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One-pot process to *Z*-α-benzoylamino-acrylic acid methyl esters via potassium phosphate-catalyzed Erlenmeyer reaction

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ABSTRACT

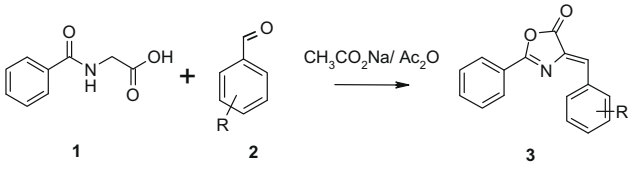
A practical and efficient two reaction sequence one-pot process for the synthesis of *Z*-α-benzoylamino-acrylic acid methyl esters was developed. The process involves a potassium phosphate-catalyzed Erlenmeyer reaction of aromatic aldehydes with hippuric acid followed by an oxazolone ring-opening methanolysis. This process afforded a good overall yield and an excellent product quality via a simple workup.

The synthesis of chiral building blocks has become important in the development of new drugs. Amino acids are essential components found in the chemical structures of enzymes, hormones, antibiotics, and other biologically active compounds.[1] Moreover, α,β-dehydro-amino acids are precursors for saturated amino acids. In effect, these precursors could be synthesized by Horner–Emmons, Heck, or Erlenmeyer–Plöchl reactions[2] followed by a complementary asymmetric hydrogenation reaction. The asymmetric hydrogenation is well established due to the availability of chiral ligands[3] that facilitate the preparation of enantiomerically pure compounds.

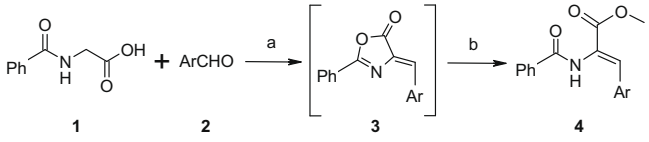
Therefore, α-amidoacrylates can be accessed via a practical synthetic process. The Erlenmeyer–Plöchl[4] reaction is a well-known approach to these key intermediates because the condensation of hippuric acid with an aromatic aldehyde provides the *Z*-oxazolone isomer as the main product[5] (Scheme 1).

We extended this methodology to develop a one-pot process for the synthesis of α-amidoacrylates via two sequential reactions: an Erlenmeyer reaction followed by an oxazolone ring opening. The Erlenmeyer reaction was performed using potassium phosphate as the base to catalyze the condensation of hippuric acid **1** with an aromatic aldehyde **2** in the presence of acetic anhydride as the dehydrating agent. Next, methanolysis was carried out in situ to produce the respective acrylic acid methyl ester **4** as shown in Scheme 2.

Potassium phosphate was evaluated as a catalyst for the Erlenmeyer reaction instead of sodium acetate which is the typical base in this reaction. Compared to sodium acetate, K_3PO_4 is a cheaper commercially available material which affords good oxazolone conversion reactions using less than 1 equiv. In this approach, the relative reaction rate depended on the aromatic aldehyde substituents in accord with a previously reported study.[6] The electron-withdrawing groups (EWGs) increased the reaction rate, and the opposite was true for the electron-donating groups (EDGs). Due to this aldehyde substituent effect, Erlenmeyer reactions with EWG-aldehydes were easily performed using 5–10 mol % potassium phosphate; however, with the more



Scheme 1. General Erlenmeyer–Plöchl reaction.



Scheme 2. General synthesis of *Z*-α-benzoylamino acrylic acid methyl esters. Reagents: (a) K_3PO_4, Ac_2O; and (b) MeONa, MeOH.

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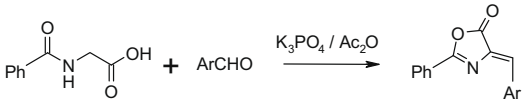
Table 1
Isolated oxazolones from the K_3PO_4-catalyzed Erlenmeyer reaction



1 2 3

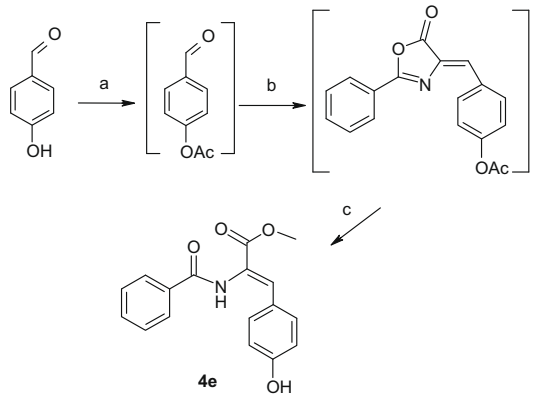
Entry	2, Ar=	Oxazolone[a]	Reaction time[b] (h)	Yield[e] (%)	Mp found (°C)	Mp lit. (°C)
1	C_6H_4–	**3a**	2	83	166	167[7]
2	4-$NO_2C_6H_4$–	**3b**	0.5[c]	93	239	241[7]
3	3-$NO_2C_6H_4$–	**3c**	0.5	88	175	175[7]
4	2-Cl–C_6H_4–	**3d**	1	81	162	161[8]
5	4-Cl–C_6H_4–	**3e**	1	91	196	197[7]
6	4-BrC_6H_4–	**3f**	3	93	204	196[11]
7	4-MeC_6H_4–	**3g**	3[d]	87	144	143[7]
8	4-MeOC_6H_4–	**3h**	3[d]	84	159	157[7]
9	4-$(CH_3)_2NC_6H_4$–	**3i**	3	86	214	213[7]
10	4-FC_6H_4–	**3j**	3	86	183	185[9]
11	3-MeO-4-OH–	**3k**	3	80	194	199[12]
12		**3l**	3	90	169	170[9]
13		**3m**	6.5	89	176	179[10]

[a] DCE used for improving mixing-compounds **3b–j**.
[b] 10 mol % K_3PO_4 catalyst.
[c] 5 mol % K_3PO_4 catalyst.
[d] 50 mol % K_3PO_4 catalyst.
[e] Isolated yield.

sluggish EDG-aldehydes, and fluorosubstituted aldehyde the conversion was improved by adding acetic anhydride in portions (3 equiv total) and, in some cases, increasing the catalyst loading up to 50 mol % (Table 1, entries 7–10). The Erlenmeyer reaction was performed by mixing hippuric acid, aldehyde, and acetic anhydride followed by the addition of potassium phosphate and heating the mixture to 80 °C. After the exotherm[13] subsided, heavy slurry was observed, and, if required, 1,2-dichloroethane (DCE) was charged to improve reaction mixing (Table 1, entries 2–10). The data provided in Table 1 include the reaction times, yields of isolated oxazolones, and melting point comparisons for product identity confirmation.

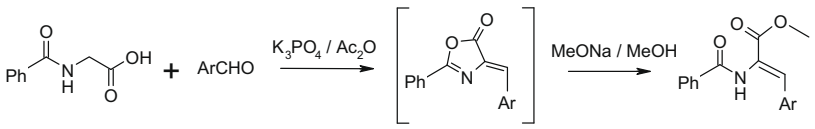
Once the reaction conditions for the Erlenmeyer reaction were established, the oxazolone ring-opening methanolysis was performed in situ by adding methanol to the oxazolone reaction mixture. Next, the pH was adjusted to 7–8 with sodium methoxide/methanol solution, and the mixture was heated at reflux. Upon reaction completion, a simple workup and isolation was performed by the addition of water to produce the respective α-amidoacrylates in acceptable yield and excellent quality (Table 2). Compound **4i** showed slow methanolysis reaction but adding a catalytic amount of DBU speeded up the reaction and drove it to completion (Table 2, entry 6).

A unique example in this series of aromatic aldehydes was vanillin, containing a reactive 4-hydroxyl group (Table 2, entry 7). This hydroxyl functionality was initially acylated in the presence of acetic anhydride/K_3PO_4, and then the addition of hippuric acid and acetic anhydride completed the condensation reaction. As compared to the reported reaction conditions,[12] a faster reaction and better conversion to oxazolone **3k** were observed. Methanolysis was complete after approximately one hour, but



Scheme 3. General synthesis of Z-α-benzoylamino-3-(4-hydroxyphenyl)-acrylic acid methyl esters. Reagents: (a) K_3PO_4, Ac_2O; (b) hippuric acid, Ac_2O; and (c) MeONa/MeOH, **4e** was isolated from methylene chloride/toluene.

Table 2
One-pot process for α-amidoacrylates representative examples



1 2 3 4

Entry	Compound	Ar=	Reaction time[a] (h)	Overall yield[b] (%)	Mp found (°C)	Mp lit. (°C)
1	**4b**	4-$NO_2C_6H_4$–	2	89	192	193[14]
2	**4e**	4-Cl–C_6H_4–	1	82	138	138[14]
3	**4f**	4-BrC_6H_4–	1	90	138	–
4	**4g**	4-MeC_6H_4–	1	90	111	107[17]
5	**4h**	4-MeOC_6H_4–	1	83	154	153[14]
6	**4i**	4-$(CH_3)_2NC_6H_4$–	5[c]	83	183	184[14]
7	**4k**	3-MeO-4-OH–	24[d]	82[e]	158	157[15]
8	**4l**		1	75	140	139[16]

[a] Methanolysis reaction only.
[b] Isolated yield.
[c] MeONa–DBU.
[d] Transesterification reaction time included.
[e] Crystallization from toluene.

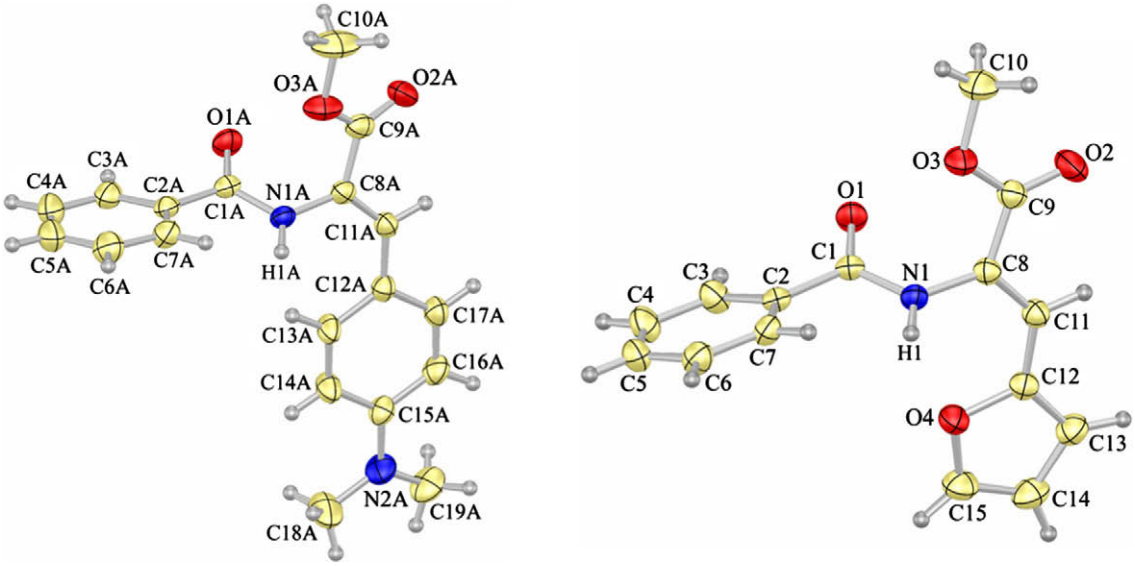


Figure 1. Crystal structure of *Z*-α-benzoylamino acrylic acid methyl esters **4i** and **4l** respectively.

the transesterification reaction to remove the acetyl group required extended time (Scheme 3). In addition, compound **4k** was isolated from methylene chloride and crystallized from toluene because **4k** was soluble in methanol.

X-ray analysis for representative compounds (**4i** and **4l**) showed the C=C as expected with the *Z*-configuration (Fig. 1).

Thus, a practical and efficient method has been developed and demonstrated for the preparation of *Z*-α-amido-acrylic acid methyl esters via two sequential reactions in a one-pot process.[18] The initial Erlenmeyer reaction is catalyzed by the inexpensive and commercially available potassium phosphate, which is used in the range of 5–50 mol % depending on the aldehyde substrate. The subsequent ring-opening methanolysis reaction is carried out with methanol/sodium methoxide. In most cases, isolation simply involves the addition of water. Because this one-pot process generates an exceptional overall yield and excellent isolated product quality,[19] tedious chromatography purification techniques are avoided.

Acknowledgments

The authors wish to thank Dr. Mark D. Smith for the structure determination by X-ray crystallography (The University of South Carolina) and Dr. Shan-Ming for his valuable help. Dr. Ashish Shankar and Maethonia Thompson for the RC1 data.

Supplementary data

Supplementary data (^{1}H NMR data of oxazolones **3** and (^{1}H NMR/^{13}C NMR for *Z*-α-benzoylamino-acrylic acid methyl esters **4** products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.081.

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13. The enthalpy of reaction for oxazolone **3l** (Table 1, entry 12) was measured on a RC1 classic equipment and scaled to g/moles of hippuric acid. Observed values $\Delta H_{rxn} = -40.6$ kJ/g moles; $\Delta T_{addition\text{-}rise} = 41.7$ °C
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18. *One-pot process for Z-α-benzoylamino-4-chlorophenyl-acrylic acid methyl ester* **4e**: To a mixture of hippuric acid (2.5 g, 14 mmol), 4-chlorobenzaldehyde (1.63 g, 11.6 mmol), and acetic anhydride (3.14 g, 31 mmol) at room temperature under nitrogen was added potassium phosphate (0.3 g, 1.4 mmol). The resulting slurry was stirred in a pre-heated 70 °C aluminum block until the exotherm subsided. The reaction mixture was then heated to 80 °C and stirred under nitrogen, and, after observing a heavy yellow slurry, 1,2-dichloroethane was added (2 mL). The slurry was held for one hour at 80 °C, and the reaction was monitored for completion by HPLC. Then, the slurry was cooled to approximately 40 °C followed by the dropwise addition of methanol (12–15 mL). After 30 min, sodium methoxide 25 wt % in methanol (6.5 mL) was added and the mixture was refluxed under nitrogen for one hour. Upon reaction completion, confirmed by HPLC, the mixture was cooled to room temperature, and water was added dropwise (12–15 mL). The slurry was stirred for 30 min and then cooled overnight (10 °C). The *N*-benzoylamino-2-(4-chlorophenyl) acrylic acid methyl ester **4e** was collected by vacuum filtration and washed with precooled 1:1 methanol/water (−15 °C) followed by water. After drying at 60 °C under vacuum for 24 h, the product was characterized by HPLC, ^{1}H NMR, ^{13}C NMR, and melting point for purity.
19. *Melting points and ^{1}H NMR/^{13}C NMR data for N-benzoylamino acrylic acids methyl esters. N-Benzoylamino-3-(4-nitrophenyl) acrylic acid methyl ester* (**4b**): Mp 192 °C; ^{1}H NMR (500 MHz, DMSO): δ 10.30 (s, 1H), 8.26 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 7.4 Hz, 2H), 7.91 (d, *J* = 8.9 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.45 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.25, 165.15, 147.04, 140.36, 132.95, 132.11, 130.65, 129.86, 129.42, 128.52, 127.82, 123.65, 52.50.
N-Benzoylamino-3-(4-chlorophenyl) acrylic acid methyl ester (**4e**): Mp 138 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.12 (s, 1H), 7.99 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.42 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.14, 165.35,

133.95, 133.13, 132.40, 131.97, 131.48, 131.45, 128.68, 128.50, 127.72, 127.20, 52.31.

N-Benzoylamino-3-(4-bromophenyl) acrylic acid methyl ester (**4f**): Mp 138 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.12 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H) 7.61 (d, J = 9.4 Hz, 5H), 7.54 (t, J = 7.6 Hz, 2H), 7.40 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.12, 165.36, 133.15, 132.76, 131.95, 131.64, 131.60, 131.55, 128.49, 127.72, 127.34, 122.72, 52,31.

N-Benzoylamino-3-(4-methylphenyl) acrylic acid methyl ester (**4g**): Mp 111 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.06 (s, 1H), 8.01 (d, J = 7.5 Hz, 2H), 7.61 (dd, J = 7.7, 15.1 Hz, 3H), 7.54 (t, J = 7.5 Hz, 2H), 7.44 (s, 1H), 7.22 (d, J = 8.1 Hz, 2H), 3.74 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.03, 165.56, 139.47, 133.51, 133.33, 131.86, 130.65, 129.89, 129.23, 128.48, 125.68, 52.17, 20.93.

N-Benzoylamino-3-(4-methoxyphenyl) acrylic acid methyl ester (**4h**): Mp 154 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.01 (s, 1H), 8.03 (d, J = 7.4 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H), 7.46 (s, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.02, 165.66, 160.34, 133.69, 133.41, 131.83, 131.80, 128.49, 127.67, 125.90, 114.16, 55.25, 52.10.

N-Benzoylamino-3-(4-dimethylaminophenyl) acrylic acid methyl ester (**4i**): Mp 183 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.87 (s, 1H), 8.04 (d, J = 7.3 Hz, 2H), 7.60 (dd, J = 7.7, 15.0 Hz, 2H), 7.55 (m, 3H), 7.43 (s, 1H), 6.69 (d, J = 9.0 Hz, 2H), 3.71 (s, 3H), 2.93 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.89, 165.79, 151.07, 135.28, 133.66, 131.80, 131.67, 128.45, 127.61, 120.98, 120.58, 111.56, 51.86, 39.56.

N-Benzoylamino-3-(3-methoxy-4-hydroxyphenyl) acrylic acid methyl ester (**4k**): Mp 158 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.99 (s, 1H), 9.63 (s, 1H), 8.04 (d, J = 7.3 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.54 (t, J = 7.5 Hz, 2H), 7.45 (s, 1H), 7.37 (d, J = 1.8 Hz, 1H), 7.18 (dd, J = 1.8, 8.3 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 3.73 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.94, 165.76, 148.63, 147.35, 134.68, 133.43, 131.86, 128.50, 127.60, 124.70, 124.66, 123.19, 115.33, 113.57, 55.26, 52.07.

N-Benzoylamino-3-(furan-2-yl) acrylic acid methyl ester (**4m**): Mp 140 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.99 (s, 1H), 8.03 (d, J = 7.3 Hz, 2H), 7.86 (m, 1H), 7.61 (m, 1H), 7.54 (dd, J = 4.7, 10.4 Hz, 2H), 7.31 (s, 1H), 6.90 (d, J = 3.5 Hz, 1H), 6.63 (dd, J = 1.8, 3.4 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.62, 165.07, 149.16, 145.61, 133.42, 131,83, 128.47, 127.68, 123.31, 120.84, 116.04, 112.54, 52.20.