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Acrylamide in the Baylis−Hillman Reaction: Expanded Reaction Scope and the Unexpected Superiority of DABCO over More Basic Tertiary Amine Catalysts

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Abstract: DMAP, DBU, and quinuclidine efficiently promote novel hydroalkoxylation reactions of acrylamide in primary alcohol solvents. DABCO is a comparatively poor hydroalkoxylation promoter and can effect clean, selective Baylis−Hillman reactions between acrylamide and aldehydes in alcoholic/aqueous media in which more basic nucleophilic catalysts promote hydroalkoxylation preferentially. Optimization of the reaction conditions has allowed acrylamide to be reacted with a range of aromatic aldehydes in moderate to excellent yields, including the first examples involving deactivated, electron-rich substrates such as *p*-tolualdehyde and *o*-anisaldehyde.

The nucleophile-catalyzed Baylis−Hillman reaction[1] between a carbonyl-based electrophile and a Michael acceptor is an extremely useful carbon−carbon bond- and stereogenic center-forming reaction that has received considerable synthetic attention over the past decade.[2] Although this process furnishes densely functionalized products amenable to further structural elaboration from relatively simple starting materials, it suffers from low reaction rates and limited substrate scope. Early efforts to accelerate the Baylis−Hillman reaction relied on physical methods (i.e., high pressures or microwave radiation),[2e] whereas more convenient strategies based on the use of strongly nucleophilic catalysts,[3] protic solvents,[4,5] ionic additives,[5,6] and Lewis acid catalysts[7] have been reported recently. Despite these advances, a number of α,*β*-unsaturated substrates of low electrophilicity remain somewhat reluctant coupling partners in this reaction. Principal among these challenging substrates are acrylates and acrylamides, and although significant progress has been made of late with regard to the former class of Michael acceptor,[2a] few examples of the use of acrylamide in an efficient Baylis−Hillman reaction have been disclosed, and to our knowledge the coupling of acrylamide with deactivated aromatic aldehydes has yet to be reported. Hu and Lu[8] found that acrylamide underwent Baylis−Hillman coupling with highly activated electrophiles such as nitrobenzaldehydes in good yields in a 1:1 dioxane/H_2O solvent mixture; however, less electrophilic aldehydes were unreactive.[9] More recently, Aggarwal et al. have reported the use of methanolic quinuclidine to promote the efficient reaction between acrylamide and activated aromatic aldehydes, including a lone example of reaction with benzaldehyde itself giving the allylic alcohol product in 55% yield. It was therefore our view that considerable room for scope expansion of Baylis−Hillman reactions involving acrylamide existed, particularly in view of the recent interest in α-substituted acrylamide derivatives as novel radical polymerization monomers[10] and targets for both antithrombotic and antidepression drug design.[11]

The rate-determining step of the Baylis−Hillman reaction involves an aldol-type reaction between the zwitterionic enolate **1** and an aldehyde (Figure 1);[12] thus our initial strategy for promoting the reaction with acrylamide involved the use of a strongly nucleophilic amine such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in protic solvent, with the goal of maximizing the equi-

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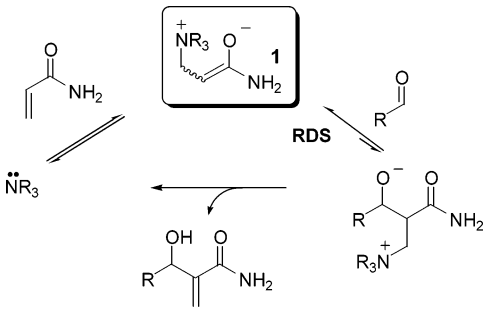
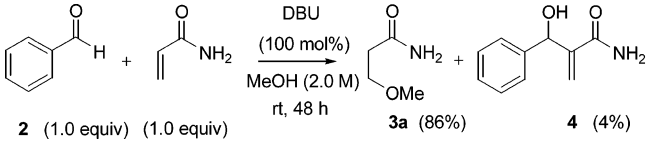


FIGURE 1. Baylis−Hillman reaction catalytic cycle.

SCHEME 1. Baylis-Hillman Reaction Catalyzed by DBU in Methanol

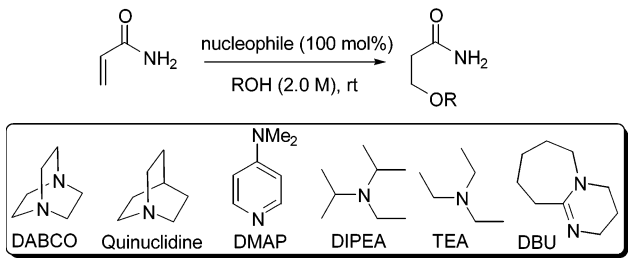


librium concentration of enolate **1**.[3g,13] Treatment of acrylamide with methanolic DBU in the presence of benzaldehyde (**2**) (Scheme 1) gave the unexpected addition product **3a** with only trace amounts of the desired alcohol **4**.

The phosphine-catalyzed Michael addition of alcohols to α,β-unsaturated ketones has recently been reported;[14,15] however, to the best of our knowledge an efficient amine-catalyzed process is unknown and no such nucleophile-catalyzed hydroalkoxylation processes involving acrylamide have been disclosed. Attempts to avoid the formation of **3a** by carrying out the reaction in a range of polar aprotic solvents (HMPA, DMSO, MeCN, 1,4-dioxane, THF, and DMF) were unsuccessful and gave low acrylamide conversion even after extended reaction times. Therefore, given the necessity for a protic medium and the novel nature of addition reaction leading to **3a**, an investigation of the acrylamide-methanolysis reaction catalyzed by amine nucleophiles seemed warranted. The results of these experiments are outlined in Table 1.

Under pseudo-first-order conditions, it was found that the observed addition rate depended strongly on the nucleophilicity of the amine catalyst, with amines of high basicity and low steric hindrance around the nucleophilic nitrogen atom (entries 3 and 5) proving the best promoters of the reaction. In this context, the relatively slow reaction with quinuclidine compared to that promoted by the less basic and less hindered DMAP (entries 3 and 4) and the failure of bulky amines such as TEA and DIPEA to catalyze the reaction (entries 6 and 7) are illustrative. These experiments indicate that direct deprotonation of MeOH by the catalyst followed by addition

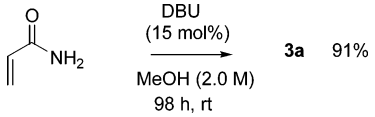
TABLE 1. Addition of Alcohols to Acrylamide Catalyzed by Various Nucleophiles



entry	nucleophile	pK_a [a]	R	k_{obs} [b,c] (h^{-1})	k_{rel}
1	none		Me	0	
2	DABCO	8.8	Me	1.8×10^{-4}	1.0
3	DMAP	9.7	Me	9.9×10^{-3}	55.0
4	quinuclidine	11.3	Me	5.95×10^{-3}	33.1
5	DBU	n/a	Me	8.7×10^{-2}	483.3[d]
6	TEA	10.9	Me	0	
7	DIPEA	11.4	Me	0	
8	PBu_3[e]	8.4	Me	6.1×10^{-2}	339.0
9	DMAP	9.7	CH_2CH_2OH	4.0×10^{-2}	

[a] Refers to the pK_a of the corresponding conjugate acid in H_2O at 25 °C.[16] [b] Determined by ^{1}H NMR spectroscopy using anisole as an internal standard. [c] From ln[acrylamide] vs *t* plot (>30% conversion, average of two runs within ±3% of k_{obs}) in 2.0 M MeOH. [d] 92% yield after 29 h. [e] 10 mol % loading of PBu_3.

SCHEME 2. Efficient Hydroalkoxylation Using Catalytic Loading of DBU



of the resultant alkoxide to acrylamide is not responsible for the formation of **3a** and that Michael addition of the catalyst to acrylamide is a key step in the reaction mechanism.[15b] This is supported by the observation of fast reaction rates with only 10 mol % of the weakly basic yet strongly nucleophilic Bu_3P. The air-insensitive and inexpensive DBU in substoichiometric loading was also found to be an efficient promoter of the reaction, affording **3a** in excellent yield (Scheme 2) without the necessity for rigorous solvent distillation/degassing associated with the use of oxygen-sensitive trialkylphosphines.

In contrast, the moderately hindered weakly basic DABCO was identified as a poor hydroalkoxylation catalyst and therefore held the most promise as a nucleophilic catalyst in the corresponding Baylis−Hillman reaction. Screening studies (Table 2) involving the reaction between benzaldehyde and acrylamide in methanol over 44 h (entries 1, 3, 7, and 9−11) demonstrated that of the catalysts tested only DABCO promoted the *selective* (albeit slow) formation of the Baylis−Hillman adduct **4** without furnishing solvolysis product **3a**. As expected, the more nucleophilic catalysts such as DMAP or DBU predominantly catalyzed the formation of **3a**. The use of aqueous reaction media (entries 2, 5, and 8) generally afforded higher yields of Baylis−Hillman products after 44 h. However, with the exception of the DABCO-catalyzed process (entry 2) these reactions were not clean; numerous unidentifiable addition and polymeric products were observed by ^{1}H NMR spectroscopy. Ethanol and *tert*-butyl alcohol (7.5 M) were poor reaction

(13) For studies concerning the stability of amide tautomers, see: (a) Mukhopadhyaya, J. K.; Sklenák, S.; Rappoport, Z. *J. Am. Chem. Soc.* **2000**, *122*, 1325. (b) Lei Y. X.; Casarini, D.; Cerioni, G.; Rappoport, Z. *J. Org. Chem*. **2003**, *68*, 947. (c) Basheer, A.; Rappoport, Z. *J. Org. Chem*. **2004**, *69*, 1151.

(14) For use of trialkylphosphines under high pressure, see: (a) Jenner, G. *Tetrahedron Lett*. **2001**, *42*, 4807. (b) Jenner, G. *Tetrahedron* **2002**, *58*, 4311.

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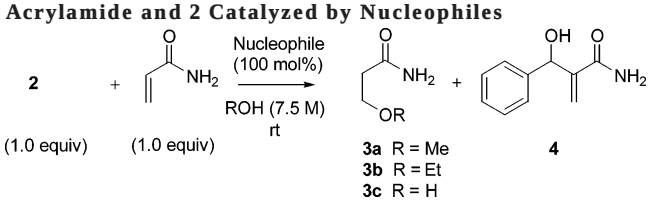
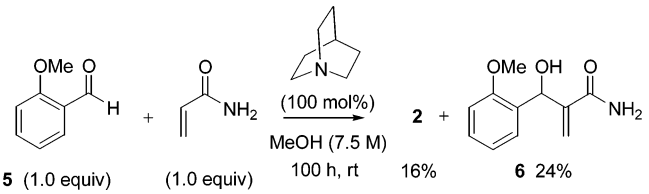
TABLE 2. Baylis−Hillman Reaction between Acrylamide and 2 Catalyzed by Nucleophiles



entry	nucleophile	solvent	time (h)	yield **3** (%)[a]	yield **4** (%)[a]	**3**:**4**
1	DABCO	MeOH	44	0	4	0:100
2	DABCO	^{t}BuOH/H_2O (3:7)	44	0	11[b]	0:100
3	DMAP	MeOH	44	22	13	63:37
4	DMAP	EtOH[c]	44	1	3	25:75
5	DMAP	^{t}BuOH[c]	44	0	0	
6	DMAP	^{t}BuOH/H_2O (3:7)	44	6	27	18:82[d,e]
7	quinuclidine	MeOH	44	11	50	18:82
8	quinuclidine	^{t}BuOH/H_2O (3:7)	44	n/d[e]	52	n/d[d,g]
9	DBU	MeOH	44	71	8	90:10
10	PBu_3[i]	MeOH	44	72	0	100:0
11	TEA	MeOH	44	0	0	

[a] Determined by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard. [b] 12% conversion of acrylamide. [c] Reaction not homogeneous. [d] Numerous unidentifiable side products present. [e] 84% conversion of acrylamide. [f] n/d = not determined. [g] 86% conversion of acrylamide. [h] 10 mol % of PBu_3.

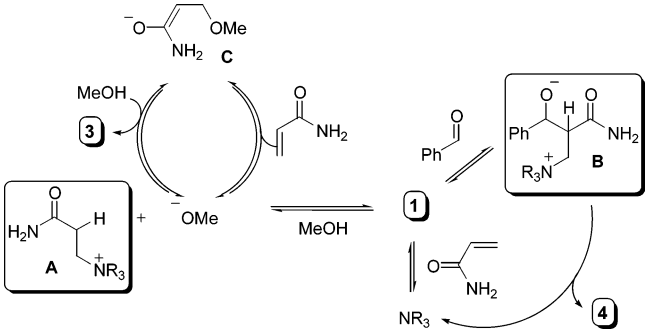
SCHEME 3. Quinuclidine-Catalyzed Baylis-Hillman Reaction of 5



solvents in which the reagents were only partially soluble. The relatively high yield of **4** obtained using methanolic quinuclidine would at first appear to signal its potential as a fast and efficient catalyst; however, when tested using less reactive aldehydes such as *o*-anisaldehyde (**5**) (Scheme 3), the formation of **3a** becomes competitive with the slow Baylis−Hillman reaction pathway, with a resultant significant loss of synthetic utility.

The experiments in Tables 1 and 2 suggest that both **3** and **4** are formed via the common enolate intermediate **1**. The hydroalkoxylation pathway proceeds via deprotonation of the solvent by **1** generating a quaternary ammonium amide **A** and an alkoxide anion,[17] which can then either undergo reprotonation to reform the starting materials or participate in a Michael addition with acrylamide[18] to generate **3** via enolate **C** (Scheme 4).[19] In the case of catalysis by DMAP, **A** is the sole intermediate observable by ^{1}H NMR spectroscopy,[20] suggesting that it represents the resting state of the hydroalkoxylation catalytic cycle.[21,22] This mechanistic rationale can be used to explain why nucleophiles of varying base strength and steric requirement can preferentially catalyze either the Baylis−Hillman or a competing hydroalkoxylation reaction through a generic ammonium enolate of general structure **1**. More basic and unhindered nucleophiles such as DMAP and DBU would be expected to form relatively stable analogues of **A**, thus giving rise to higher equilibrium concentrations of alkoxide ion, leading to the fast generation of **3**. By contrast, weakly basic and moderately hindered nucleophiles such as DABCO furnish relatively unstable analogues of **A**,[21] leaving addition of **1** to benzaldehyde as the favored pathway, in which the moderate basicity (and hence leaving-group ability) of DABCO facilitates the rapid collapse of **B** to **4**. Thus the use of DABCO results in long reaction times due to the low equilibrium concentrations of the critical enolate **1**, however **4** is formed selectively due to the thermodynamic instability of **A**. The lower hydroalkoxylation rates and more selective Baylis−Hillman reaction observed using quinuclidine as opposed to the less hindered DMAP as a reaction catalyst indicate that steric factors may also contribute significantly to the stability of intermediate **A** toward deprotonation/nucleophile elimination.

SCHEME 4. Formation of 3 and 4: Mechanistic Rationale



Having identified DABCO as the most suitable catalyst for the selective conversion of acrylamide to **4**, attention then turned to the questions of yield optimization and reaction scope. After considerable experimentation, two sets of conditions were found under which DABCO could catalyze the efficient coupling of acrylamide with a range

(16) pK_a values (25 °C) are taken from (a) (quinuclidine and 3-hydroxyquinuclidine) Grob, C. A. *Helv. Chim. Acta* **1985**, *68*, 882. (b) (DABCO) Hine, J.; Kaufmann, C.; Cholod, S. *J. Am. Chem. Soc.* **1987**, *52*, 2091. (c) (DMAP) Chrystuik, E.; Williams, A. *J. Am. Chem. Soc.* **1987**, *109*, 3040. (d) (TEA) Kuna S.; Pawlak, Z.; Tusk, M. *J. Chem. Soc., Faraday Trans.* **1982**, *78*, 2685. (e) (Bu_3P) Henderson, W. A.; Streuli, C. A. *J. Am. Chem. Soc.* **1960**, *82*, 5791. (f) (DIPEA) Fujii, T.; Nishida, H.; Abiru, Y.; Yamamoto, M.; Kise, M. *Chem. Pharm. Bull.* **1995**, *43*, 1872.

(17) It has been demonstrated (ref 8) that acrylamide undergoes H/D exchange (1:1 D_2O/1,4-dioxane-d_8) α to the carbonyl moiety in the presence of DABCO. The rate of exchange was found to be strongly dependent on the catalyst loading.

(18) Direct S_N2-type displacement of the ammonium moiety from **A** by alkoxide ion is an alternative mechanistic possibility. However, few examples of such reactions exist in the literature.

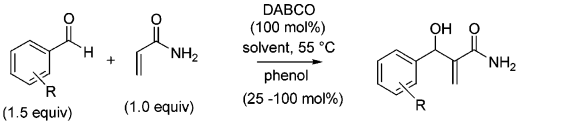
(19) It is worth noting at this juncture that the possibility of both uncatalyzed addition of MeOH to acrylamide (Table 1, entry 1) and direct Brønsted-base catalysis by the amine nucleophiles (Table 1, entries 6 and 7) have been experimentally excluded.

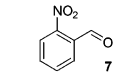
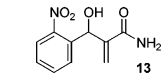
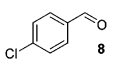
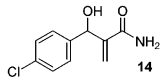
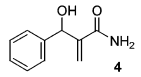
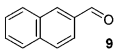
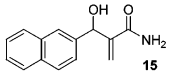
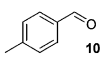
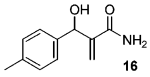
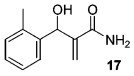
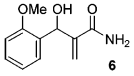
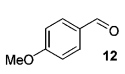
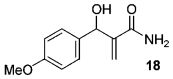
(20) In the case of NR_3 = DMAP, intermediate **A** can be observed by ^{1}H NMR spectroscopy during analysis of the hydromethoxylation reaction (Table 1, entry 3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14 (t, 2H, J = 6.5 Hz), 3.24 (s, 6H), 4.51 (t, 2H, J = 6.5 Hz), 6.81 (d, 2H, J = 7.5 Hz), 8.46 (d, 2H, J = 7.5 Hz). After 1.16 h reaction time ca. 2% of the DMAP catalyst had converted to **A**.

(21) Using DABCO as a catalyst, intermediate **A** was not observed, indicating that its equilibrium concentration is considerably lower than that observed using DMAP.

(22) Bergman, Toste et al. (ref 15b) unambiguously identified β-phosphonium ketones (analogous to **A**) as intermediates in hydroalkoxylation reactions of ketones catalyzed by trialkylphosphines.

TABLE 3. Baylis−Hillman Reaction of Acrylamide with Aromatic Aldehydes



entry	aldehyde	product	conditions[a]	time (d)	yield (%)[b]	lit. yield (%)
1	 **7**	 **13**	**A**	0.75	91[c]	85[d]
2	 **8**	 **14**	**A**	3.2	67	N/A
3	 **2**	 **4**	**A**	5	70[e]	55[f]
4	 **9**	 **15**	**B**	6	50	N/A
5	 **10**	 **16**	**B**	11	72	N/A
6	 **11**	 **17**	**B**	7	37	N/A
7	 **5**	 **6**	**B**	5	74	N/A
8	 **12**	 **18**	**B**	11	21[g]	N/A

[a] Conditions: **A** = aldehyde (3.0 mmol), acrylamide (2.0 mmol), DABCO (2.0 mmol), phenol (0.5 mmol), H_2O/^{t}BuOH (7:3, 120 μL) Ar atmosphere; **B** = aldehyde (3.0 mmol), acrylamide (2.0 mmol), DABCO (2.0 mmol), phenol (2.0 mmol), neat, Ar atmosphere. [b] Refers to isolated yields after chromatography. [c] Reaction at room temperature. [d] Reference 8. [e] 71% conversion of acrylamide: the corresponding reaction without phenol additive gave 42% yield and 60% conversion. [f] Reference 3j. [g] Yield determined using (*E*)-stilbene as an internal standard.

of aromatic aldehydes (Table 3). To reduce otherwise prohibitively inconvenient reaction times, reaction at 55 °C was required for all but the most reactive electrophiles (entry 1), and this in turn generally led to adduct decomposition and competitive side product formation. A significant modification, which exploits the weak basicity of DABCO, is the utilization of phenol as an additive.[23] Although the exact role of this additive is as yet unclear, we propose that phenol can act both as a Brønsted acid alkoxide scavenger[24] and as a H-bonding (or Brønsted acid) catalyst in its own right. In any case, addition of 25−100 mol % of phenol results in clean Baylis−Hillman reactions and a significant rate acceleration relative to the corresponding phenol-free reactions.[25] Electrophilic aldehydes such as **7** and **8** reacted efficiently in phenolic aqueous media, and the watershed case **2** underwent a smooth and clean Baylis−Hillman reaction with acrylamide in 70% yield, which represents a significant improvement upon the previous optimum conditions in the literature.[26,27] With more challenging aldehyde substrates, best results were obtained using stoichiometic phenol at 55 °C in the absence of solvent. Under these organocatalytic conditions, deactivated aldehydes (**5** and **9**−**12**) that were previously outside the scope of the Baylis−Hillman reaction of acrylamide afforded the corresponding adducts (**6** and **15**−**18**) in moderate to good yields.

In summary, we have found that acrylamide undergoes a novel hydroalkoxylation reaction catalyzed by nucleophiles in protic solvents. The hydroalkoxylation reaction is effected by either stoichiometric or catalytic amounts of an amine nucleophile and is promoted efficiently by the air- and moisture-insensitive DBU, with excellent yields of the β-methoxyamide product possible. As a result of the inert nature of acrylamide in aprotic media, the weakly basic DABCO was found to be superior to more nucleophilic catalysts such as DBU, quinuclidine, or DMAP for the selective promotion of Baylis−Hillman reactions involving acrylamide, as DABCO does not catalyze competing hydroalkoxylation reactions in either alcoholic or aqueous solvent to any appreciable extent. This has been rationalized in terms of the relative stability of ammonium salt **A** (derived from various tertiary amines): the more stable the intermediate **A**, the greater the propensity of a given amine for catalysis of hydroalkoxylation over Baylis−Hillman processes. The slow Baylis−Hillman reaction rates associated with the use of DABCO could be improved by the use of elevated temperature and the introduction of phenol as an additive, exploiting a synergistic bifunctional cooperation between the Brønsted-basic DABCO and Brønsted-acidic phenol resulting in clean, synthetically useful reactions and a significant expansion of the acrylamide Baylis−Hillman reaction scope to include deactivated aromatic aldehydes.

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Supporting Information Available: General experimental procedures, sample rate plots, and characterization data for the Baylis−Hillman adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) For the use of phenols as an additive in phosphine-catalyzed Baylis−Hillman reactions, see: (a) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165. (b) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094.

(24) The phenoxide anion is not nucleophilic enough to undergo a hydroalkoxylation reaction with acrylamide, as no such addition products are observed.

(25) The use of phenol in conjunction with other, more basic amines such as DMAP resulted in dramatically reduced reaction rates due to protonation and deactivation of the catalyst.

(26) It was also possible to carry out this reaction on a multigram scale in reproducible yield.

(27) It is noteworthy that these reactions are verifiably reversible: when isolated Baylis−Hillman adduct **4** is resubjected to the reaction conditions (diluted by a factor of 2) an equilibration occurs, giving a mixture containing ca. 7:3 ratio of **4**:acrylamide after 5 days