Successful Baylis−Hillman Reaction of Acrylamide with Aromatic Aldehydes

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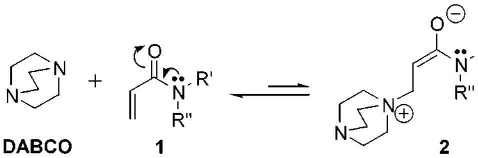
Acrylamide and aromatic aldehydes were found to undergo the Baylis−Hillman reaction at ambient temperature in an aqueous medium in the presence of a stoichiometric amount of base catalyst, DABCO, to give the corresponding 3-hydroxy-2-methylenepropionamides in 61−99% yield. A faster competing, but reverible, non-Baylis−Hillman reaction was initially observed under the conditions to form N-acylhemiaminals, which later disappeared, as the desired Baylis−Hillman adduct was formed as the major product over an extended period of time (12−48 h). This represents the first demonstration of the Baylis−Hillman reaction of aldehydes with acrylamides, which were thought to be inert under atmospheric pressure and at ambient temperature.

Introduction

The Baylis−Hillman reaction, which mainly entails a tertiary amine-catalyzed coupling of an α,*β*-unsaturated carbonyl compound with an aldehyde, is among the most economical and useful C−C bond-forming reactions in organic synthesis.[1] The α,*β*-unsaturated carbonyl compounds that have been shown to undergo the Baylis−Hillman reaction include acrylonitrile, acrolein, acrylates, and α,*β*-unsaturated ketones. But, few examples are known for acrylamides.[1c,2] The diethylmethylamine-catalyzed reaction of acetaldehyde with acrylamide and the 1,4-diazabicyclo[2,2,2]octane (DABCO)-catalyzed addition of acetone to acrylamide, both under 5-kbar pressure, were reported in 1986 to produce the Baylis−Hillman products in 83%[3] and 5%[4] yields, respectively. In 1994, a DABCO-catalyzed addition of acrylamide with 3,4,5-trimethoxybenzaldehyde was reported in methanol to afford α-hydroxyalkylation product in 40% yield.[5] However, neither experimental details nor structural evidences were provided in these reports. This led Ciganek to conclude in his 1997 review on the Baylis−Hillman reaction that acrylamide does not react with aldehydes under ambient conditions.[1c]

Recently, Kim and co-workers reported an alternative route to obtain such challenging Baylis−Hillman adducts by using a Grignard addition to aldehydes of vinyl samarium species formed from α-bromoacrylamides.[6] These vinyl samarium reagents would add to aldehydes forming 3-hydroxy-2-methylenepropionamides in good yields (52−89%). However, this method does not work with aromatic aldehydes, as these reactive aldehydes are more easily reduced by vinyl samarium reagents than undergoing the addition reaction.

Scheme 1



As shown in Scheme 1, electron delocalization of the lone pair of electrons on the nitrogen of acrylamide decreases the electron-withdrawing capability of the carbonyl group, making acrylamide **1** a weak Michael acceptor. In addition, the delocalization would not favor the formation of the zwitterionic intermediate **2**.[2] Therefore, conditions that favor the localization of electrons and the formation of the zwitterionic intermediate might facilitate the Michael addition of a nucleophilic base to acrylamides and, thus, promote the Baylis−Hillman reaction of acrylamides with aldehydes.

In an earlier report, we developed a set of efficient and practical conditions that used a stoichiometric amount of DABCO in a 1:1 (v/v) mixture of 1,4-dioxane and water and demonstrated their efficiency in obtaining 3-hydroxy-2-methylenepropionic acid methyl esters via the Baylis−Hillman reaction.[7] The effect of water in promoting the Baylis−Hillman reaction under these conditions was attributed to an increase in the equilibrium constant for the formation of the zwitterionic intermediates through intermolecular charge−dipole interactions as well as hydrogen-bonding interactions. This effect of water in promoting bimolecular reactions is well-known.[8] We hypothesized that water might also help stabilize the transition state(s)/intermediate(s) in the Baylis−Hillman coupling of acrylamides with aldehydes since acrylamide

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[2] Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1809−1813.

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[4] Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.* **1986**, *27*, 5007−5010.

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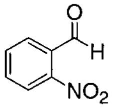
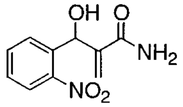
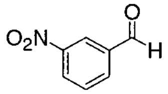
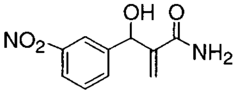
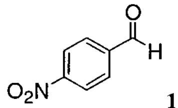
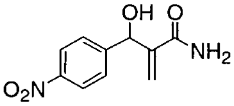
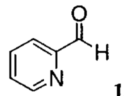
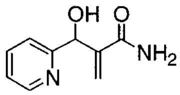
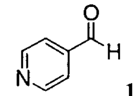
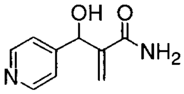
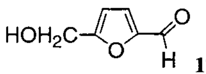
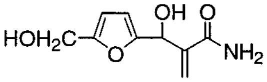
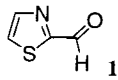
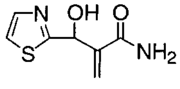
Table 1. The Baylis–Hillman Reaction of Aromatic Aldehydes with Acrylamide[a]

entry	substrate	product	time (h)	yield %[b]
1	 **7**	 **8**	24	85
2	 **9**	 **10**	24	73
3	 **11**	 **12**	24	95
4	 **13**	 **14**	24	89
5	 **15**	 **16**	24	93
6	 **17**	 **18**	48	61
7	 **19**	 **20**	12	99

[a] General conditions: substrate aldehyde (2 mmol), acrylamide (2 mmol), DABCO (100 mol %), 1,4-dioxane–water (1:1, 10 mL), rt. [b] Isolated yields.

has two heteroatoms (N and O) that could form hydrogen bonds with water molecules. In this paper, we report the successful Baylis–Hillman coupling of simple acrylamide with several commercially available aromatic aldehydes using the conditions we developed for the efficient coupling of aldehydes with methyl acrylate.[7]

Results and Discussion

We found that several aromatic aldehydes, when incubated for an extended period of time (12–48 h) at ambient temperature in the presence of a stoichiometric amount of DABCO in a 1:1 (v/v) mixture of 1,4-dioxane and water, would react with acrylamide to give the corresponding Baylis–Hillman adducts, 3-hydroxy-2-methylenepropionamides (**5**), in moderate to good yields from 61 to 99% as shown in Table 1. We also observed during the first few hours of incubation a faster competing nucleophilic addition reaction of the nitrogen of acrylamide to the aldehyde-forming *N*-acylhemiaminals (**6**). Fortunately, this competing non-Baylis–Hillman reaction was reversible and the *N*-acylhemiaminals later disappeared as the corresponding Baylis–Hillman adducts were formed.

As shown in Table 1, seven aromatic aldehydes we examined were found to react with acrylamide (**4**) under our conditions to give the desired Baylis–Hillman adducts in moderate to good yields. All of the products were identified by ^{1}H NMR, ^{13}C NMR, IR, and HRMS. To our knowledge, this is the first demonstration of the Baylis–Hillman reactions of acrylamide with full spectroscopic data provided for the products. In general, nitrobenzaldehydes (**7**, **9**, **11**) and pyridinecarboxaldehydes (**13**, **15**) were good substrates for the Baylis–Hillman reactions under our conditions. For nitrobenzaldehydes, the reaction rate and product yield were in the following order: 4-NO_2 > 2-NO_2 > 3-NO_2. Similarly, for pyridinecarboxaldehydes, the reactivity order was 4-N > 2-N, while there was no reaction for 3-pyridinecarboxaldehyde under the same conditions. These results suggest that the electron-withdrawing resonance effect of the nitro group in nitrobenzaldehydes and the nitrogen on the pyridine ring in pyridinecarboxaldehydes is a very important factor in accelerating the Baylis–Hillman reaction with acrylamide. Furthermore, we found that by replacing the nitro group in 4-nitrobenzaldehyde (**11**) with a fluorine atom or the hydroxymethyl group in 5-(hydroxymethyl)-2-furaldehyde (**17**) with a methyl group failed to give any Baylis–Hillman product. This suggests that Baylis–Hillman coupling of aromatic aldehydes to acrylamide might not be simply promoted by the activation of the aldehydes via the introduction of electron-withdrawing groups onto aromatic rings. The fact that 5-(hydroxymethyl)-2-furaldehyde (**17**) worked well (61%) while 5-methyl-2-furaldehyde failed to react under our conditions indicates the importance of hydrogen-bonding interactions in the Baylis–Hillman coupling of aldehydes with acrylamide. We also found that *N*-isopropylacrylamide and *N*,*N*-dimethylacrylamide were inert substrates under our conditions. The failure of these two *N*-substituted acrylamides might be due to the stronger delocalization of the lone-pair of electrons facilitated by the alkyl

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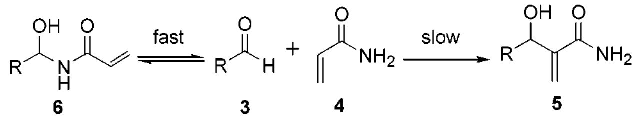
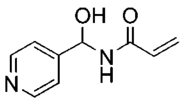
Scheme 2[a]



[a] Reaction conditions: DABCO (100 mol %), rt, 1,4-dioxane−H_2O (1:1, v/v).

substituents on the nitrogen of acrylamides. Thus, our success of the Baylis−Hillman reaction of simple acrylamide with aromatic aldehydes may be attributed to the sufficient stabilization of the zwitterionic intermediates via hydrogen-bonding interactions and/or dipole−dipole interactions that are only possible or strong enough in the simple acrylamide in the aqueous medium. It should be noted that the Baylis−Hillman reaction of acrylamide under our conditions was slower than the corresponding reaction of methyl acrylate and that our conditions are not suitable for the coupling of aliphatic aldehydes to acrylamides. Aldol condensation of aliphatic aldehydes would take over during the long reaction time needed for the Baylis−Hillman reaction.



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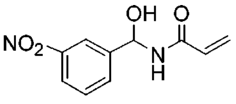

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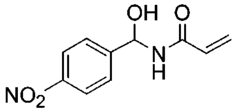

23

Characterization of the Competing Non-Baylis−Hillman Addition Reaction. The time needed for the Baylis−Hillman coupling reaction of aromatic aldehydes with acrylamide was between 12 and 48 h. TLC monitoring of the reaction mixtures showed the appearance and disappearance of what appeared to be “an intermediate” during the course of the reaction. To characterize the “intermediate”, we terminated the reaction early and isolated and characterized the “intermediate” as an *N*-acylhemiaminal, the product of a competing nucleophilic addition of the acrylamide nitrogen to the aldehyde (Scheme 2). A similar non-Baylis−Hillman reaction in methylene chloride in the presence of DABCO was recently reported by Bussolari and co-workers.[9] Apparently, this competing reaction was faster than the Baylis−Hillman coupling reaction, but is reversible. The *N*-acylhemiaminal would appear first in the reaction and later reverted back to the starting aldehydes and acrylamide as the desired thermodynamically more stable Baylis−Hillman adduct was formed. Indeed, if the reaction of 4-pyridinecarboxaldehyde (**15**) with acrylamide was terminated after 4 h, *N*-acylhemiaminal **21** was isolated in 27% yield and the desired Baylis−Hillman adduct in less than 2% yield. If the reaction was allowed to continue for 24 h, the desired Baylis−Hillman product **16** was obtained in 93% yield. Similarly, the reaction of acrylamide with 3-nitrobenzaldehyde (**9**) produced the corresponding *N*-acylhemiaminal product **22** in 17% isolated yield after 4 h and the desired Baylis−Hillman product **10** in 73% yield after 24 h. The reaction with 4-nitrobenzaldehyde (**11**) gave the corresponding *N*-acylhemiaminal **23** in 25% isolated yield after 4 h and the desired Baylis−Hillman product **12** in 95% yield after 24 h.

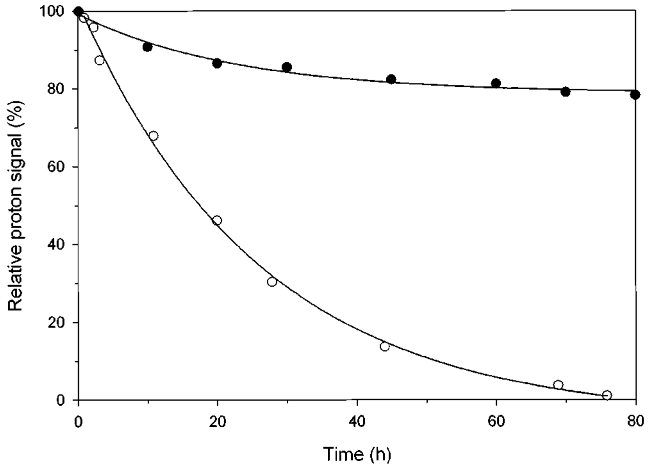

Figure 1. Time-dependent deuterium exchange of C_α-H of acrylamide in a 1:1 (v/v) mixture of D_2O and 1,4-dioxane-d_8 as monitored by ^{1}H NMR. Acrylamide (0.15 mmol) was incubated at room temperature in 0.75 mL of a 1:1 (v/v) mixture of D_2O and 1,4-dioxane-d_8 in the presence of 100 mol % (○) or 10 mol % (●) of DABCO.

To confirm that the *N*-acylhemiaminal formation is reversible under our reaction conditions, we incubated the *N*-acylhemiaminals **21**, **22**, and **23** at ambient temperature in a 1:1 (v/v) mixture of 1,4-dioxane-d_8 and D_2O in the presence of DABCO (1 equiv) and monitored the resulting solution using TLC and ^{1}H NMR. Within hours of incubation, we observed the formation of acrylamide, the starting aromatic aldehyde, and the corresponding Baylis−Hillman product. After 24 h of incubation, the corresponding Baylis−Hillman product was found to be the major product and most of the *N*-acylhemiaminals had disappeared. On the other hand, incubation of the Baylis−Hillman adducts under the same conditions showed no detectable starting aromatic aldehydes and acrylamide after 72 h. These results suggest that under our basic aqueous conditions, the formation of the non-Baylis−Hillman adduct, *N*-acylhemiaminal, was kinetically faster but reversible while the formation of the Baylis−Hillman adduct was slow but thermodynamically more stable. Thus, the yield of desired Baylis−Hillman adduct could be increased simply by prolonging the reaction time until TLC shows most of the competing adduct, *N*-acylhemiaminal, disappears.

Kinetic Studies and the Effect of Base. The use of a stoichiometric amount of DABCO is necessary since decreasing the amount of base used to a catalytic amount dramatically slowed the Baylis−Hillman reactions of acrylamide. On the basis of kinetic analysis using ^{1}H NMR (Figure 1), the deuterium-exchange of C_α-H of acrylamide in the presence of 100 mol % DABCO had a half-life of about 18 h, while only about 20% of C_α-H of acrylamide was exchanged in the presence of a catalytic amount (10 mol %) of DABCO after 80 h of incubation. This deuterium-exchange could only occur through the reversible Michael addition of nucleophilic DABCO to acrylamide, the necessary first step in the Baylis−Hillman reaction of acrylamide. The observed rate of

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reaction and the final yield of the Baylis−Hillman adduct were directly related to the amount of base used as well as the reactivity of the substrate aldehyde, suggesting that the addition of the zwitterionic intermediate to the substrate aldehyde was the rate-determining step in the Baylis−Hillman reaction of acrylamide. The slower deuterium-exchange of the C_α-H of acrylamide as compared to that of methyl acrylate in the presence of 100 mol % DABCO is consistent with the fact that acrylamide is a poorer Michael acceptor and, thus, much less reactive in the Baylis−Hillman reaction.

In summary, we have demonstrated that aromatic aldehydes and acrylamide could undergo two competing addition reactions at ambient temperature in an aqueous medium in the presence of 100 mol % DABCO, namely, the addition of amide nitrogen to the aldehydes forming *N*-acylhemiaminals and the Baylis−Hillman addition reaction forming 3-hydroxy-2-methylenepropionamides. The formation of *N*-acylhemiaminals was faster but reversible while the corresponding Baylis−Hillman reaction products were thermodynamically more stable. Therefore, the reactions gave the corresponding to thermodynamically more stable Baylis−Hillman products as the major product in good yields over 12−48 h. This represents the first demonstration of the Baylis−Hillman reaction of aldehydes with acrylamides, which were thought to be inert under atmospheric pressure and at ambient temperature.

Experimental Section

General Methods. All reactions were performed without protection by an inert gas. Solvents were either ACS reagent grade or HPLC grade. 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, unless otherwise noted. All reagents were purchased at the highest commercial quality and used without further purification.

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 the internal reference. Chemical shifts (200 MHz for ^{1}H and 50 MHz for ^{13}C) are reported in parts per million (δ) relative to CD_3OD (δ 3.3 for ^{1}H and 49.0 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. To a clear solution of substrate aromatic aldehyde (2.0 mmol) and acrylamide (2.0 mmol) in 5 mL of 1,4-dioxane was slowly charged while stirring 5 mL of deionized water.[10] The homogeneous reaction mixture was stirred at ambient temperature in the presence of one equiv of DABCO and the reaction progress was monitored by TLC. Upon completion or as indicated, the reaction mixture was partitioned with ethyl acetate (250 mL) and brine (20 mL). The aqueous layer was extracted with chloroform (3 × 60 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate and/or methanol to give the desired product.

Kinetic Analysis of the Deuterium Exchange of C_α-H of Acrylamide Using ^{1}H NMR. Acrylamide (0.15 mmol) was incubated at ambient temperature in a 1:1 (v/v) mixture of 1,4-dioxane-d_8 and deuterium oxide in the presence of either 100 mol % or 10 mol % of DABCO. ^{1}H NMR spectra were taken at various time intervals. The integral of various signals were normalized based on the 1,4-dioxane proton signals at 3.84. The pseudo first-order rate constants were then calculated for the disappearance of the C_α-H signal of acrylamide due to deuterium exchange.

3-Hydroxy-2-methylene-3-(2-nitrophenyl)propionamide (8). ^{1}H NMR (CD_3OD): δ 7.93 (dd, J = 8.1, 0.7 Hz, 1H), 7.79−7.66 (m, 2H), 7.52 (dt, J = 3.0, 1.8 Hz, 1H), 6.24 (s, 1H), 5.97 (s, 1H), 5.50 (d, J = 1.2 Hz, 1H). ^{13}C NMR (CD_3OD): δ 170.0, 148.2, 145.0, 136.2, 132.2, 128.2, 127.8, 123.5, 119.2, 66.6. IR (neat): ν 3360, 1652, 1634 cm^{-1}. ESIMS *m*/*z* (relative intensity): 223.10 (MH^+, 100), 255.16 ($M + Na^+$, 25). HRMS (ESI) *m*/*z*: calcd for $C_{10}H_{11}N_2O_4$ (MH^+) 223.0719; found 223.0700.

3-Hydroxy-2-methylene-3-(3-nitrophenyl)propionamide (10). ^{1}H NMR (CD_3OD): δ 8.28 (s, 1H), 8.15 (dd, J = 8.2, 2.2 Hz, 1H), 7.79 (dd, J = 7.6, 1.2 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 6.01 (d, J = 0.8 Hz, 1H), 5.81 (d, J = 0.6 Hz, 1H), 5.71 (s, 1H). ^{13}C NMR (CD_3OD): δ 169.9, 147.8, 145.3, 144.2, 132.3, 128.6, 121.5, 120.7, 119.0, 71.1. IR (neat): ν 3362, 1656, 1631 cm^{-1}. FABMS *m*/*z* (relative intensity): 223.1 (MH^+, 35), 205.1 (M − OH, 100). HRMS (FAB^+) *m*/*z*: calcd for $C_{10}H_{10}N_2O_4$ (MH^+) 223.0718; found 223.0719.

3-Hydroxy-2-methylene-3-(4-nitrophenyl)propionamide (12). ^{1}H NMR (CD_3OD): δ 8.21 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 6.00 (d, J = 0.8 Hz, 1H), 5.78 (d, J = 0.8 Hz, 1H), 5.71 (s, 1H). ^{13}C NMR (CD_3OD): δ 169.9, 149.3, 145.3, 127.0, 122.5, 122.4, 119.2, 71.2. IR (neat): ν 3540, 3387, 1687, 1621 cm^{-1}. FABMS *m*/*z* (relative intensity): 223.1 (MH^+, 10), 205.1 (M − OH, 6), 154.1 (100). HRMS (FAB^+) *m*/*z*: calcd for $C_{10}H_{10}N_2O_4$ (MH^+) 223.0720; found 223.0719.

3-Hydroxy-2-methylene-3-(pyridin-2-yl)propionamide (14). ^{1}H NMR (CD_3OD): δ 8.50−8.47 (m, 1H), 7.83 (dt, J = 7.7, 1.8 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.35−7.29 (m, 1H), 6.04 (s, 1H), 5.71 (s, 1H), 5.67 (s, 1H). ^{13}C NMR (CD_3OD): δ 170.0, 160.3, 147.6, 144.6, 136.9, 122.3, 121.0, 120.6, 73.0. IR (neat): ν 3326, 1660, 1652, 1614, 1573, 1436 cm^{-1}. ESIMS *m*/*z* (relative intensity): 179.12 (MH^+, 100). HRMS (ESI) *m*/*z*: calcd for $C_9H_{11}N_2O_2$ (MH^+) 179.0821; found 179.0820.

3-Hydroxy-2-methylene-3-(pyridin-4-yl)propionamide (16). ^{1}H NMR (CD_3OD): δ 8.49 (dd, J = 5.6, 1.6 Hz, 2H), 7.47 (d, J = 5.8 Hz, 2H), 6.02 (s, 1H), 5.78 (s, 1H), 5.63 (s, 1H). ^{13}C NMR (CD_3OD): δ 169.7, 152.3, 148.1, 144.8, 121.5, 119.9, 70.8. IR (neat): ν 3534, 3400, 1696, 1586 cm^{-1}. FABMS *m*/*z* (relative intensity): 179.1 (MH^+, 100). HRMS (FAB^+) *m*/*z*: calcd for $C_9H_{11}N_2O_2$ (MH^+) 179.0821; found 179.0837.

3-Hydroxy-2-methylene-3-(5-hydroxymethylfuran-2-yl)propionamide (18). ^{1}H NMR (CD_3OD): δ 6.25 (AB*q*, $\Delta\gamma$ = 7.0 Hz, J = 3.2 Hz, 1H), 6.21 (AB*q*, $\Delta\gamma$ = 7.0 Hz, J = 3.2 Hz, 1H), 6.00 (s, 1H), 5.78 (s, 1H), 5.61 (s, 1H), 4.49 (s, 2H). ^{13}C NMR (CD_3OD): δ 154.0, 143.5, 130.0, 125.8, 119.2, 107.3, 107.1, 65.8, 55.6. IR (neat): ν 3385, 1650, 1605, 1410 cm^{-1}. ESIMS *m*/*z* (relative intensity): 180.20 (M-OH, 100). HRMS (ESI) *m*/*z*: calcd. for $C_9H_{10}NO_3$ (M − OH) 180.0661; found 180.0681.

3-Hydroxy-2-methylene-3-(thiazol-2-yl)propionamide (20). ^{1}H NMR (CD_3OD): δ 7.73 (d, J = 3.4 Hz, 1H), 7.56 (d, J = 3.2 Hz, 1H), 6.08 (s, 1H), 5.88 (s, 1H), 5.79 (s, 1H). ^{13}C NMR (CD_3OD): δ 173.5, 169.4, 143.7, 141.4, 120.9, 119.4, 70.1. IR (neat): ν 3535, 3390, 1682, 1554 cm^{-1}. ESIMS *m*/*z* (relative intensity): 185.19 (MH^+, 100). HRMS (ESI) *m*/*z*: calcd for $C_7H_9N_2O_2S$ (MH^+) 185.0385; found 185.0384.

***N*-(Hydroxypyridin-4-ylmethyl)acrylamide (21).** ^{1}H NMR (CD_3OD): δ 8.55 (dd, J = 4.8, 1.4 Hz, 2H), 7.56 (dd, J = 3.1, 1.4 Hz, 2H), 6.53 (s, 1H), 6.33 (d, J = 4.8 Hz, 1H), 6.32 (d,

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[10] Keeping a clear solution of substrate aromatic aldehyde in 1,4-dioxane−water was critical for achieving a good yield of the Basylis−Hillman reaction product under our conditions.

$J = 7.2$ Hz, 1H), 5.75 (dd, $J = 7.2, 4.8$ Hz, 1H). ^{13}C NMR (CD_3OD): δ 165.7, 151.0, 148.3, 130.0, 126.3, 121.0, 72.0. IR (neat): ν 3538, 3412, 1695, 1585 cm^{-1}. ESIMS m/z (relative intensity): 179.06 (MH^+, 100). HRMS (ESI) m/z: calcd for $C_9H_{11}N_2O_2$ (MH^+) 179.0821; found 179.0822.

***N*-[Hydroxy-(3-nitrophenyl)methyl]acrylamide (22).** ^{1}H NMR (CD_3OD): δ 8.41 (s, 1H), 8.23 (d, $J = 7.6$ Hz, 1H), 7.88 (d, $J = 7.8$ Hz, 1H), 7.65 (t, $J = 8.1$ Hz, 1H), 6.60 (s, 1H), 6.33 (d, $J = 4.2$ Hz, 1H), 6.32 (d, $J = 7.6$ Hz, 1H), 5.75 (dd, $J = 7.8, 4.2$ Hz, 1H). ^{13}C NMR (CD_3OD): δ 165.6, 147.9, 143.2, 131.7, 130.0, 128.8, 126.1, 122.1, 120.1, 72.5. IR (neat): ν 3495, 3380, 1688, 1591 cm^{-1}. ESIMS m/z (relative intensity): 205.08 (M − OH, 100). HRMS (ESI) m/z: calcd for $C_{10}H_{11}N_2O_4$ (MH^+) 223.0719; found 223.0720.

***N*-[Hydroxy(4-nitrophenyl)methyl]acrylamide (23).** ^{1}H NMR (CD_3OD): δ 8.27 (d, $J = 9.2$ Hz, 2H), 7.75 (d, $J = 9.2$ Hz, 2H), 6.60 (s, 1H), 6.32 (d, $J = 4.4$ Hz, 1H), 6.31 (d, $J = 7.8$ Hz, 1H), 5.75 (dd, $J = 7.8, 4.4$ Hz, 1H). ^{13}C NMR (CD_3OD): δ 165.6, 148.0, 147.3, 130.0, 126.5, 126.1, 122.6, 72.6. IR (neat): ν 3537, 3415, 1690, 1620 cm^{-1}. ESIMS m/z (relative intensity): 223.00 (MH^+, 10), 205.06 (M − OH, 90). HRMS (ESI) m/z: calcd for $C_{10}H_{11}N_2O_4$ (MH^+) 223.0719, found 223.0697; calcd for $C_{10}H_9N_2O_3$ (M − OH) 205.0613, found 205.0598.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **8**, **10**, **12**, **14**, **16**, **18**, **20**, **21**, **22**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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