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An efficient synthesis of Baylis–Hillman adducts of acrylamide: Pd-catalyzed hydration of Baylis–Hillman adducts of acrylonitrile

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ABSTRACT

An efficient palladium-catalyzed two-step protocol for the synthesis of Baylis–Hillman adducts of acrylamide was developed. The method involved the preparation of Baylis–Hillman adducts of acrylonitrile and a Pd-catalyzed hydration of nitrile with acetaldoxime.

The Baylis–Hillman reaction, which involves the coupling of activated vinylic systems with electrophiles under the catalytic influence of a tertiary amine, gives rise to adducts, so called Baylis–Hillman adducts, with a new stereocenter and has proven to be a very useful carbon–carbon bond-forming method in the synthesis of highly functionalized molecules.[1]

As the activated vinyl compounds, various compounds have been used in the Baylis–Hillman reaction including acrylates, acrylonitrile, vinyl ketones, vinyl sulfones, and acrylamides.[1] However, among the activated vinyl compounds acrylamide has not been used much for the synthesis of the corresponding Baylis–Hillman adducts due to its sluggish reactivity.[1–3] The use of polar solvent in combination with 1.0 equiv of amine catalyst[2a–e] or expensive catalyst[2c,d,f] showed marginal success. In addition, most of the conditions can be applied to only reactive aldehydes like 4-nitrobenzaldehyde and pyridine 2-carboxaldehyde.[2b,c] As an example, the yield of Baylis–Hillman adducts of *p*-anisaldehyde and acrylamide remained maximum 21% up to date.[2a] An enzymatic hydration of Baylis–Hillman adduct of acrylonitrile to the corresponding amide derivative has been examined;[4] however, an efficient access to Baylis–Hillman adducts of acrylamide is highly required based on the usefulness of these compounds in organic synthesis.[5]

The hydration of nitriles to the corresponding amides is very important in view of its broad industrial and pharmacological applications.[6–8] Hydrolysis of amides to carboxylic acids is a serious problem in many cases under the conventional hydration conditions.[7] Some useful methods for the selective hydration of nitrile to amide have been developed including the use of TFA/H_2SO_4[7a] or the use of H_2O_2/K_2CO_3/DMSO at low temperature.[7b] Recently, transition metal-catalyzed selective hydration of nitriles has also been reported involving the use of Rh,[8a,b] Pt,[8c,d] Ru,[8e–h] Ir,[8i] Mo,[8j] and Co.[8k,l] Very recently, we reported an efficient Pd-catalyzed hydration method of nitriles to amides with the aid of acetaldoxime (Scheme 1).[9] In these contexts, synthesis of Baylis–Hillman adducts of acrylamide could be realized in high yields via the indirect way combining the synthesis of Baylis–Hillman adducts of acrylonitrile and the following conversion of nitrile into amide functionality.

Thus we examined the feasibility for the synthesis of **2a** from **1a** under Pd-catalyzed hydration conditions using acetaldoxime.[9] Fortunately, compound **2a** was obtained in high yield (81%) as shown in Scheme 2.[10] As a comparison experiment, we examined the hydration of **1a** under different conditions including the use of MeOH/H_2SO_4,[5f] TFA/H_2SO_4,[5a,b,7a] and H_2O_2/K_2CO_3/DMSO.[7b] Treatment of **1a** with MeOH/H_2SO_4 (rt to 50 °C) showed the formation of rearranged alcohol **4**, methoxy derivative **6,** and dimeric ether compound **7** in variable yields (see Fig. 1). We did not observe the formation of any trace amounts of **2a**. The use of TFA/H_2SO_4[5a,b,7a] showed the formation intractable complex mixtures and we did not observe the formation of **2a** again. The use of H_2O_2/K_2CO_3 in aqueous DMSO showed sluggish reactivity and we observed the formation of compound **2a** in trace amounts. However we could not improve the conditions. The use of $FeCl_3$/AcOH (reflux)[5g]

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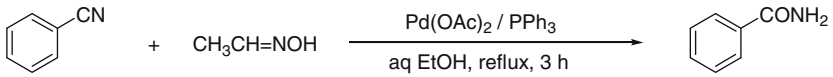
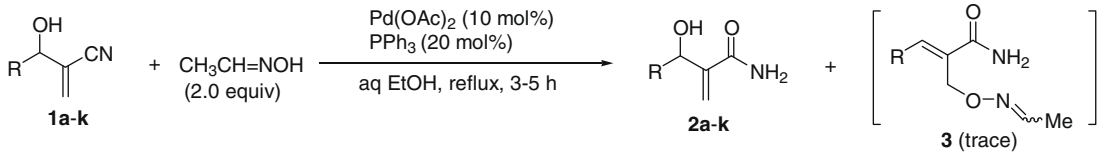


Scheme 1.



Scheme 2.

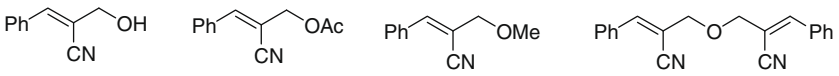
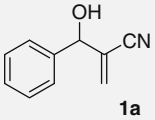
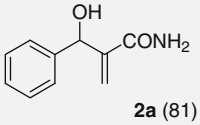
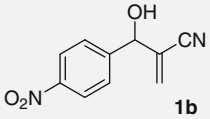
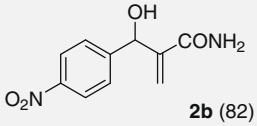
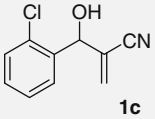
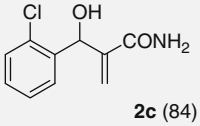
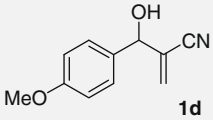
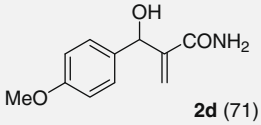
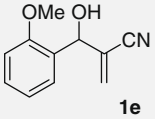
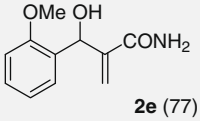
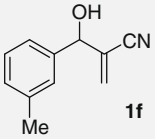
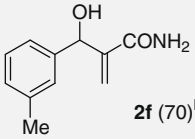
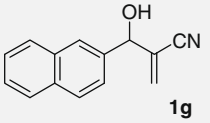
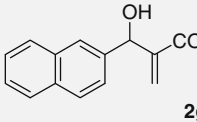
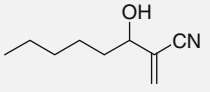
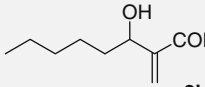


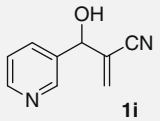
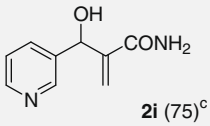
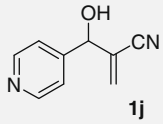
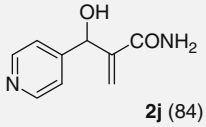
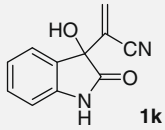
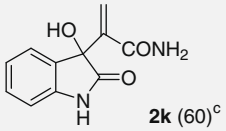
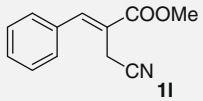
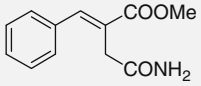
Figure 1.

Table 1
Pd-catalyzed hydration of Baylis–Hillman nitrile to the corresponding amide derivatives

Entry	Nitrile **1**	Conditions[a] (h)	Amide **2** (%)
1	 **1a**	3	 **2a** (81)
2	 **1b**	3	 **2b** (82)
3	 **1c**	3	 **2c** (84)
4	 **1d**	4	 **2d** (71)
5	 **1e**	4	 **2e** (77)
6	 **1f**	4	 **2f** (70)[b,c]
7	 **1g**	5	 **2g** (75)[c]
8	 **1h**	4	 **2h** (70)[c]

(*continued on next page*)

Table 1 (*continued*)

Entry	Nitrile **1**	Conditions[a] (h)	Amide **2** (%)
9	 **1i**	5	 **2i** (75)[c]
10	 **1j**	4	 **2j** (84)
11	 **1k**	4	 **2k** (60)[c]
12	 **1l**	3	 **2l** (92)

[a]Conditions: Nitrile (1.0 mmol), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), and $CH_3CH{=}NOH$ (2.0 equiv), aq EtOH, reflux.
[b]Oxime ether **3** (3%) was isolated as a *syn/anti* (1:1) mixture.
[c]Trace amounts of starting materials were recovered (5–8%).

showed the formation of rearranged acetate **5** and intractable polar side products.

Encouraged by the results, we prepared various Baylis–Hillman adducts of acrylonitrile **1b–k** according to the known method[1] in good to high yields (69–98%). Pd-catalyzed hydration of **1b–k** was carried out under the influence of $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), and $CH_3CH{=}NOH$ (2.0 equiv) in refluxing aqueous EtOH for 3–5 h, and the results are summarized in Table 1.

As shown in Table 1, the yields of amides **2b–k** were good to high in all cases (60–84%) including the Baylis–Hillman adducts of 4-methoxy (entry 4, 71%), 2-methoxy (entry 5, 77%), and 3-pyridyl (entry 9, 75%). It is interesting to note that the yield of 4-methoxy derivative **2d** reached 71%. This compound was synthesized in a very low yield (21%) via the direct Baylis–Hillman reaction approach with acrylamide (vide supra).[2a] In addition, the reaction of 3-pyridyl derivative **1i** under the same reaction conditions provided **2i** in 75% yield. Synthesis of this compound failed completely by the Baylis–Hillman reaction of acrylamide and pyridine-3-carboxaldehyde.[2b,11]

The Baylis–Hillman adducts of aliphatic aldehyde (entry 8) and isatin (entry 11) showed the same reactivity. Cinnamonitrile derivative **1l** (entry 12), prepared from Baylis–Hillman adduct produced the corresponding amide **2l** in 92%. It is interesting to note that oxime ether derivative **3** was isolated as a side product (3%, see Scheme 2) in the reaction of *m*-methyl derivative **1f** (entry 6). This compound must be formed from the product **2f** by further reaction with acetaldoxime. The yield of **3** was increased up to 9% when we ran the reaction of **1f** with 5.0 equiv of acetaldoxime. This type of side product was observed in other cases also in trace amounts, but we did not isolate them in most cases. Starting material remained in some cases even after 3–5 h (5–8% for entries 6–9 and 11); however, when we allowed the reaction mixture to run for a longer time the amount of side product **3** increased.

In summary, we developed an efficient palladium-catalyzed two-step protocol for the synthesis of Baylis–Hillman adducts of acrylamide. The method involved the preparation of Baylis–Hillman adducts of acrylonitrile and the following Pd-catalyzed hydration of nitrile with acetaldoxime.

Acknowledgments

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10. Typical procedure for the conversion of **1a** to **2a**: A mixture of Baylis–Hillman adduct **1a** (159 mg, 1.0 mmol), acetaldoxime (118 mg, 2.0 mmol), $Pd(OAc)_2$ (22.5 mg, 10 mol %), and PPh_3 (52.5 mg, 20 mmol %) in aqueous EtOH (H_2O/EtOH, 1:4, 3 mL) was heated to reflux for 3 h under nitrogen atmosphere. The reaction mixture was diluted with EtOH (5 mL), filtered through a Celite pad, and washed with EtOH and CH_2Cl_2. After the removal of solvent and column chromatographic purification process (hexanes/EtOAc/$CHCl_3$, 1:1:1) compound **2a** was obtained as a white solid, 144 mg (81%). Other compounds were synthesized similarly and the representative spectroscopic data of unknown compounds (**2f**, **2h**, **2i**, **2k,** and **2l**) are as follows. Known compounds were identified by their melting points and ^{1}H NMR spectra by comparison with the reported data, **2a**,[2a,2c,4a] **2b**,[2b,2c] **2c**,[4a] **2d**,[4a] **2e**,[2a,4a] **2g**,[2a] **2j**.[2b]Compound **2f**: 70%; white solid, mp 110–112 °C; IR (film) 3326, 3189, 1668, 1624, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ2.30 (s, 3H), 4.47 (br s, 1H), 5.41 (s, 1H), 5.44 (s, 1H), 5.91 (s, 1H), 6.06 (br s, 1H), 6.55 (br s, 1H), 7.05–7.22 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.44, 74.30, 122.59, 123.21, 126.83, 128.36, 128.55, 138.16, 140.66, 144.46, 169.64; ESIMS *m*/*z* 192 (M^++1). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.13; H, 7.02; N, 7.24.Compound **2h**: 70%; white solid, mp 86–88 °C; IR (KBr) 3376, 3189, 2929, 1655, 1630, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, *J* = 6.6 Hz, 3H), 1.22–1.39 (m, 6H), 1.51–1.67 (m, 2H), 3.39 (d, *J* = 5.4 Hz, 1H), 4.25–4.32 (m, 1H), 5.43 (s, 1H), 5.82 (s, 1H), 5.96 (br s, 1H), 6.68 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.96, 22.52, 25.57, 31.53, 35.59, 73.54, 121.24, 144.73, 169.87; ESIMS *m*/*z* 172 (M^++1). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.42; H, 10.27; N, 8.03.
Compound **2i**: 75%; pale yellow solid, mp 113–115 °C; IR (KBr) 3316, 3179, 2924, 1670, 1592 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 5.53 (s, 1H), 5.70 (s, 1H), 5.85 (br s, 1H), 5.87 (s, 1H), 7.01 (br s, 1H), 7.32 (dd, *J* = 7.8 and 4.8 Hz, 1H), 7.52 (br s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 8.43 (d, *J* = 4.8 Hz, 1H), 8.50 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 69.12, 117.70, 123.23, 134.29, 138.61, 146.71, 148.21, 148.40, 168.42; ESIMS *m*/*z* 179 (M^++1). Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.54; H, 5.87; N, 15.49.
Compound **2k**: 60%; pale yellow solid, mp 181–183 °C; IR (KBr) 3322, 3272, 3199, 1716, 1666, 1621 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.00 (s, 1H), 6.05 (s, 1H), 6.23 (s, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.82 (br s, 1H), 6.85 (td, *J* = 7.5 and 1.2 Hz, 1H), 6.95 (d, *J* = 6.6 Hz, 1H), 7.15 (td, *J* = 7.5 and 1.5 Hz, 1H), 7.58 (br s, 1H), 10.10 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 75.67, 109.29, 119.75, 120.87, 123.20, 128.86, 132.38, 143.23, 144.08, 167.57, 177.30; ESIMS *m*/*z* 219 (M^++1). Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.63; H, 4.76; N, 12.55.Compound **2l**: 92%; white solid, mp 128–130 °C; IR (KBr) 3315, 3172, 1711, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.46 (s, 2H), 3.85 (s, 3H), 5.98 (br s, 1H), 6.25 (br s, 1H), 7.34–7.45 (m, 3H), 7.57–7.60 (m, 2H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.29, 52.40, 125.58, 128.61, 129.28, 129.60, 134.45, 143.06, 168.64, 172.71; ESIMS *m*/*z* 220 (M^++1). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.79; H, 6.07; N, 6.15.
11. Although Radha Krishna et al. reported the synthesis of **2i** in 62% yield,[2e] we could not obtain the compound in any trace amounts under the reported conditions, very unfortunately. Although they suggested Ref. [2b] as the reference of compound **2i** without spectroscopic data, the authors of Ref. [2b] described that they failed to prepare compound **2i**.