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Uncatalyzed synthesis of 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones

Hamid Reza Shaterian · Mohammad Ranjbar

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Abstract Uncatalyzed one-pot pseudo-four-component reaction of ethyl pyruvate, anilines, and aldehydes in *n*-hexane as solvent, under reflux, affords a variety of 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones in high yield. *n*-Hexane is an excellent driving force in preparation of the desired products. These compounds have biological and pharmacological properties and are also used in medicinal chemistry. Use of a non-toxic and inexpensive solvent, simple and efficient synthesis, clean work-up, and high yields of the products are the advantages of this method. We report the first catalyst-free method for synthesis this class of compounds.

Keywords Uncatalyzed · Ethyl pyruvate · Anilines · Aldehydes · 3-Amino-1,5-dihydro-2*H*-pyrrol-2-ones

Introduction

1,5-Dihydro-2*H*-pyrrol-2-ones, particularly their 3-amino-substituted derivatives, interesting lactams found in many natural products, have promising biological and pharmacological properties [1–7]. Examples include the lipopeptides microcolin A and B [8, 9]. When an amino substituent is present at the 3-position, these heterocycles are also enamines; these have attracted much attention and have applications in organic and medicinal chemistry [10–19]. For construction of this class of molecules, two-component condensation of aromatic aniline derivatives with β,γ-unsaturated α-oxo esters has been reported [6]. Literature survey also revealed three-component coupling of aniline, aldehyde, and pyruvate in the presence of stoichiometric amount of $Ti(OEt)_4$ and sulfuric acid [7] and

H. R. Shaterian (✉) · M. Ranjbar
Department of Chemistry, Faculty of Sciences, University of Sistan and Baluchestan, 98135-674 Zahedan, Iran
e-mail: hrshaterian@chem.usb.ac.ir

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organocatalytic hydrogen-bonding of phosphoric acid and thiourea [20] for synthesis of these lactams. To the best of our knowledge, this is the first report of catalyst-free preparation of 3-amino-1,5-dihydro-2H-pyrrol-2-ones (Scheme 1).

Experimental

General

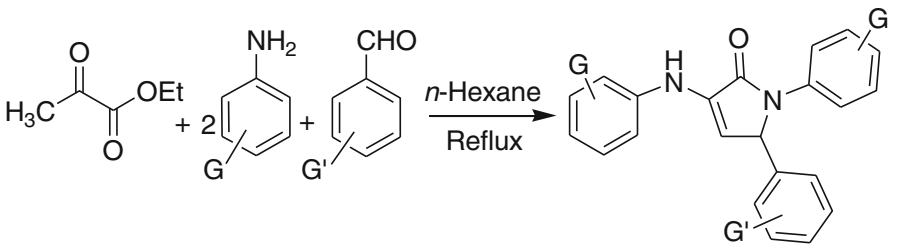
All reagents were purchased from Merck and Sigma-Aldrich and were used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison of physical and spectroscopic (IR and NMR) data with those of authentic samples. NMR spectra were recorded on a Bruker Advance DPX 500 MHz instrument. The spectra were measured in DMSO relative to TMS (0.00 ppm). IR spectra were recorded on a Jasco FT-IR 460 plus spectrophotometer. TLC was performed on Polygram SIL G/UV254 silica gel plates.

General experimental procedure for uncatalyzed synthesis of 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones

n-Hexane (5 mL) was added to a mixture of ethyl pyruvate (10 mmol), aniline (20 mmol), and aldehyde (10 mmol). The reaction mixture was stirred at reflux for appropriate time (Table 1) and monitored by TLC analysis using 4:1 *n*-hexane–EtOAc as mobile phase. On completion, the reaction mixture was cooled to room temperature. Recrystallization from *n*-hexane afforded the corresponding products.

The desired pure products were characterized by comparison of their physical data with those of known compounds. Spectral data for unknown products are given below:

1-(4-Methoxyphenyl)-3-(4-methoxyphenylamino)-5-(propyl)-1*H*-pyrrol-2(5*H*)-one (Table 1, Entry 24): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.22$ (t, $J = 7.6$ Hz, 3H), 1.51–1.59 (m, 4H), 3.78 (s, 3H), 3.80 (s, 3H), 4.13–4.18 (m, 1H), 5.81 (s, 1H), 6.43 (s, 1H), 6.87 (d, $J = 6.9$ Hz, 2H), 6.92 (d, J = 6.9 Hz, 2H), 7.01 (d, $J = 6.8$ Hz, 2H), 7.24 (d, $J = 6.9$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.0$, 14.1, 21.4, 55.4, 55.6, 62.0, 105.8, 114.5, 114.8, 118.7, 124.7, 128.1,



Scheme 1 Catalyst-free preparation of 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones

Table 1 Uncatalyzed synthesis of 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones

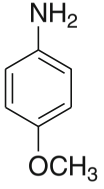
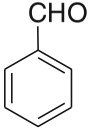
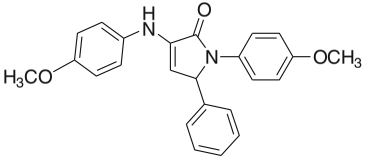
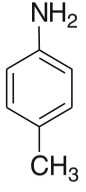
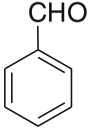
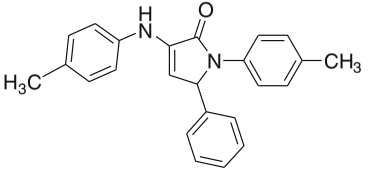
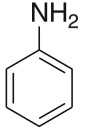
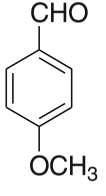
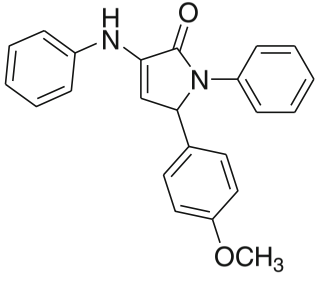
Entry	Aniline	Aldehyde	Product	Time (h)	Yield (%)[a]	Found m.p (°C)	Lit. m.p (°C) [Ref.]
1				4.5	93	197	197–199 [6]
2				6	90	217–218	215–217 [6]
3				5.5	97	169–170	171–173 [6]

Table 1 continued

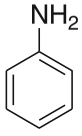
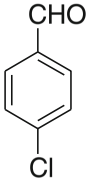
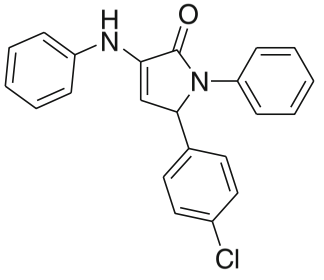
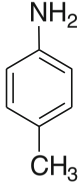
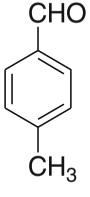
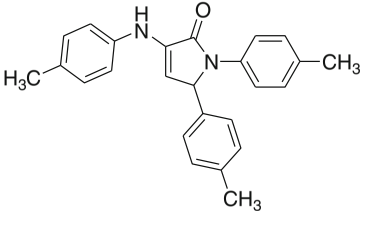
Entry	Aniline	Aldehyde	Product	Time (h)	Yield (%)[a]	Found m.p (°C)	Lit. m.p (°C) [Ref.]
4				4	89	227–228	222–224 [6]
5				3	92	249–252	249–251 [6]

Table 1 continued

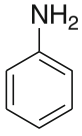
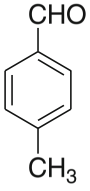
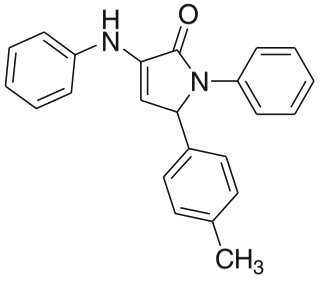
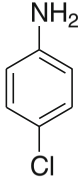
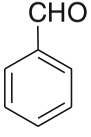
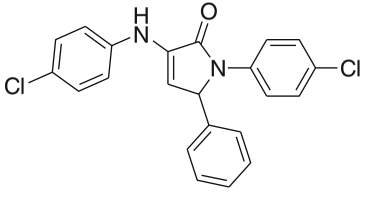
Entry	Aniline	Aldehyde	Product	Time (h)	Yield (%)[a]	Found m.p (°C)	Lit. m.p (°C) [Ref.]
6				4	93	230–231	234–236 [6]
7				4	60	221–223	217–219 [6]

Table 1 continued

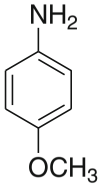
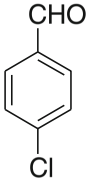
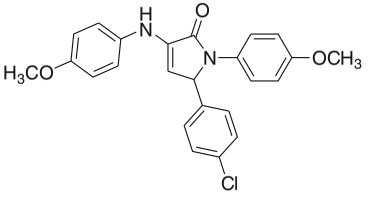
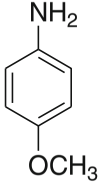
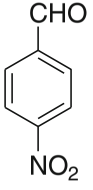
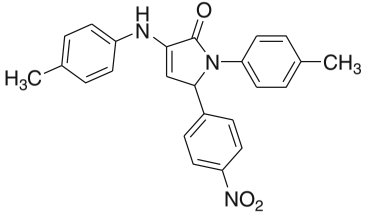
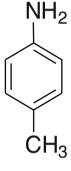
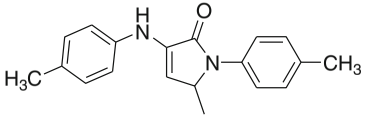
Entry	Aniline	Aldehyde	Product	Time (h)	Yield (%)[a]	Found m.p (°C)	Lit. m.p (°C) [Ref.]
8				5.5	85	157–159	160–161 [20]
9				3.5	90	140–143	142–145 [7]
10		CH_3CHO		4	78	119–120	121–122 [7]

Table 1 continued

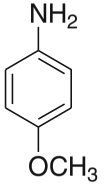
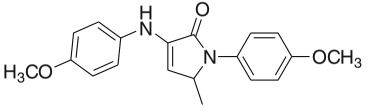
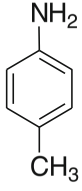
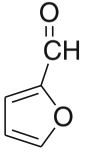
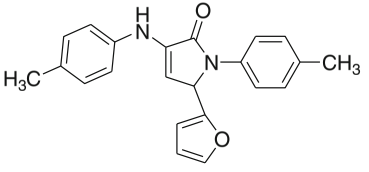
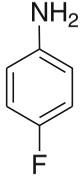
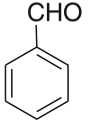
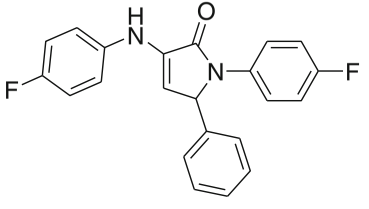
Entry	Aniline	Aldehyde	Product	Time (h)	Yield (%)[a]	Found m.p (°C)	Lit. m.p (°C) [Ref.]
11		CH_3CHO		3	70	153–154	151–152 [7]
12				6	90	152–153	151–152 [7]
13				6	80	237–239	240–242 [6]

Table 1 continued

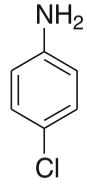
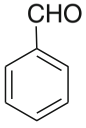
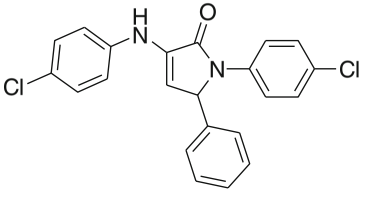
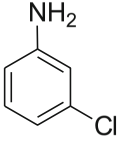
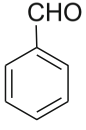
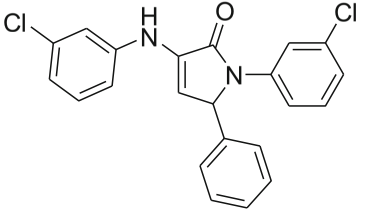
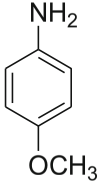
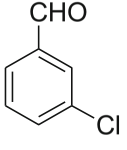
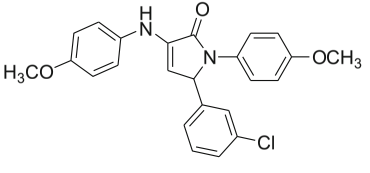
Entry	Aniline	Aldehyde	Product	Time (h)	Yield (%)[a]	Found m.p (°C)	Lit. m.p (°C) [Ref.]
14				4	92	215–217	217–219 [6]
15				3.5	89	210–211	207–209 [6]
16				4	80	166–169	171–173 [20]

Table 1 continued

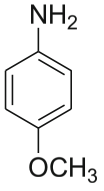
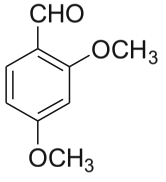
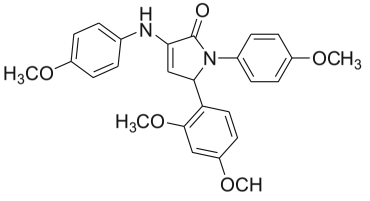
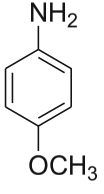
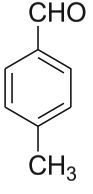
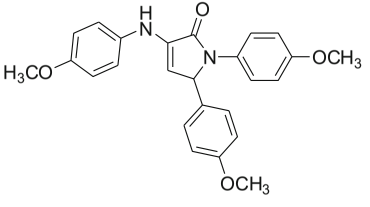
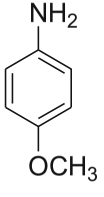
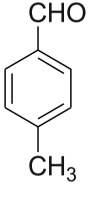
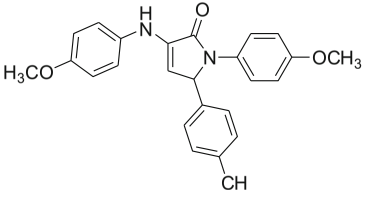
Entry	Aniline	Aldehyde	Product	Time (h)	Yield (%)[a]	Found m.p (°C)	Lit. m.p (°C) [Ref.]
17				3	95	147–149	153–155 [20]
18				4	89	152–153	156–158 [20]
19				3.5	93	220–222	218–220 [6]

Table 1 continued

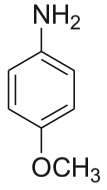
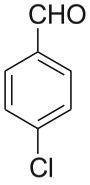
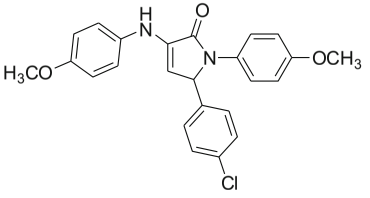
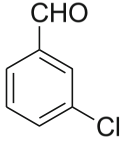
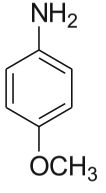
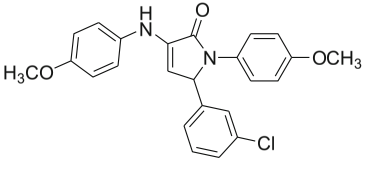
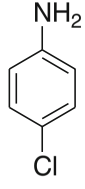
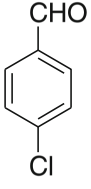
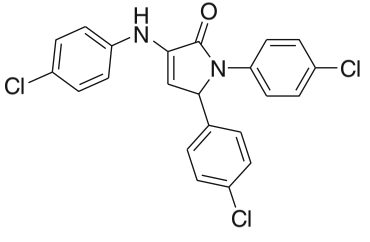
Entry	Aniline	Aldehyde	Product	Time (h)	Yield (%)[a]	Found m.p (°C)	Lit. m.p (°C) [Ref.]
20				5	95	157–159	160–161 [20]
21				3.5	90	170–172	170–173 [20]
22				5	85	255–258	258–260 [6]

Table 1 continued

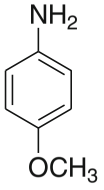
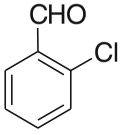
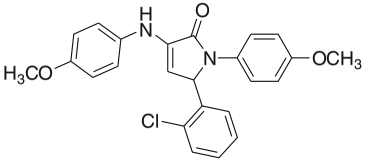
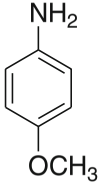
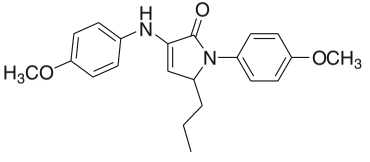
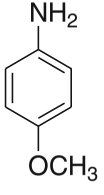
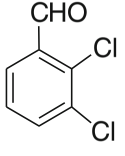
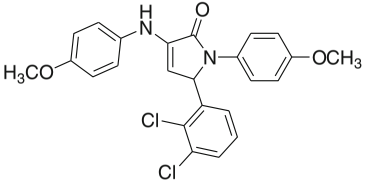
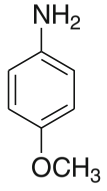
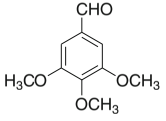
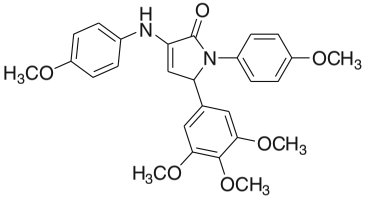
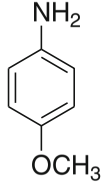
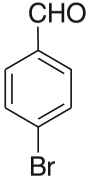
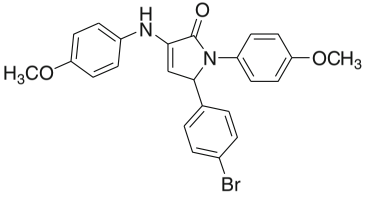
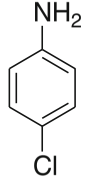
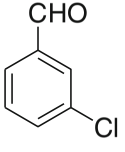
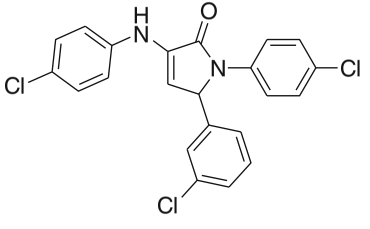
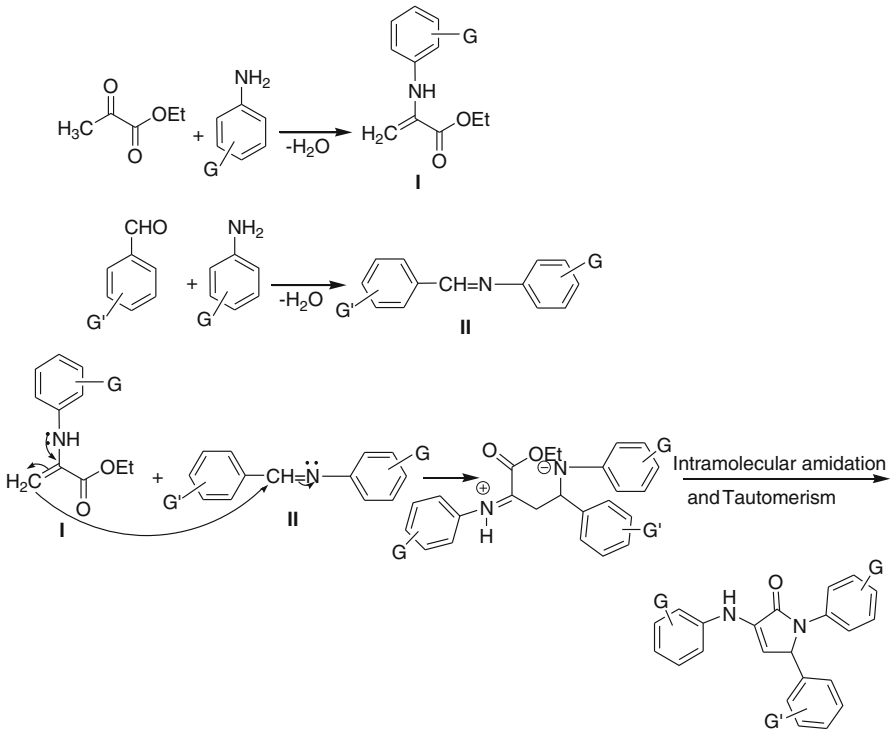
Entry	Aniline	Aldehyde	Product	Time (h)	Yield (%)[a]	Found m.p (°C)	Lit. m.p (°C) [Ref.]
23				6	95	219–220	218–220 [20]
24		$CH_3CH_2CH_2CHO$		3.5	65	212–214	New Product
25				3	85	205–207	New Product

Table 1 continued

Entry	Aniline	Aldehyde	Product	Time (h)	Yield (%)[a]	Found m.p (°C)	Lit. m.p (°C) [Ref.]
26				4.5	95	215–216	New Product
27				3.5	96	210	New Product
28				3	91	263–265	New Product

[a] Yields refer to the isolated pure products. The desired pure products were characterized by comparison of their physical data (melting points, IR, ^{1}H and ^{13}C NMR) with those of known compounds



Scheme 2 Suggested mechanism for preparation of 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones

134.5, 154.7, 158.6, 167.7, 171.6 ppm; FT-IR (KBr): 3,309, 2,991, 2,935, 1,694, 1,650, 1,609, 1,538, 1,513, 1,462, 1,372, 1,297, 1,246, 1,177, 1,111, 1,031, 834, 780, 726 cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 396 (70), 352 (14), 323 (100), 309 (12), 279 (13), 246 (6), 202 (5), 148 (35),132 (5),107 (4), 92 (8), 77 (12), 64 (3); calcd. for [$C_{21}H_{24}N_2O_3$]: C, 71.57; H, 6.86; N, 7.95 %; Found: C, 71.67; H, 6.93; N, 8.01 %.

5-(2,3-Dichlorophenyl)-1-(4-methoxyphenyl)-3-(4-methoxyphenylamino)-1*H*-pyrrol-2(5*H*)-one (Table 1, Entry 25): ^{1}H NMR (500 MHz, $CDCl_3$): 3.78 (s, 3H), 3.80 (s, 3H), 5.99 (d, $J = 2.6$ Hz, 1H), 6.24 (d, $J = 2.3$ Hz, 1H), 6.47 (s, 1H), 6.86–6.92 (m, 4H), 6.94 (d, $J = 1.25$ Hz, 1H), 7.04 (d, $J = 8.9$ Hz, 2H), 7.09 (t, $J = 8.2$ Hz, 1H), 7.34–7.36 (dd, $J = 1.6$, 7.8 Hz, 1H), 7.47 (d, $J = 9.1$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 55.4$, 55.6, 60.9, 103.6, 114.4, 114.8, 118.6, 118.7, 122.4, 125.2, 128.0, 129.7, 130.2, 133.4, 133.8, 134.5, 137.7, 154.7, 156.8, 167.0 ppm; IR (KBr): 3,329, 3,052, 3,003, 2,903, 1,680, 1,654, 1,616, 1,606, 1,512, 1,422, 1,299, 1,249, 1,105, 1,035, 810, 781, 728, 670 cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 304 (2), 269 (1), 254 (6), 149 (9), 134 (27), 122 (51), 106 (12), 92 (14), 77 (30), 57 (18), 43 (100); calcd. for [$C_{24}H_{20}Cl_2N_2O_3$]: C, 63.31; H, 4.43; N, 6.15 %; Found: C, 63.40; H, 4.48; N, 6.23 %.

1-(4-Methoxyphenyl)-3-(4-methoxyphenylamino)-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrrol-2(5*H*)-one (Table 1, Entry 26): ^{1}H NMR (500 MHz, $CDCl_3$): 3.74 (s, 3H), 3.75 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 5.46 (d, $J = 2.5$ Hz, 1H),

5.90 (d, $J = 2.6$ Hz, 1H), 6.36 (s, 2H), 6.44 (s, 1H), 6.81–6.85 (m, 4H), 7.02 (d, $J = 8.9$ Hz, 2H), 7.34 (d, $J = 9.0$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 55.4$, 55.6, 56.2, 60.8, 62.0, 65.1, 103.8, 106.0, 114.2, 114.7, 118.7, 123.9, 128.1, 130.4, 133.9, 133.3, 134.8, 153.6, 154.5, 157.1, 167.2 ppm; IR (KBr): 3,905, 3,855, 3,752, 3,650, 3,317, 2,938, 1,660, 1,591, 1,541, 1,519, 1,459, 1,399, 1,335, 1,302, 1,252, 1,184, 1,129, 1,032, 824, 789, 671, 524 cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 476 (93), 396(5), 354 (38), 326 (100), 300(6), 238 (8), 194(4), 148 (7), 122 (17),92 (5), 77(10); calcd. for [$C_{27}H_{28}N_2O_6$]: C, 68.05; H, 5.92; N, 5.88 % Found: C, 68.11; H, 5.99; N, 5.91 %.

5-(4-Bromophenyl)-1-(4-methoxyphenyl)-3-(4-methoxyphenylamino)-1*H*-pyrrol-2(5*H*)-one (Table 1, Entry 27):^{1}H NMR (500 MHz, $CDCl_3$): 1.23 (s, 3H, $J = 7.13$), 1.6 (s, 3H), 5.50 (d, $J = 2.5$ Hz, 1H), 5.86 (d, $J = 2.6$ Hz, 1H), 6.4 (s, 1H), 6.86–6.88 (m, 3H), 6.92–7.01 (m, 4H), 7.24-7.25 (m, 4H), 7.37 (d, 1H, $J = 6.6$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 55.3$, 55.4, 61.9, 64.1, 68.8, 105.8, 107.6, 114.7, 118.7, 121.9, 123.8, 128.6, 129.0, 129.3, 129.4, 132.1, 133.3, 136.9, 154.7, 158.6, 171.5, ppm; IR (KBr): 3,905, 3,855, 3,762, 3,309, 1,728, 1,600, 1,648, 1,542, 1,510, 1,459, 1,440, 1,399, 1,298, 1,248, 1,178, 1,111, 1,032, 830, 525 cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 466 (6), 396 (18), 323 (100), 279 (3),235 (2),220 (3),189 (1), 148 (16),122 (4),107 (3),92 (5), 77(6); calcd. for [$C_{24}H_{21}BrN_2O_3$]: C, 61.95; H, 4.55; N, 6.02 % Found: C, 61.90; H, 4.62; N, 6.10 % .

3-(4-Chlorophenylamino)-1,5-bis(3-chlorophenyl)-1*H*-pyrrol-2(5*H*)-one (Table 1, Entry 28): ^{1}H NMR (500 MHz, $CDCl_3$): 1.53 (s, 1H), 5.6 (s, 1H), 6.02 (s, 1H), 6.6 (s, 1H), 6.97 (d, $J = 8.80$ Hz, 2H), 7.10 (d, $J = 8.30$ Hz, 2H), 7.23–7.26 (m, 5H), 7.43 (d, $J = 8.85$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 63.5$, 107.8, 117.9, 122.5, 126.4, 127.5, 128.1, 129.1, 129.4, 131.3, 132.7, 133.2, 135.4, 139.5, 166.7, ppm; IR (KBr): 3,905, 3,855, 3,752, 3,650, 331, 1,670, 1,647, 1,601, 1,533, 1,492, 1,422, 1,384, 1,089, 814, 624, 470 cm^{-1}; MS (EI, 70 eV) *m/z* (%) = 430 (100), 302 (54),274 (98), 253 (6), 239 (16), 218 (3), 204 (22), 177 (4),162 (6), 89 (5), 138 (22), 111 (31), 75 (124), 51 (5); calcd. for [$C_{22}H_{15}Cl_3N_2O$]: C, 61.49; H, 3.52; N, 6.52 % Found: C, 61.52; H, 3.55; N, 6.60 %.

Results and discussion

We were interested in preparation of 3-amino-1,5-dihydro-2*H*-pyrrol-2-one derivatives by pseudo four-component reaction of ethyl pyruvate, anilines, and aldehydes. First, several catalysts ($Al(HSO_4)_3$, silica–sulfuric acid, $FeCl_3$–SiO_2, and P_2O_5–SiO_2), different solvents (ethanol, dichloromethane, chloroform, ethyl acetate, diethyl ether, and *n*-hexane), and solvent-free conditions were studied. We found the catalysts performed better in *n*-hexane under reflux conditions than under other conditions. The heterogeneous catalysts were not all soluble in *n*-hexane but the reactions were complete. We then decided to perform the reaction in *n*-hexane under reflux conditions without use of any catalyst. The reactions were complete in the absence of the catalysts in *n*-hexane. It seems that *n*-hexane provides a good driving force for completion of the reaction because the product is not soluble in the

solvent and heterogeneous catalysts did not act efficiently in *n*-hexane as nonpolar solvent.

To investigate the range of anilines and aldehydes suitable for the reaction, a variety of substituted anilines and aldehydes bearing either electron-withdrawing or electron-donating groups were used in the reaction; all led to the desired products in high yields (Table 1). Reaction of aliphatic aldehydes, for example *n*-butyaldehyde, afforded the desired product in moderate yield (Table 1, Entry 24).

The mechanism proposed for reaction of ethyl pyruvate, aniline, and aldehyde are shown in Scheme 2. Two equivalents of aniline first react with the ethyl pyruvate and the aldehyde to form enamine I and imine II, respectively (Scheme 2). Subsequent condensation of I and II followed by the intramolecular amidation with loss of ethanol afforded the 3-amino-1,5-dihydro-2*H*-pyrrol-2-one as product. This proposed mechanism was confirmed in the literature [7, 20].

Literature survey revealed little research on synthesis of this class of compounds. We compared the suitability of our method with results reported in the literature, for example $Ti(OEt)_4$ (200 mol %) with sulfuric acid [7] and organocatalytic hydrogen-bonding of phosphoric acid and thiourea (10 mol %, 18 h) [20], and found that this catalyst-free method is most efficient in respect of reaction times and temperature and has broad applicability in terms of yield.

Conclusions

We report, for the first time, an uncatalyzed one-pot, pseudo-four-component reaction of ethyl pyruvate, anilines, and aldehydes, under reflux conditions in *n*-hexane, which affords a variety of 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones in high yield. Use of a non-toxic and inexpensive solvent, simple reaction, and clean work-up are advantages of this method.

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