ν 3470, 1716, 1531, 1497, 1356 cm^{-1}. ESIMS *m/z* (relative intensity): 250.03 (M + Na$^+$, 100). HRMS (ESI) *m/z*: calcd for $C_9H_{13}N_2O_6$ (M + NH_4^+), 245.0774; found, 245.0774.

2-(Hydroxy-thiazol-2-yl-methyl)-acrylic Acid, 1-Methyl Ester (32). ^{1}H NMR ($CDCl_3$): δ 7.68 (d, J = 3.0 Hz, 1H), 7.30 (d, J = 3.4 Hz, 1H), 6.42 (s, 1H), 6.03 (d, J = 1.0 Hz, 1H), 5.79 (br s, 1H), 4.98 (br s, 1H), 3.74 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.9, 166.5, 142.5, 139.9, 128.0, 119.9, 71.3, 52.3. IR (neat): ν 3210, 2944, 1718, 1631, 1436 cm^{-1}. ESIMS *m/z* (relative intensity): 222.02 (M + Na$^+$, 20), 200.00 (MH$^+$, 100). HRMS (ESI) *m/z*: calcd for $C_8H_{10}NO_3S$ (MH$^+$), 200.0381; found, 200.0356.

2-[Hydroxy-(1-methyl-1*H*-imidazol-2-yl)-methyl]-acrylic Acid, 1-Methyl Ester (34). ^{1}H NMR ($CDCl_3$): δ 6.90 (s, 1H), 6.81 (s, 1H), 6.41 (s, 1H), 5.95 (s, 1H), 5.64 (s, 1H), 3.75 (d, J = 2.2 Hz, 3H), 3.72 (d, J = 2.2 Hz, 3H), 2.89 (d, J = 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 166.8, 140.0, 127.2, 126.1, 121.8, 65.9, 52.2, 46.4, 33.3. IR (neat): ν 3448, 3039, 2851, 2724, 1712 cm^{-1}. ESIMS *m/z* (relative intensity): 198.16 (M + 2H$^+$, 10), 197.05 (MH$^+$, 100). HRMS (ESI) *m/z*: calcd for $C_9H_{13}N_2O_3$ (MH$^+$), 197.0926; found, 197.0953.

2-(Hydroxy-pyridin-2-yl-methyl)-acrylic Acid, 1-Methyl Ester (36). ^{1}H NMR ($CDCl_3$): δ 8.49 (d, J = 4.8 Hz, 1H), 7.66−7.61 (m, 1H), 7.39 (d, J = 7.4 Hz, 1H), 7.17 (t, J = 6.1 Hz, 1H), 6.32 (d, J = 5.4 Hz, 1H), 5.93 (d, J = 5.9 Hz, 1H), 5.60 (d, J = 5.2 Hz, 1H), 5.05−4.60 (br s, 1H, OH), 3.69 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 166.7, 159.8, 148.4, 141.9, 137.0, 127.0, 122.8, 121.5, 72.3, 52.0. IR (neat): ν 3418, 3011, 2953, 1722, 1593 cm^{-1}. ESIMS *m/z* (relative intensity): 194.05 (MH$^+$, 100), 175.99 (79). HRMS (ESI) *m/z*: calcd for $C_{10}H_{12}NO_3$ (MH$^+$), 194.0817; found, 194.0822.

2-(Hydroxy-pyridin-3-yl-methyl)-acrylic Acid, 1-Methyl Ester (38). ^{1}H NMR ($CDCl_3$): δ 8.37 (br s, 1H), 8.26 (d, J = 3.6 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.16 (dd, J = 4.8, 8.0 Hz, 1H), 6.30 (s, 1H), 5.97 (s, 1H), 5.21 (s, 1H), 5.16 (br s, 1H), 3.60 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 166.4, 148.4, 148.4, 142.1, 138.1, 135.1, 126.1, 123.7, 70.4, 52.1. IR (neat): ν 3180, 1718, 1626, 1436 cm^{-1}. ESIMS *m/z* (relative intensity): 195.13 (M + 2H$^+$, 10), 194.02 (MH$^+$, 100). HRMS (ESI) *m/z*: calcd for $C_{10}H_{12}NO_3$ (MH$^+$), 194.0817; found, 194.0834.

2-{Hydroxy-[6-(1-hydroxy-2-methoxycarbonyl-allyl)-pyridin-2-yl]-methyl}-acrylic Acid, 1-Methyl Ester (40). ^{1}H NMR ($CDCl_3$): δ 7.64 (t, J = 7.7 Hz, 1H), 7.26 (d, J = 7.6 Hz, 2H), 6.25 (s, 2H), 5.82 (s, 2H), 5.53 (s, 2H), 4.55 (br s, 2H, OH), 3.64 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 166.8, 158.7, 158.7, 141.6, 137.9, 127.0, 120.3, 120.3, 72.6, 52.1. IR (neat): ν 3423, 1716, 1633, 1594, 1577 cm^{-1}. ESIMS *m/z* (relative intensity): 308.14 (MH$^+$, 100), 272.09 (16). HRMS (ESI) *m/z*: calcd for $C_{15}H_{18}NO_6$ (MH$^+$), 308.1134; found, 308.1132.

Betaine 44a. Mp 172−174 °C (sublimated at 163 °C). ^{1}H NMR (D_2O): δ 3.40 (s, 2H), 3.29 (t, J = 7.1 Hz, 6H), 3.08 (t, J = 7.2 Hz, 6H). ^{13}C NMR (D_2O + DMSO-d_6): δ 173.9, 59.6, 50.2, 42.4, 27.8 (p, J = 17.4 Hz, ^{13}C−D). IR (neat): ν 1597, 1365 cm^{-1}. ESIMS *m/z* (relative intensity): 187.14 (MH$^+$, 93), 373.30 (2M + H$^+$, 38). HRMS (FAB) *m/z*: calcd for $C_9H_{15}D_2N_2O_2$ (MH$^+$), 187.1414; found, 187.1408.

Betaine 44b. Mp 151 °C (sublimation). ^{1}H NMR (D_2O): δ 3.45−3.36 (m, 2H), 3.26 (t, J = 3.8 Hz, 6H), 3.09 (d, J = 5.2 Hz, 6H), 2.55 (t, J = 7.6 Hz, 2H). ^{13}C NMR (D_2O + DMSO-d_6): δ 173.1, 60.1, 50.3, 42.7, 28.6. IR (neat): ν 1596, 1360 cm^{-1}. ESIMS *m/z* (relative intensity): 185.19 (MH$^+$, 100), 369.31 (2M + H$^+$, 10).

Acknowledgment. We gratefully acknowledge the financial support of grant GM 62752 from the National Institutes of Health.

Supporting Information Available: Kinetic analysis of the reaction between DABCO and methyl acrylate using ^{1}H NMR and spectroscopic data for new compounds **4**, **14**, **20**, **24**, **26**, **28**, **30**, **32**, **34**, **36**, **38**, **40**, **44a**, and **44b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO015628M