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Organocatalytic Three-Component Reactions of Pyruvate, Aldehyde and Aniline by Hydrogen-Bonding Catalysts

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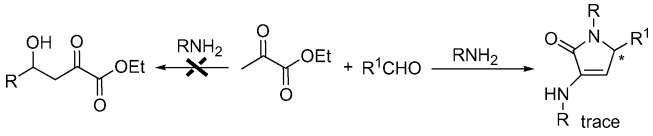
Hydrogen-bonding catalysts have been found to catalyze one-pot three-component reactions of pyruvate, anilines and aldehydes to afford versatile 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones in high yields. Both, thioureas and phosphoric acids are viable catalysts for these reactions and have comparable activity. The corresponding chiral thioureas and phosphoric acids have also been used in these three-component reactions to give pyrrol-2-ones in high yields and with moderate enantioselectivities.

Introduction

Multicomponent reactions (MCRs) are convergent reactions in which three or more starting materials react to form a product,[1] thus making possible the speedy synthesis of molecular libraries that have a high degree of structural diversity. Such processes are therefore of great value in the search for new drugs. Accordingly, the development of new catalytic MCR pathways, particularly enantioselective ones, has received increasing attention in the past few years. Breakthroughs in this area include the identification of several asymmetric catalysts for highly enantioselective MCRs. For example, Zhu and co-workers have developed a chiral lanthanide complex for the asymmetric Biginelli reaction.[2] Later, Wang et al. found that chiral (salen)Al complexes served as efficient and effective asymmetric catalysts for truncated Ugi reactions.[3] Recently, Gong reported that chiral phosphoric acids were able to catalyze some MCR reactions with excellent stereoselectivity.[4] Despite these successes, the development of further catalytic asymmetric MCRs is still highly desirable when considering the vast number of MCRs and the potential of their optically pure products.

1,5-Dihydro-2*H*-pyrrol-2-ones, particularly their 3-amino-substituted derivatives, are an interesting type of lactams that are found in many natural products and exhibit promising biological properties.[5–7] Accordingly, synthetic efforts have been made towards the construction of this class of molecules. In general, 3-aminopyrrol-2-ones are obtained by the two-component condensation of anilines with pyrrolidine-2,3-diones[6c] or β,γ-unsaturated α-oxo esters.[7] As pyrrolidinediones and β,γ-unsaturated α-oxo esters are normally prepared from the corresponding aldehydes and pyruvate derivatives, a one-pot three-component coupling of aniline, aldehyde and pyruvate would be the ideal process for the synthesis of these targeted lactams. In this regard, a single example of such a three-component coupling reaction in the presence of sulfuric acid has recently been reported.[7b] An asymmetric catalytic one-pot three-component coupling of aniline, aldehyde and pyruvate, to the best of our knowledge, is hitherto unknown. In the process of our study on the direct aldol reaction of pyruvate,[8] we found that the reaction of pyruvate and aldehyde in the catalysis of a primary amine unexpectedly afforded trace amounts of the three-component-coupling product [Equation (1)] instead of the desired aldol product. This interesting MCR reaction was next explored, and hydrogen-bonding organocatalysts such as thioureas and phosphoric acids were found to be effective catalysts for the reaction. Provided with the easily accessible chiral hydrogen-bonding organocatalysts, an asymmetric catalytic one-pot three-component condensation of pyruvate, aldehyde and aniline has been attempted for the first time. Herein we present the results of this study.



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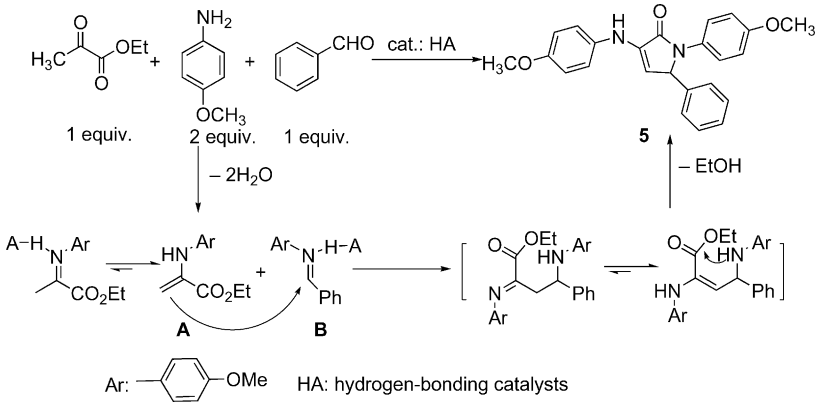
Results and Discussion

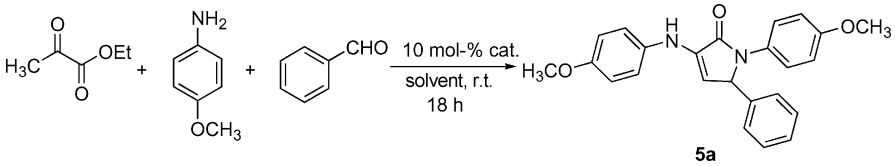
Through the pioneering work of Sigman and Jacobsen,[9] hydrogen-bonding donors have recently become a prominent type of organocatalyst that have enabled the realization of a range of transformations. Among the hydrogen-bonding organocatalysts explored so far, thioureas[10] and phosphoric acids[11] have attracted the most attention due to their success in a number of versatile transformations, particularly in reactions involving the activation of carbonyl groups or imines. In the three-component reaction of pyruvate, aldehyde and aniline, aniline first reacts with the pyruvate and aldehyde to form enamine **A** and imine **B**, respectively (Scheme 1). The subsequent condensation of enamine **A** and imine **B** followed by the intramolecular amidation and loss of ethanol afforded the 3-aminopyrrol-2-one product. In this process, hydrogen-bonding catalysts would activate the imine by forming hydrogen bonds with the nitrogen atoms, thereby promoting the formation of enamine **A** and imine **B** as well as the key coupling step. It is envisaged that the overall reaction is accelerated by using typical hydrogen-bonding catalysts such as thioureas or phosphoric acids and, to the best of our knowledge, the use of these types of catalysts has not been examined in the present reaction. Indeed, both phosphoric acids and thioureas were found to promote the three-component reactions (Table 1).

As revealed in Table 1, the reaction of ethyl pyruvate, benzaldehyde and *p*-anisidine was very sluggish in the ab-



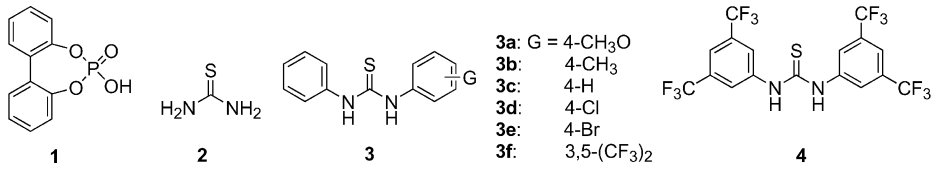
Scheme 1. Proposed mechanism for the reaction of pyruvate, *p*-anisidine and aldehyde.

Table 1. Catalyst screening.[a]



Entry	Catalyst	Solvent	Yield[b] [%]	pK_a
1	none	toluene	6	–
2	**1**	THF	33	ca. 10
3	**1**	1,4-dioxane	5	–
4	**1**	CH_3CN	5	–
5	**1**	$CHCl_3$	52	–
6	**1**	CH_2Cl_2	57	–
7	**1**	benzene	64	–
8	**1**	toluene	70	–
9	**2**	toluene	38	21.1[c]
10	**3a**	toluene	50	14.0[d]
11	**3b**	toluene	54	13.9[d]
12	**3c**	toluene	54	13.4[c]
13	**3d**	toluene	58	12.8[d]
14	**3e**	toluene	61	12.7[d]
15	**3f**	toluene	62	10.8[d]
16	**4**	toluene	69	8.4[d]
17	**1**	toluene	86[e]	–
18	**4**	toluene	82[e]	–

[a] The reactions were carried out on a 0.1 mmol scale in 200 μL of toluene at room temperature with a molar ratio of pyruvate/*p*-anisidine/benzaldehyde of 3:2:1. [b] Isolated yield based on the aldehyde. [c] Reference: F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456. [d] Determined in this work with an uncertainty of ±0.1. [e] 0.3 mmol Na_2SO_4 was added to the reaction mixture.

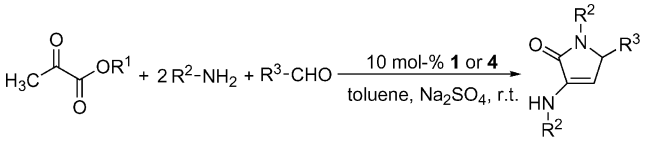


sence of any catalysts, affording only 6% yield after 18 h. In comparison, the use of phosphoric acid **1** for the same reaction in toluene gave 70% yield, showing significant catalytic activity. Further investigations indicated that the catalysis of phosphoric acid **1** was highly solvent-dependent. Although the reaction occurred smoothly in non-polar solvents such as toluene and benzene (Table 1, Entries 7 and 8), the same reaction barely occurred in polar solvents such as dioxane and CH_3CN (Table 1, Entries 3 and 4). With toluene as the optimal solvent, the reaction with thiourea-type catalysts was also examined. A series of thioureas with different substituents were synthesized and their corresponding pK_a values were determined by using "overlapping indicator methods".[12] As shown in Table 1 (Entries 10–16), a correlation between the catalytic activity of the thiourea and its corresponding pK_a is evident, with lower pK_a values, that is, higher acidity, leading to better yields. Following this trend, the most acidic thiourea examined, thiourea **4**, gave the best result with 69% yield in 18 h (Table 1, Entry 16). With the identified optimal catalysts **1** and **4** further improvements in the reaction were achieved by using molecular sieves (4 Å) or anhydrous sodium sulfate as an additive. In the presence of anhydrous Na_2SO_4, the yields increased to 86 and 82% with the catalysts **1** and **4**, respectively.

Under the optimized conditions, reactions were performed with both phosphoric acid **1** and thiourea **4** to explore the substrate scope with regard to the anilines and aldehydes (Table 2). As shown in Table 2, various substituted anilines bearing either electron-withdrawing or -donating groups were used in the reaction which led to the desired products in high yields (Table 2, Entries 1–5). The reaction was also quite general with regard to the aldehydes. A variety of aromatic aldehydes underwent the reaction with ethyl pyruvate and *p*-anisidine to afford the desired products in yields ranging from 57 to 81% with thiourea **4** as catalyst (Table 2, Entries 6–15). Notably, the reaction also accommodated aliphatic aldehydes such as isovaleraldehyde, affording the desired 3-aminopyrrol-2-one product in a moderate yield (Table 2, Entry 16). Among the cases examined, phosphoric acid **1** and thiourea **4** demonstrated similar catalytic behaviour, which suggests they are both viable catalysts for this three-component reaction.

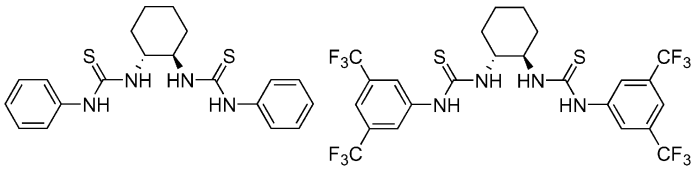
With a mild three-component reaction protocol in hand, we next briefly examined the asymmetric catalysis of this reaction by using readily available chiral thioureas[13] and phosphoric acids.[14] A series of known chiral thioureas **6**–**10** and chiral phosphoric acids **11a**–**i** were tested in the reaction of ethyl pyruvate, benzaldehyde and *p*-anisidine. After many attempts, our initial efforts led to only moderate

Table 2. Synthesis of 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones catalyzed by **1** or **4**.[a]



Entry	R^1	R^2NH_2	R^3CHO	**5**	Yield[b] [%]	Yield[c] [%]
1	Et	4-$CH_3OC_6H_4$	C_6H_5	**5a**	82	86
2	Et	4-$CH_3C_6H_4$	C_6H_5	**5b**	84	84
3	Et	C_6H_5	C_6H_5	**5c**	85	85
4	Et	4-ClC_6H_4	C_6H_5	**5d**	79	81
5	Et	4-BrC_6H_4	C_6H_5	**5e**	78	77
6	Et	4-$CH_3OC_6H_4$	2,4-$(CH_3O)_2C_6H_4$	**5f**	57	64
7	Et	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	**5g**	81	80
8	Et	4-$CH_3OC_6H_4$	3-$CH_3C_6H_4$	**5h**	65	71
9	Et	4-$CH_3OC_6H_4$	4-ClC_6H_4	**5i**	80	90
10	Et	4-$CH_3OC_6H_4$	3-ClC_6H_4	**5j**	79	81
11	Et	4-$CH_3OC_6H_4$	2-ClC_6H_4	**5k**	79	82
12	Et	4-$CH_3OC_6H_4$	3-BrC_6H_4	**5l**	77	75
13	Et	4-$CH_3OC_6H_4$	2-BrC_6H_4	**5m**	58	62
14	Et	4-$CH_3OC_6H_4$	4-$O_2NC_6H_4$	**5n**	81	89
15	Et	4-$CH_3OC_6H_4$	3-$O_2NC_6H_4$	**5o**	75	71
16	Et	4-$CH_3OC_6H_4$	$(CH_3)_2CHCH_2$	**5p**	48	51

[a] The reactions were carried out on a 0.1 mmol scale in 200 μL of toluene at room temperature with a molar ratio of pyruvate/*p*-anisidine/benzaldehyde of 3:2:1. All new compounds were characterized by ^1H and ^{13}C NMR spectroscopy and MS. [b] Isolated yield with catalyst **4**. [c] Isolated yield with catalyst **1**.



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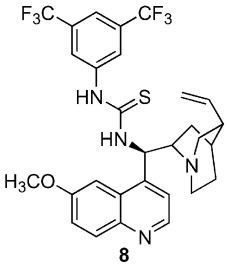

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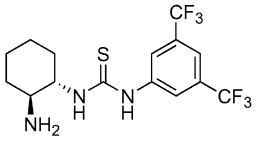

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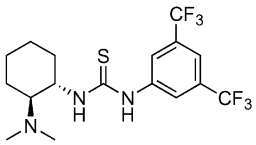

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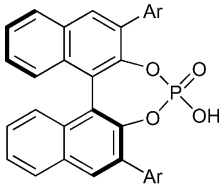


11a: Ar = H
11b: Ar = Ph
11c: Ar = 3,5-bis(trifluoromethyl)phenyl
11d: Ar = 4-nitrophenyl
11e: Ar = 1-naphthyl
11f: Ar = anthryl
11g: Ar = $SiPh_3$
11h: Ar = 4-biphenyl
11i: Ar = 2,4,6-(triisopropyl)phenyl

enantioselectivities, as shown in Tables 3 and 4. Of the chiral thioureas, Takemoto's catalyst **10**[13a] seemed to be the best, providing **5a** in 20% *ee* (Table 3, Entry 5). Of the chiral phosphoric acids studied, **11i** with the large steric bulk at the 3,3′-positions, which was first used in asymmetric catalysis by List and co-workers,[14c] gave the best results with a moderate level of enantioselectivity (44% *ee*, Table 4, Entry 9). These results suggest that the use of chiral hydrogen-bonding catalysts is indeed a viable strategy for the asymmetric catalytic three-component coupling reaction, but new designs of catalysts are clearly required for better stereocontrol.

Table 3. Reaction of ethyl pyruvate, *p*-anisidine and benzaldehyde catalyzed by chiral thioureas.[a]

Entry	Catalyst	Yield[b] [%]	*ee*[c] [%]
1	**6**	57	11
2	**7**	72	5
3	**8**	85	2
4	**9**	82	7
5	**10**	78	20

[a] The reaction was carried out on a 0.1 mmol scale in 200 μL of toluene at room temperature with a ratio of **1/2/3** = 3:2:1. [b] Isolated yield based on the aldehyde. [c] Determined by HPLC analysis.

Table 4. Reaction of ethyl pyruvate, *p*-anisidine and benzaldehyde catalyzed by chiral phosphoric acids.[a]

Entry	Catalyst	Yield[b] [%]	*ee*[c] [%]
1	**11a**	78	11
2	**11b**	88	13
3	**11c**	83	3
4	**11d**	80	7
5	**11e**	85	6
6	**11f**	87	6
7	**11g**	85	19
8	**11h**	81	22
9	**11i**	77	44

[a] The reaction was carried out on a 0.1 mmol scale in 200 μL of toluene at room temperature with a ratio of **1/2/3** = 3:2:1. [b] Isolated yield based on the aldehyde. [c] Determined by HPLC analysis.

Conclusions

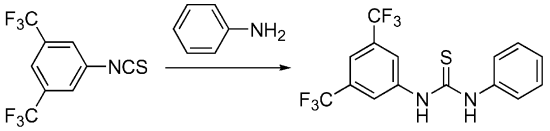
We have demonstrated that hydrogen-bonding donors such as phosphoric acid and thiourea derivatives are efficient catalysts for the three-component reactions of pyruvate, anilines and aldehydes. This study has provided a rather mild procedure for the synthesis of versatile 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones. Asymmetric catalysis with chiral phosphoric acids and thioureas was also explored but gave only moderate enantioselectivity. The development of more stereoselective catalysts for three-component reactions is currently underway in our laboratory.

Experimental Section

General Information: Commercial reagents were used as received unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded with a Bruker DPX 300 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br. = broad. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br.). Mass spectra were obtained by using an electrospray ionization (EI) mass spectrometer (Surveyor MSQ PLUS). IR spectra were recorded with an FT/IR-480Plus spectrometer. Catalyst **2** was purchased from Aldrich. Catalysts **1**,[15] **3a**,[16] **3b**,[17] **3c**,[18] **3d**,[19] **3e**,[20] **4**,[16] **6**,[21] **7**,[22] **8**,[13e] **9**,[23] **10**[13a] and **11**[14] were prepared according to literature procedures. Catalyst **3f** was synthesized in this work.

Preparation of Catalyst 3f: 5-Isothiocyano-1,3-bis(trifluoromethyl)-benzene (3 mmol) was added to a solution of aniline (3 mmol) in dichloromethane (20 mL). The mixture was stirred at room tem-

perature for 8 h (TLC) and concentrated. The crude product was purified by flash chromatography to afford 980 mg (90%) of **3f** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.41 (m, 3 H, 3 CH Ar), 7.48–7.53 (m, 2 H, 2 CH Ar), 7.68 (s, 1 H, CH Ar), 7.79 (br., NH, NHC), 7.98 (s, 2 H, 2 CH Ar), 8.66 (br., NH, NHC) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 119.50, 121.10, 124.72, 125.56, 128.35, 130.57, 131.37, 131.82, 132.27, 132.71, 135.55, 139.54, 179.72 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1604 (s, C=S) cm^{-1}. MS (EI$^+$): *m*/*z* = 364. HRMS (EI$^+$): calcd. for [$C_{15}H_{10}F_6N_2S$] 363.0469; found 364.0472.



3f

General Experimental Procedure: The pyruvate (0.3 mmol), aniline (0.2 mmol), aldehyde (0.1 mmol) and catalyst (0.01 mmol) were placed in a 5-mL vial equipped with a Teflon-coated stirring bar. The solvent (200 μL) was added under air. The vial was capped with a white polyethylene stopper, and the resulting mixture was stirred at room temperature for the indicated time. Then the reaction solution was concentrated in vacuo, and the crude product was purified by flash chromatography to afford the product. Compounds **5a**,[7a] **5b**,[7a] **5c**,[24] **5d**[7a] and **5g**[7a] are already known.

1-(4-Bromophenyl)-3-[(4-bromophenyl)amino]-5-phenyl-1*H*-pyrrol-2(5*H*)-one (5e): Yield: 37.6 mg (78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.62 (d, ^3J = 2.74 Hz, 1 H, CHN), 6.04 (d, ^3J = 2.74 Hz, 1 H, CH=), 6.72 (s, 1 H, NH), 6.94 (d, ^3J = 9.06 Hz, 2 H, 2 CH Ar), 7.17–7.19 (m, 2 H, 2 CH Ar), 7.25–7.30 (m, 3 H, 3CH Ar), 7.35–7.39 (m, 3 H, 3CH Ar), 7.43–7.46 (m, 3 H, 3 CH Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.13, 108.85, 113.46, 118.05, 118.28, 122.77, 126.62, 128.49, 129.22, 131.65, 131.98, 132.25, 136.18, 136.72, 140.19, 166.99 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3327 (s, N–H enamine), 1674 (s, C=O amide) cm^{-1}. MS (EI$^+$): *m*/*z* = 482, 484, 486. HRMS (EI$^+$): calcd. for [$C_{22}H_{16}Br_2N_2O$] 481.9629, 483.9609, 485.9588; found 481.9619, 483.9603, 485.9597.

5-(2,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-3-[(4-methoxyphenyl)amino]-1*H*-pyrrol-2(5*H*)-one (5f): Yield: 28.5 mg (64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, CH_3O), 3.75 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 3.87 (s, 3 H, CH_3O), 5.96 (d, ^3J = 2.74 Hz, 1 H, CH-N), 6.07 (d, ^3J = 2.47 Hz, 1 H, CH=), 6.33 (dd, ^3J = 2.74, 8.23 Hz, 1 H, NH), 6.44 (t, ^3J = 2.47 Hz, 2 H, 2 CH Ar), 6.81–6.86 (m, 5 H, 5 CH Ar), 7.03 (d, ^3J = 9.33 Hz, 2 H, 2 CH Ar), 7.48 (d, J = 9.33 Hz, 2 H, 2 CH Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.31, 55.35, 55.61, 57.23, 98.55, 104.97, 106.28, 114.00, 114.64, 117.49, 118.25, 122.72, 127.44, 130.79, 132.79, 135.19, 154.18, 156.46, 158.10, 160.32, 167.28 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3330 (s, N–H enamine), 1674 (s, C=O amide) cm^{-1}. MS (EI$^+$): *m*/*z* = 446. HRMS (EI$^+$): calcd. for [$C_{26}H_{26}N_2O_5$] 446.1842; found 446.1844.

1-(4-Methoxyphenyl)-3-[(4-methoxyphenyl)amino]-5-(*m*-tolyl)-1*H*-pyrrol-2(5*H*)-one (5h): Yield: 28.4 mg (71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, CH_3), 3.74 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 5.53 (d, ^3J = 2.47 Hz, 1 H, CHN), 5.93 (d, ^3J = 2.47 Hz, 1 H, CH=), 6.50 (s, 1 H, NH), 6.80–6.87 (m, 4 H, 4 CH Ar), 7.00–7.05 (m, 4 H, 4 CH Ar), 7.14–7.18 (m, 1 H, 1 CH Ar), 7.39 (d, ^3J = 8.51 Hz, 2 H, 2 CH Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.41, 55.35, 55.60, 64.71, 106.41, 114.13, 114.66, 118.40, 123.65, 124.01, 127.42, 128.76, 128.91, 130.41, 132.83, 134.92, 137.59, 138.64, 154.35, 156.88, 167.26 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3317 (s, N–H enamine), 1672 (s, C=O amide) cm^{-1}. MS (EI$^+$): *m*/*z* = 400. HRMS (EI$^+$): calcd. for [$C_{25}H_{24}N_2O_3$] 400.1787; found 400.1790.

5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-[(4-methoxyphenyl)amino]-1*H*-pyrrol-2(5*H*)-one (5i): Yield: 37.8 mg (90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 5.54 (d, ^3J = 2.47 Hz, 1 H, CHN), 5.89 (d, ^3J = 2.47 Hz, 1 H, CH=), 6.49 (s, 1 H, NH), 6.80–6.87 (m, 4 H, 4 CH Ar), 7.03 (d, ^3J = 8.51 Hz, 2 H, 2 CH Ar), 7.11 (d, ^3J = 8.51 Hz, 2 H, 2 CH Ar), 7.22–7.26 (m, 2 H, 2 CH Ar), 7.32 (d, ^3J = 9.06 Hz, 2 H, 2 CH Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.37, 55.60, 64.07, 105.44, 114.25, 114.71, 118.55, 123.89, 128.35, 129.12, 129.93, 133.28, 133.84, 134.69, 136.31, 154.53, 157.12, 167.02 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3313 (s, N–H enamine), 1675 (s, C=O amide) cm^{-1}. MS (EI$^+$): *m*/*z* = 420. HRMS (EI$^+$): calcd. for [$C_{24}H_{21}ClN_2O_3$] 420.1241; found 420.1244.

5-(3-Chlorophenyl)-1-(4-methoxyphenyl)-3-[(4-methoxyphenyl)amino]-1*H*-pyrrol-2(5*H*)-one (5j): Yield: 34.0 mg (81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3O), 5.53 (d, ^3J = 2.47 Hz, 1 H, CHN), 5.89 (d, ^3J = 2.47 Hz, 1 H, CH=), 6.52 (s, 1 H, NH), 6.81–6.88 (m, 4 H, 4 CH Ar), 7.02–7.08 (m, 3 H, 3 CH Ar), 7.19–7.20 (m, 3 H, 3 CH Ar), 7.35 (d, ^3J = 9.33 Hz, 2 H, 2 CH Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.38, 55.60, 64.13, 105.26, 114.28, 114.70, 118.59, 123.77, 125.08, 127.04, 128.36, 129.95, 130.22, 133.29, 134.66, 134.73, 140.00, 154.54, 157.11, 167.06 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3315 (s, N–H enamine), 1673 (s, C=O amide) cm^{-1}. MS (EI$^+$): *m*/*z* = 420. HRMS (EI$^+$): calcd. for [$C_{24}H_{21}ClN_2O_3$] 420.1241; found 420.1243.

5-(2-Chlorophenyl)-1-(4-methoxyphenyl)-3-[(4-methoxyphenyl)amino]-1*H*-pyrrol-2(5*H*)-one (5k): Yield: 34.4 mg (82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 5.98 (d, ^3J = 2.47 Hz, 1 H, CHN), 6.19 (d, ^3J = 2.47 Hz, 1 H, CH=), 6.52 (s, 1 H, NH), 6.82–6.87 (m, 4 H, 4 CH Ar), 6.98–7.05 (m, 3 H, 3 CH Ar), 7.08–7.18 (m, 2 H, 2 CH Ar), 7.35 (dd, ^3J = 2.47, 7.96 Hz, 1 H, CH Ar), 7.47 (d, ^3J = 9.06 Hz, 2 H, 2 CH Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.31, 54.54, 59.31, 103.30, 113.19, 113.64, 117.51, 121.51, 126.22, 126.60, 127.99, 128.76, 129.26, 132.15, 132.43, 133.68, 133.95, 153.43, 155.65, 166.14 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3318 (s, N–H enamine), 1683 (s, C=O amide) cm^{-1}. MS (EI$^+$): *m*/*z* = 420. HRMS (EI$^+$): calcd. for [$C_{24}H_{21}ClN_2O_3$] 420.1241; found 420.1244.

5-(3-Bromophenyl)-1-(4-methoxyphenyl)-3-[(4-methoxyphenyl)amino]-1*H*-pyrrol-2(5*H*)-one (5l): Yield: 35.7 mg (77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3O), 5.52 (d, ^3J = 2.74 Hz, 1 H, CHN), 5.89 (d, ^3J = 2.74 Hz, 1 H, CH=), 6.51 (s, 1 H, NH), 6.82–6.88 (m, 4 H, 4 CH Ar), 7.04 (d, ^3J = 9.06 Hz, 2 H, 2 CH Ar), 7.09–7.16 (m, 2 H, 2 CH Ar), 7.34–7.36 (m, 4 H, 4 CH Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.38, 55.61, 64.10, 105.27, 114.30, 114.71, 118.60, 122.88, 123.80, 125.54, 129.95, 130.51, 131.29, 133.29, 134.64, 140.24, 154.55, 157.13, 167.07 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3313 (s, N–H enamine), 1673 (s, C=O amide) cm^{-1}. MS (EI$^+$): *m*/*z* = 464, 466. HRMS (EI$^+$): calcd. for [$C_{24}H_{21}BrN_2O_3$] 464.0736, 466.0715; found 464.0731, 466.0720.

5-(2-Bromophenyl)-1-(4-methoxyphenyl)-3-[(4-methoxyphenyl)amino]-1*H*-pyrrol-2(5*H*)-one (5m): Yield: 28.8 mg (62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 5.99 (d, ^3J = 2.47 Hz, 1 H, CHN), 6.17 (d, ^3J = 2.47 Hz, 1 H, CH=), 6.51 (s, 1 H, NH), 6.82–6.87 (m, 4 H, 4 CH Ar), 6.97–7.10 (m, 4 H, 4 CH Ar), 7.13–7.18 (m, 1 H, CH Ar), 7.47 (d, ^3J = 9.06 Hz, 2 H, 2 CH Ar), 7.54 (dd, ^3J = 1.37, 7.96 Hz, 1 H, 1 CH Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.35, 55.59, 62.87, 104.42, 114.24, 114.69, 118.56, 122.54, 123.28, 127.41, 128.29, 129.38, 130.30, 133.07, 133.43, 134.71, 136.54, 154.49, 156.67,

167.21 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3319 (s, N–H enamine), 1679 (s, C=O amide) cm^{-1}. MS (EI^+): *m*/*z* = 464, 466. HRMS (EI^+): calcd. for $[C_{24}H_{21}BrN_2O_3]$ 464.0736, 466.0715; found 464.0732, 466.0712.

1-(4-Methoxyphenyl)-3-[(4-methoxyphenyl)amino]-5-(4-nitrophenyl)-1*H*-pyrrol-2(5*H*)-one (5n): Yield: 38.4 mg (89%). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 5.68 (d, ^3J = 2.47 Hz, 1 H, CHN), 5.88 (d, ^3J = 2.47 Hz, 1 H, CH=), 6.53 (s, 1 H, NH), 6.80–6.88 (m, 4 H, 4 CH Ar), 7.03 (d, ^3J = 8.51 Hz, 2 H, 2 CH Ar), 7.32–7.37 (m, 4 H, 4 CH Ar), 8.12 (d, ^3J = 9.06 Hz, 2 H, 2 CH Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.38, 55.59, 63.84, 104.14, 114.42, 114.74, 118.78, 123.66, 124.27, 127.78, 129.62, 133.84, 134.35, 145.55, 147.69, 154.75, 157.25, 166.89 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3311 (s, N–H enamine), 1680 (s, C=O amide) cm^{-1}. MS (EI^+): *m*/*z* = 431. HRMS (EI^+): calcd. for $[C_{24}H_{21}N_3O_5]$ 431.1481; found 431.1483.

1-(4-Methoxyphenyl)-3-[(4-methoxyphenyl)amino]-5-(3-nitrophenyl)-1*H*-pyrrol-2(5*H*)-one (5o): Yield: 32.3 mg (75%). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 5.69 (d, ^3J = 2.47 Hz, 1 H, CHN), 5.90 (d, ^3J = 2.47 Hz, 1 H, CH=), 6.50 (s, 1 H, NH), 6.81–6.88 (m, 4 H, 4 CH Ar), 7.04 (d, ^3J = 8.51 Hz, 2 H, 2 CH Ar), 7.34 (d, ^3J = 8.51 Hz, 2 H, 2 CH Ar), 7.42–7.51 (m, 2 H, 2 CH Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.39, 55.60, 63.85, 104.27, 114.45, 114.74, 118.80, 122.17, 123.29, 123.90, 129.48, 130.01, 132.86, 133.81, 134.36, 140.38, 148.57, 154.75, 157.32, 166.90 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3333 (s, N–H enamine), 1683 (s, C=O amide) cm^{-1}. MS (EI^+): *m*/*z* = 431. HRMS (EI^+): calcd. for $[C_{24}H_{21}N_3O_5]$ 431.1481; found 431.1478.

5-Isobutyl-1-(4-methoxyphenyl)-3-[(4-methoxyphenyl)amino]-1*H*-pyrrol-2(5*H*)-one (5p): Yield: 18.7 mg (51%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, ^3J = 6.86 Hz, 3 H, CH_3-CH), 0.98 (d, ^3J = 6.86 Hz, 3 H, CH_3CH), 1.17–1.26 (m, 2 H, CH_2CH), 1.55–1.65 (m, 1 H, $CHCH_3$), 3.80 (s, 3 H, CH_3O), 3.83 (s, 3 H, CH_3O), 4.62–4.68 (m, 1 H, CHN), 6.02 (d, ^3J = 2.47 Hz, 1 H, CH=), 6.41 (s, 1 H, NH), 6.88–6.98 (m, 4 H, 4 CH Ar), 7.06 (d, ^3J = 8.51 Hz, 2 H, 2 CH Ar), 7.36 (d, ^3J = 8.78 Hz, 2 H, 2 CH Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.05, 23.92, 25.18, 41.77, 55.48, 55.62, 58.92, 104.36, 114.37, 114.71, 118.38, 124.74, 129.76, 133.87, 135.17, 154.28, 157.30, 166.08 ppm. IR (KBr):$\tilde{\nu}$ = 3305 (s, N–H enamine), 1676 (s, C=O amide) cm^{-1}. MS (EI^+): *m*/*z* = 366. HRMS (EI^+): calcd. for $[C_{22}H_{26}N_2O_3]$ 366.1943; found 366.1941.

Supporting Information (see footnote on the first page of this article): NMR spectra for new compounds and HPLC trace for **5a**.

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