Efficient Synthesis of 3-Arylaminopyrroline-2-ones by the Tandem Reaction of Anilines and β,γ-Unsaturated α-Ketoesters

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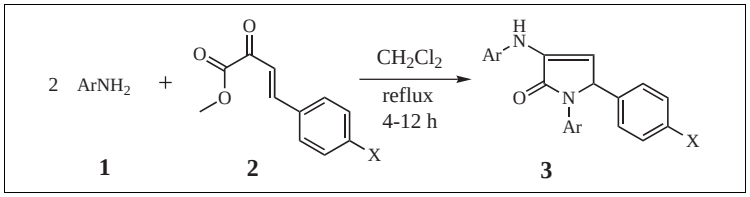
Received September 24, 2005



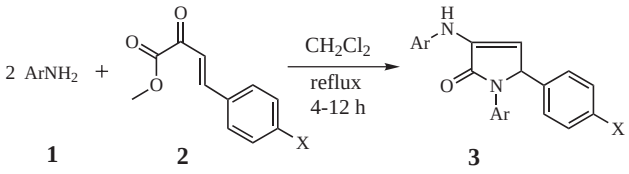
A concise and efficient synthetic approach to 3-arylaminopyrroline-2-ones from anilines and β,γ-unsaturated α-ketoesters in boiling dichloromethane has been developed. This protocol possesses many advantages such as short reaction time, high isolated yields, and expanding substrate scopes. According to the isolated intermediates and controlled reactions, the reaction was tentatively proposed to involve the Michael addition/condensation and subsequent intramolecular cyclization. The structures of the title compounds were unambiguously confirmed by various spectral data such as X-ray crystallographic analysis.

J. Heterocyclic Chem., **43**, 949 (2006).

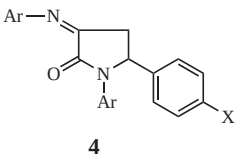
Introduction.

The development of synthetic methods for constructing pyrroles and their analogues has been of great interest to organic chemists for many years due to the presence of these structural units in a variety of biologically active natural products, medicinally relevant compounds, and functional materials [1-14]. It's worth mentioning that 3-arylaminopyrroline-2-ones had been reported to exhibit anti-inflammatory, analgesic [15], antiphlogistic, and analgetic activities [16]. Some strategies have been developed for the synthesis of these molecules. One is the condensation of pyruvic acid derivatives, anilines and aldehydes, in which imines or β,γ-unsaturated α-ketoesters sometimes were preformed [15-18]. Another is the condensation of anilines with pyrrolidine-2,3-diones or furan-2(5*H*)-ones [19]. These established strategies can synthesize 3-arylaminopyrroline-2-ones, but they have some shortcomings such as only low to moderate yields, long reaction time, and substrate limitation. Therefore it is still demand for efficient synthetic strategy to provide these compounds. Herein we would like to report our recent results on the convenient preparation of 3-arylaminopyrroline-2-ones (**3**) from anilines (**1**) and β,γ-unsaturated α-ketoesters (**2**), in which two molecules **1** are coupled in one pot with one molecule **2** in boiling dichloromethane (Scheme 1). On the other hand, this kind of compounds had been incorrectly identified as 3-aryliminopyrrolidin-2-ones (**4**, Scheme 2) [20] due to the historical difficulties in properly characterizing them without NMR and X-ray crystallographic technologies. In this case, we discussed here the NMR data and the X-ray crystallographic analysis, and elucidated them as 3-arylaminopyrroline-2-ones (not 3-aryliminopyrrolidin-2-ones).

Scheme 1



Scheme 2



Results and Discussion.

The new strategy for the synthesis of 3-arylaminopyrroline-2-ones came from our attempts to construct quinolines without catalyst. It is well known that many methods for the synthesis of quinolines needed various catalysts or promoters [21-25]. Therefore it was our interest to develop a simple synthetic method for quinolines. In this regard, *p*-toluidine (**1a**) and (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**2a**) were chosen to screen the reaction conditions (Scheme 3).

Scheme 3

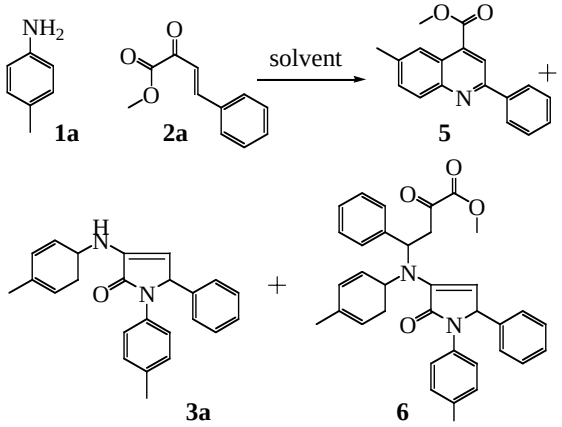


Table 1

Selected results on the solvent effects (Scheme 3).

Entry	Solvent	T (°C)	Time (hours)	**1a**: **2a**	**5**[a] (%)	**3a**[a] (%)	**6**[a] (%)
1	Toluene	110	2	1:1	2	22	8
2	THF	67	4	1:1	1	19	8
3	EtOH	78	3	1:1	2	12	6
4	$HCCl_3$	62	5	1:1	1	21	6
5	CH_2Cl_2	40	6	1:1	2	23	9
6	CH_2Cl_2	40	6	2:1	0	88	0
7	CH_2Cl_2	25	24	2:1	0	29	0
8	Dioxane	25	24	2:1	0	27	0
9	Dioxane	40	6	2:1	0	69	0
10	$HCCl_3$	40	6	2:1	0	64	0

[a] isolated yields

Representative results are listed in Table 1. It was found that when a solution of (**1a**, 0.2 mmol) and (**2a**, 0.2 mmol) in 2 mL toluene under atmospheric N_2 was refluxed for 2 hours, the expected methyl 6-methyl-2-phenylquinoline-4-carboxylate (**5**) was isolated only in extremely low isolated yield (2%, entry 1). However, we were surprised to find that 3-(*p*-tolylamino)-5-phenyl-1-(*p*-tolyl)-1*H*-pyrrol-2(5*H*)-one (**3a**, 22%) and methyl 4-(*N*-(2,5-dihydro-2-oxo-5-phenyl-1-(p-tolyl)-1*H*-pyrrol-3-yl)-*N*-(4-methylcyclohexa-2,4-dienyl)amino)-2-oxo-4-phenylbutanoate (**6**, 8%) were also obtained in this reaction mixture (entry 1). This finding promoted us to investigate the solvent effect on the reaction. So the reaction in other solvents such as tetrahydrofuran, ethanol, chloroform and dichloromethane, gave similar results (entries 2-5). Markedly, when the ratio of **1a** to **2a** was changed from 1:1 to 2:1, only **3a** was obtained in high isolated yield (88%, entry 6). The side product **6** was not detected in these reaction conditions. At room temperature in dichloromethane or dioxane, the isolated yield of **3a** decreased dramatically (entries 7-8). When the reaction is heated to the same temperature as entry 6 in dioxane or chloroform, **3a** was still obtained in lower yields than that in dichloromethane (entries 6, 9 and 10). Dichloromethane seems to be the most suitable reaction solvent in all screened media in terms of reaction temperature and isolated yields. Although the solvent effects on the reaction pathway were not fully investigated, it appears that an efficient synthetic process for 3-arylaminopyrroline-2-ones such as **3a** could be realized under the reaction conditions of entry 6.

Table 2

Synthesis of 3-arylaminopyrroline-2-ones (**3**, Scheme 1).

Entry	**1**	**2**	**3**	Time (hours)	Yield[a] (%)
1	**1a**: Ar = 4-MeC_6H_4	**2a**: X = H	**3a**	6	88
2	**1b**: Ar = 4-MeOC_6H_4	**2a**: X = H	**3b**	4	92
3	**1c**: Ar = 4-FC_6H_4	**2a**: X = H	**3c**	7	78
4	**1d**: Ar = 4-ClC_6H_4	**2a**: X = H	**3d**	7	81
5	**1e**: Ar = 3-ClC_6H_4	**2a**: X = H	**3e**	8	70
6	**1f**: Ar = 2-naphthyl	**2a**: X = H	**3f**	9	64
7	**1g**: Ar = 4-$NO_2C_6H_4$	**2a**: X = H	--	12	0
8	**1h**: Ar = C_6H_5	**2b**: X = OMe	**3g**	6	80
9	**1h**: Ar = C_6H_5	**2c**: X = Me	**3h**	6	83
10	**1a**: Ar = 4-MeC_6H_4	**2c**: X = Me	**3i**	5	84
11	**1b**: Ar = 4-MeOC_6H_4	**2c**: X = Me	**3j**	4	86
12	**1h**: Ar = C_6H_5	**2d**: X = Cl	**3k**	6	87
13	**1d**: Ar = 4-ClC_6H_4	**2d**: X = Cl	**3l**	7	84

[a] isolated yields

With the view to understanding the generality of the reaction, we carried out the reaction with various anilines (**1**) and β,γ-unsaturated α-ketoesters (**2**) under identical reaction conditions as outlined above and representative results as listed in Table 2. It is evident that a wide range of **1** and **2**, which were subjected to this procedure, could afford the corresponding 3-arylaminopyrroline-2-ones (**3**) in high isolated yields. In most cases, the electron-donating group or electron-withdrawing group on **1** or **2** has no significant impact on yields (entries 1-4, 8-13). However, there was a decrease in the yield when using 3-substituted aniline in comparison with its 4-substituted analogue (entries 4-5), or using bulky aromatic amine (entry 6). This process did not work, however, with aniline bearing strong electron-withdrawing groups such as a nitro one (entry 7).

The ^{1}H NMR diagram of three non-aryl hydrogen atoms in compound **3d** was elucidated in Figure 1. If **3d** were 3-(4-chlorophenylamino)-1-(4-chlorophenyl)-5-phenyl-1*H*-pyrrol-2(5*H*)-one (upper structure), the three non-aryl hydrogen atoms should be one single-peak (N-H) and two double-peaks (AB system). If **3d** were 3-(4-chlorocyclohexa-2,4-dienylimino)-1-(4-chlorophenyl)-5-phenylpyrrolidin-2-one (nether structure), the three non-aryl hydrogen atoms should be three quadruple-peaks (ABX system) because C-2 is a chiral carbon center. Three groups of peaks can be easily observed in Figure 1, one single-peak (N-H, Ha) and two double-peaks (Hb and Hc). These results confirmed that **3d** belongs to 3-arylaminopyrroline-2-ones (not 3-aryl-iminopyrrolidin-2-ones).

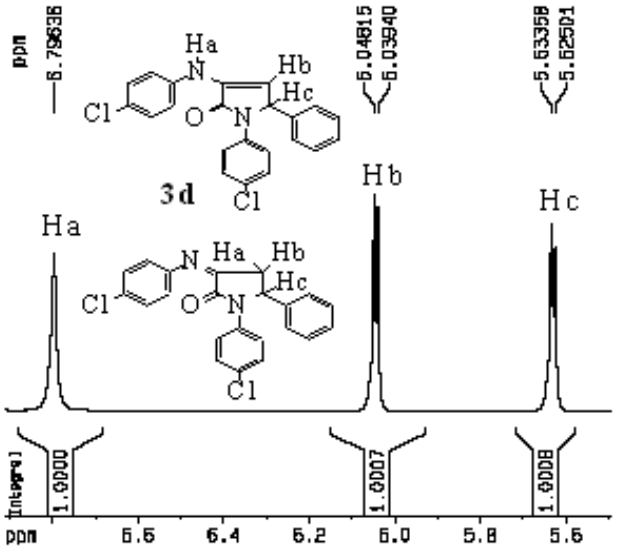


Figure 1. The ^{1}H NMR of **3d**.

The structure of compound **3d** was further determined by X-ray crystallographic analysis [26] (Figure 2). On one hand, the bond lengths of C(7)-C(8), C(8)-C(9) and C(9)-C(10) are 1.509 Å, 1.317 Å and 1.487 Å, respectively. Obviously, C(8)-C(9) is a double bond that is shorter than C(7)-C(8) (or C(9)-C(10), single bond). On the other hand, the bond length of C(9)-N(2) is 1.371Å that belongs to C-N single bond. A packing diagram of the crystal structure shows that the crystal of this compound is formed with aromatic π-π interactions and the intermolecular hydrogen bonds of N-H···O. These results also confirmed that **3d** belongs to 3-arylaminopyrroline-2-ones (not 3-aryliminopyrrolidin-2-ones).

After screening various reaction conditions, it was found that the reaction intermediate could be obtained under certain reaction conditions. As Scheme 4 showed, methyl 2,4-bis(4-fluorophenylamino)-4-phenylbut-2-enoate

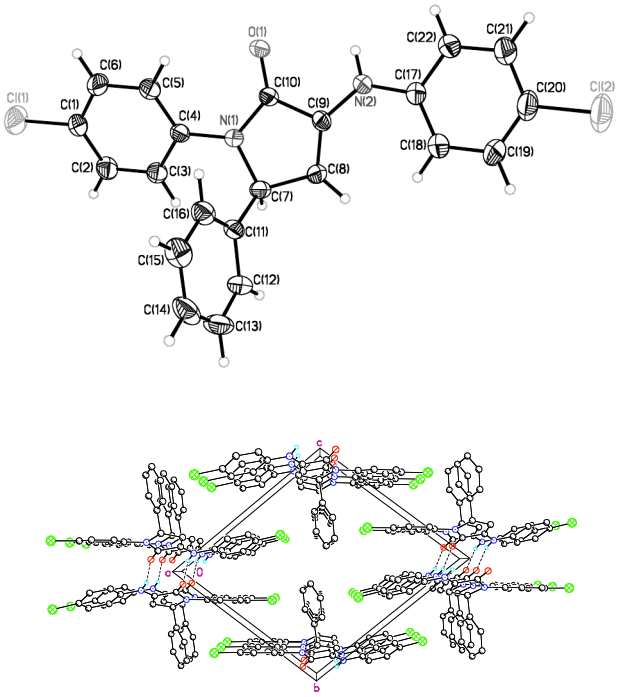
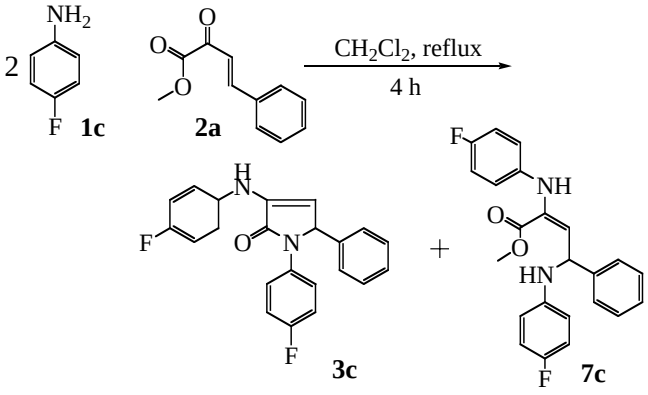


Figure 2. The X-ray structure of **3d**.

(**7c**, 0.21%) along with the title product of 3-(4-fluorophenylamino)-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrrol-2(5*H*)-one (**3c**, 63%) were produced when a solution of 4-fluorobenzenamine (**1c**) and (*E*)-2-oxo-4-phenylbut-3-enoic acid methyl ester (**2a**) in dichloromethane under atmospheric N_2 was refluxed for 4 hours.

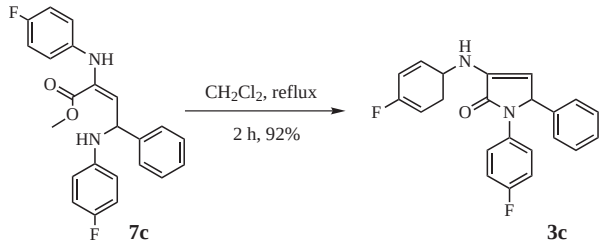
Scheme 4



As Scheme 5 showed, intermediate **7c** was isolated and found to convert into **3c** in high yield (92%) by refluxing it in dichloromethane under atmospheric N_2 for 2 hours.

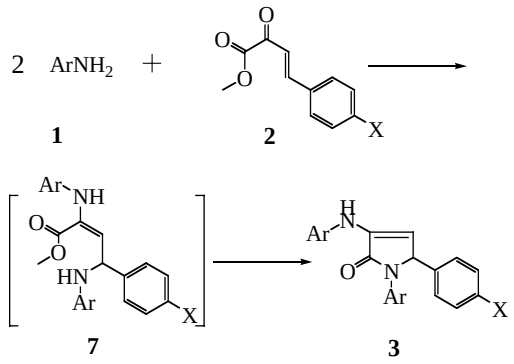
Based on above results, the title reaction mechanism was tentatively proposed to take a two-step route as

Scheme 5



shown in Scheme 6: Two molecules of anilines (**1**) might react with one molecule β,γ-unsaturated α-ketoesters (**2**) *via* aza-Michael addition/condensation to afford intermediates **7**, and the intramolecular cyclization of **7** to give 3-arylamino-pyrroline-2-ones (**3**).

Scheme 6



Tentatively proposed reaction mechanism.

Conclusion.

In summary, the synthetic protocol reported here represents an efficient synthesis of 3-arylaminopyrroline-2-ones that is confirmed with X-ray crystallographic analysis. This discovery might trigger others to revisit the other established molecules to obtain constructive results. Applications of this synthetically useful reaction are now in progress in our laboratory.

EXPERIMENTAL

General Methods.

All reactions were performed using oven-dried glassware under a positive atmosphere of dry nitrogen with magnetic stirring unless otherwise indicated. Common reagents and materials were purchased from commercial sources and purified by recrystallization or distillation. Flash chromatography was performed with column chromatography silica gel (Kiesselgel 60, 200-300 mesh). Analytical thin layer chromatography was performed with 0.2 mm coated commercial silica gel plates (Kiesselgel 60 GF_{254}). NMR spectra were measured on a Bruker XL-300 (^{1}H, 300 MHz and ^{13}C, 75 MHz). Data for ^{1}H are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant (Hz) and number. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Infrared (IR) spectra were recorded on a Perkin Elmer 500 FT-IR spectrophotometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the Bruker APEX-2 FT-ICRMS spectrometer. Elemental analyses were performed on Calro-Mod 1102 instrument. Melting points were measured on a Beijing-Tike X-4 apparatus and were not corrected. The crystal X-ray structures were measured on Rigaku R-axis RAPID IP.

β,γ-Unsaturated α-ketoesters (**2**) were all reported compounds that were synthesized according to the reported procedure. [27-28]

(*E*)-2-Oxo-4-phenylbut-3-enoic acid methyl ester (**2a**).

This compound was obtained from methanol as yellow crystals in 37% yield for two steps; mp 68-70° (literature [27]. 70-71°); ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.84 (d, *J* = 16.14 Hz, 1H), 7.60 (dd, *J* = 9.45, 1.86 Hz, 2H), 7.43-7.31 (m, 4H), 3.91 (s, 3H, O*CH*$_3$); ^{13}C nmr (75 MHz, deuteriochloroform): δ 182.40 (CO), 162.53, 148.59, 133.97, 131.70, 129.10, 129.07, 120.46, 53.01 (O*CH*$_3$).

(*E*)-4-(4-Methoxyphenyl)-2-oxobut-3-enoic acid methyl ester (**2b**).

This compound was obtained from methanol as yellow crystals in 44% yield for two steps; mp 99-100° (literature [29]. 109°); ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.83 (d, *J* = 16.00 Hz, 1H), 7.58 (d, *J* = 8.38 Hz, 2H), 7.23 (d, *J* = 16.00 Hz, 1H), 6.92 (d, *J* = 8.38 Hz, 2H), 3.92 (s, 3H), 3.84 (s, 3H, O*CH*$_3$); ^{13}C nmr (75 MHz, deuteriochloroform): δ 182.20 (CO), 162.68, 148.53, 131.12, 126.76, 118.03, 114.61, 55.48 (O*CH*$_3$), 52.97 (O*CH*$_3$).

(*E*)-4-(4-Methylphenyl)-2-oxobut-3-enoic acid methyl ester (**2c**)

This compound was obtained from methanol as yellow crystals in 41% yield for two steps; mp 81-83° (literature [19]. 81°); ^{1}H nmr (300MHz, deuteriochloroform): δ 7.76 (d, *J* = 16.09 Hz, 1H), 7.44 (d, *J* = 8.06 Hz, 2H), 7.24 (d, *J* = 16.09 Hz, 1H), 7.14 (d, *J* = 8.06 Hz, 2H), 3.86 (s, 3H, O*CH*$_3$), 2.31 (s, 3H, Ar-*CH*$_3$); ^{13}C nmr (75MHz, deuteriochloroform): δ 182.38 (CO), 162.63, 148.68, 142.54, 131.24, 129.84, 129.14, 119.39, 52.95 (O*CH*$_3$), 21.60 (Ar-*CH*$_3$).

(*E*)-4-(4-Chlorophenyl)-2-oxobut-3-enoic acid methyl ester (**2d**).

This compound was obtained from methanol as yellow crystals in 31% yield for two steps; mp 112-114° (literature [30]. 116-117°); ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.70 (d, *J* = 16.13 Hz, 1H), 7.47 (d, *J* = 8.48 Hz, 2H), 7.31-7.22 (m, 3H), 3.86 (s, 3H, O*CH*$_3$); ^{13}C nmr (75MHz, deuteriochloroform): δ 182.05 (CO), 162.31, 146.74, 137.57, 132.45, 130.13, 129.35, 120.85, 53.00 (O*CH*$_3$).

Methyl 6-methyl-2-phenylquinoline-4-carboxylate (**5**).

p-Toluidine (**1a**, 21.43 mg, 0.2 mmol) and (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**2a**, 38.04 mg, 0.2 mmol) was mixed

together, flushed with atmospheric N_2, and then refluxed in 2 mL dichloromethane for 2 hours. Then the mixture was cooled to room temperature, and the products were isolated by flash chromatography (ethyl acetate: petroleum ether = 1:2, v/v) on silica gel (200-300 mesh) column to give methyl 6-methyl-2-phenylquinoline-4-carboxylate (**5**, 1.11 mg, 2%), 3-(*p*-tolylamino)-5-phenyl-1-*p*-(tolyl)-1*H*-pyrrol-2(5*H*)-one (**3a**, 7.80 mg, 22%) and methyl 4-(*N*-(2,5-dihydro-2-oxo-5-phenyl-1-(*p*-tolyl)-1*H*-pyrrol-3-yl)-*N*-*p*-tolylamino)-2-oxo-4-phenylbutanoate (**6**, 4.36 mg, 8%).

This compound **5** was obtained from ethyl acetate/petroleum as white solids in 2% yield; mp 101-103°; ir (potassium bromide): ν 2923, 2853, 1727 (CO), 1346, 1251, 1185, 1149, 1029, 826, 755, 695 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 8.25 (d, *J* = 8.66 Hz, 1H), 8.11 (s, 1H), 7.71 (s, 1H), 7.58 (d, *J* = 8.84 Hz, 1H), 7.50-7.54 (m, 5H), 4.07 (s, 3H, OCH_3), 2.48 (s, 3H, Ar-CH_3)); ^{13}C nmr (75 MHz, deuteriochloroform): δ 166.15 (CO), 149.04, 146.76, 146.52, 139.11, 137.67, 132.46, 130.81, 129.54, 128.68, 128.64, 127.87, 124.44, 121.46, 53.19 (OCH_3), 22.05 (Ar-CH_3).

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.92; H, 5.47; N, 4.91.

3-(*p*-Tolylamino)-5-phenyl-1-(*p*-tolyl)-1*H*-pyrrol-2(5*H*)-one (**3a**).

This compound was obtained from ethyl acetate/petroleum as white solids in 22% yield; mp 215-217° (literature [22]. 214.5-215.5°); ir (potassium bromide): ν 3312, 1677 (CO), 1648, 1516, 1401, 822 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.47 (d, *J* = 8.29 Hz, 2H), 7.33 -7.13 (m, 10H), 7.04 (d, *J* = 8.24 Hz, 1H), 6.71 (s, 1H), 6.07 (d, *J* = 2.14 Hz, 1H), 5.68 (d, *J* = 2.14 Hz, 1H), 2.35 (s, 3H, Ar-CH_3), 2,32 (s, 3H, Ar-CH_3); ^{13}C nmr (75 MHz, deuteriochloroform): δ 167.28 (CO), 138.93, 137.74, 134.74, 134.65, 132.41, 130.64, 129.86, 129.51, 128.96, 128.10, 126.85, 121.76, 116.84, 107.38, 64.35, 20.91 (Ar-CH_3), 20.71 (Ar-CH_3).

Anal. Calcd for $C_{24}H_{22}N_2O$: C, 81.33; H, 6.26; N, 7.90. Found: C, 81.49; H, 6.38; N, 7.75.

Methyl 4-(*N*-(2,5-dihydro-2-oxo-5-phenyl-1-(*p*-tolyl)-1*H*-pyrrol-3-yl)-*N*-*p*-tolylamino)-2-oxo-4-phenylbutanoate (**6**).

This compound was obtained from ethyl acetate/petroleum as white solids in 8% yield; mp 167-168°; ir (potassium bromide): ν 3028, 2923, 2854, 1727 (CO), 1692 (CO), 1681 (CO), 1514, 1454, 1359, 1291, 1253, 1224, 1179, 1143, 815, 755, 695 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.47 (d, *J* = 8.07 Hz, 2H), 7.26 (s, 1H), 7.20 (d, *J* = 7.95 Hz, 4H), 6.93-6.91 (m, 7H), 6.79 (s, m, 5H), 5.86 (d, *J* = 4.67 Hz, 1H), 5.38 (s, 1H), 5.30 (s, 1H), 4.63 (d, *J* = 4.67 Hz, 1H), 3.50 (s, 3H), 2.37 (s, 3H), 2.15 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 182.31 (CO), 164.09 (CO), 164.06 (CO), 139.54, 137.15, 136.10, 135.23, 134.36, 134.12, 133.46, 129.48, 129.11, 128.98, 128.57, 128.15, 128.13, 128.06, 127.66, 127.37, 126.49, 122.03, 116.44, 64.94, 52.01, 41.51, 21.31, 20.78.

Anal. Calcd for $C_{35}H_{32}N_2O_4$: C, 77.18; H, 5.92; N, 5.14. Found: C, 77.31; H, 5.96; N, 5.03.

Preparation of 3-Arylaminopyrroline-2-ones (**3**).

Anilines (**1**) (0.4 mmol) and β,γ-unsaturated α-ketoesters (**2**) (0.2 mmol) were mixed together, flushed with atmospheric N_2, and then refluxed in 2 mL dichloromethane for 4-12 hours according to Table 2 that came from the results monitored by TLC (ethyl acetate:petroleum ether = 1:2, v/v). Then the mixture was cooled to room temperature, and 3-arylaminopyrroline-2-ones (**3**) was isolated by flash chromatography (ethyl acetate:petroleum ether = 1:2, v/v) on silica gel (200-300 mesh) column.

3-(*p*-Tolylamino)-5-phenyl-1-(*p*-tolyl)-1*H*-pyrrol-2(5*H*)-one (**3a**).

This compound was obtained from ethyl acetate/petroleum as white solids in 88% yield; mp 215-217° (literature [19]. 214.5-215.5°); ir (potassium bromide): ν 3312, 1677 (CO), 1648, 1516, 1401, 822 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.47 (d, *J* = 8.29 Hz, 2H), 7.33-7.13 (m, 10H), 7.04 (d, *J* = 8.24 Hz, 1H), 6.71 (s, 1H), 6.07 (d, *J* = 2.14 Hz, 1H), 5.68 (d, *J* = 2.14 Hz, 1H), 2.35 (s, 3H), 2,32 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 167.28 (CO), 138.93, 137.74, 134.74, 134.65, 132.41, 130.64, 129.86, 129.51, 128.96, 128.10, 126.85, 121.76, 116.84, 107.38, 64.35, 20.91, 20.71.

Anal. Calcd for $C_{24}H_{22}N_2O$: C, 81.33; H, 6.26; N, 7.90. Found: C, 81.49; H, 6.38; N, 7.75.

3-(4-Methoxyphenylamino)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrol-2(5*H*)-one (**3b**).

This compound was obtained from ethyl acetate/petroleum ether as white solids in 92% yield; mp 197-199° (literature [19]. 196.5-197°); ir (potassium bromide): ν 3313, 1676 (CO), 1646, 1513, 1250, 1033, 830, 816 cm^{-1}; ^1H nmr (300 MHz, dimethylsulfoxide-d_6): δ 7.88 (s, 1H), 7.47 (d, *J* = 8.94 Hz, 2H), 7.24 -7.19 (m, 7H), 6.86 –6.81 (m, 4H), 6.10 (d, *J* =2.43 Hz, 1H), 5.90 (d, *J* = 2.43 Hz, 1H), 3.66(s, 6H); ^{13}C nmr (75 MHz, dimethylsulfoxide-d_6): δ 166.84 (CO), 156.66, 153.84, 138.76, 136.00, 133.13, 130.67, 129.15, 128.14, 127.31, 123.99, 118.76, 114.77, 114.35, 107.71, 63.31, 55.63, 55.56.

Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.44; H, 5.87; N, 7.24.

3-(4-Fluorophenylamino)-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrrol-2(5*H*)-one (**3c**).

This compound was obtained from ethyl acetate/petroleum as white solids in 78% yield; mp = 240-242°; ir (potassium bromide): ν 3333, 1676 (CO), 1653, 1509, 1391, 836 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.47-6.97 (m, 13H), 6.58 (s, 1H), 6.00 (d, *J* = 2.60 Hz, 1H), 5.61 (d, *J* = 2.60 Hz, 1H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 167.08 (CO), 162.11 (d, $^1J_{C\text{-}F}$ = 243.45 Hz), 159.87 (d, $^1J_{C\text{-}F}$ = 243.45 Hz), 137.39, 137.05, 133.21, 132.42, 129.09, 128.38, 126.78, 123.54 (d, $^3J_{C\text{-}F}$ = 7.95 Hz), 118.23 (d, $^3J_{C\text{-}F}$ = 7.73 Hz), 115.88 (d, $^4J_{C\text{-}F}$ = 2.78 Hz), 115.88 (d, $^2J_{C\text{-}F}$ = 42.23 Hz), 107.34, 64.55.

Anal. Calcd for $C_{22}H_{16}F_2N_2O$: C, 72.92; H, 4.45; N, 7.73. Found: C, 72.64; H, 4.71; N, 7.62.

3-(4-Chlorophenylamino)-1-(4-chlorophenyl)-5-phenyl-1*H*-pyrrol-2(5*H*)-one (**3d**)

This compound was obtained from ethyl acetate/petroleum as white solids in 81% yield; mp 217-219°; ir (potassium bromide): ν 3328, 1674 (CO), 1654, 1493, 1386, 824 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.51 (d, *J* = 8.98 Hz, 2H), 7.28 - 7.20 (m, 9H), 7.00 (d, *J* = 8.89 Hz, 2H), 6.80(s, 1H), 6.04 (d, *J* = 2.60 Hz, 1H), 5.63 (d, *J* = 2.60 Hz, 1H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 167.04 (CO), 139.80, 136.83, 135.73, 131.81, 130.25, 129.32, 129.21, 129.04, 128.48, 126.66, 126.11, 122.55, 117.94, 108.65, 64.20.

Anal. Calcd for $C_{22}H_{16}Cl_2N_2O$: C, 66.85; H, 4.08; N, 7.09. Found: C, 66.61; H, 4.29; N, 7.01.

3-(3-Chlorophenylamino)-1-(3-chlorophenyl)-5-phenyl-1*H*-pyrrol-2(5*H*)-one (**3e**).

This compound was obtained from ethyl acetate/petroleum as white solids in 70% yield; mp 207-209°; ir (potassium bromide): ν 3321, 1680 (CO), 1651, 1596, 1482, 1396, 780 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.71 (s, 1H), 7.39-7.07 (m, 10H), 6.93 (d, *J* = 7.95 Hz, 2H), 6.75 (s, 1H), 6.10 (d, *J* = 1.86 Hz, 1H), 5.66 (d, *J* = 1.86 Hz, 1H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 166.93 (CO), 143.69, 138.80, 137.46, 134.24, 133.89, 131.92, 130.53, 130.18, 129.16, 128.28, 126.95, 124.43, 121.11, 120.44, 119.39, 116.88, 115.35, 110.99, 63.14.

Anal. Calcd for $C_{22}H_{16}Cl_2N_2O$: C, 66.85; H, 4.08; N, 7.09. Found: C, 66.59; H, 4.32; N, 7.16.

1-(Naphthalen-3-yl)-3-(naphthalen-3-ylamino)-5-phenyl-1*H*-pyrrol-2(5*H*)-one (**3f**).

This compound was obtained from ethyl acetate/petroleum as white solids in 64% yield; mp 280-282°; ir (potassium bromide): ν 3305, 1683 (CO), 1621, 1597, 1401, 819, 748, 697 cm^{-1}; ^1H nmr (300 MHz, dimethylsulfoxide-d_6): δ 8.41 (s, 1H), 8.11 (s, 1H), 7.86-7.15 (m, 19H), 6.74 (s, 1H), 6.27 (s, 1H); ^{13}C nmr (75 MHz, dimethylsulfoxide-d_6): δ 166.61 (CO), 137.85, 134.73, 134.24, 131,51, 130.16, 128.74, 128.48, 128.20, 127.82, 127.39, 127.28, 127.02, 126.51, 126.18, 121.35, 119.98, 118.90, 109.54, 62.81.

Anal. Calcd for $C_{30}H_{22}N_2O$: C, 84.48; H, 5.20; N, 6.57. Found: C, 84.25; H, 5.41; N, 6.63.

5-(4-Methoxyphenyl)-1-phenyl-3-(phenylamino)-1*H*-pyrrol-2(5*H*)-one (**3g**).

This compound was obtained from ethyl acetate/petroleum as white solids in 80% yield; mp 171-173°; ir (potassium bromide): ν 3315, 1676 (CO), 1651, 1601, 1502, 751 cm^{-1}; ^1H nmr (300MHz, deuteriochloroform): δ 7.52 (dd, *J* = 8.66, 1.04 Hz, 2H), 7.31 –6.94 (m, 10H), 6.80 (d, *J* = 8.73 Hz, 2H), 6.64(s, 1H), 6.07 (d, *J* = 2.60 Hz, 1H), 5.64 (d, *J* = 2.60 Hz, 1H), 3,74(s, 3H); ^{13}C nmr (75MHz, deuteriochloroform): δ 167.17 (CO), 159.40, 141.32, 137.17, 131.86, 129.38, 129.08, 128.89, 128.04, 124.98, 121.80, 121.18, 116.61, 114.36, 108.45, 63.75, 55.24.

Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.37; H, 5.49; N, 7.70.

1-Phenyl-3-(phenylamino)-5-(*p*-tolyl)-1*H*-pyrrol-2(5*H*)-one (**3h**).

This compound was obtained from ethyl acetate/petroleum as white solids in 83% yield; mp 234-236°; ir (potassium bromide): ν 3318, 1684 (CO), 1597, 1265, 1093 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.55 (dd, *J* = 8.58, 0.94 Hz, 2H), 7.32 - 7.06 (m, 12H), 6.65 (s, 1H), 6.07 (d, *J* = 2.59 Hz, 1H), 5.66 (d, *J* = 2.59 Hz, 1H), 2.28 (s, 3H); ^{13}C nmr (75 MHz, deuterio-chloroform): δ 162.71 (CO), 142.61, 137.95, 134.31, 129.90, 129.36, 129.19, 126.66, 124.88, 121.56, 121.18, 119.46, 116.63, 108.47, 63.99, 53.0, 21.68.

Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 80.97; H, 6.00; N, 8.34.

3-(*p*-Tolylamino)-1,5-(di*p*-tolyl)-1*H*-pyrrol-2(5*H*)-one (**3i**).

This compound was obtained from ethyl acetate/petroleum as white solids in 84% yield; mp 249-251°; ir (potassium bromide): ν 3325, 1669 (CO), 1652, 1516, 1392, 813 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.39 (d, *J* = 8.48 Hz, 2H), 7.26 - 7.06 (m, 6H), 6.97 (d, *J* = 8.48 Hz, 2H), 6.55 (s, 1H), 5.99 (d, *J* = 2.60 Hz, 1H), 5.60 (d, *J* = 2.60 Hz, 1H), 2.29 (s, 3H), 2,27 (s, 3H), 2,26 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 167.22 (CO), 138.89, 137.84, 134.72, 134.58, 134.55, 132.25, 130.59, 129.82, 129.62, 129.46, 126.73, 121.74, 116.74, 107.56, 64.09, 21.14, 20.88, 20.65.

Anal. Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60. Found: C, 81.48; H, 6.70; N, 7.49.

3-(4-Methoxyphenylamino)-1-(4-methoxyphenyl)-5-*p*-tolyl-1*H*-pyrrol-2(5*H*)-one (**3j**)

This compound was obtained from ethyl acetate/petroleum as white solids in 86% yield; mp 218-220°; ir (potassium bromide): ν 3313, 1674 (CO), 1648, 1514, 1249, 813 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.37 (dd, *J* = 9.06, 2.15 Hz, 2H), 7.26(s, 1H), 7.03 (dd, *J* = 8.96, 2,18 Hz, 2H), 6.86-6.79 (m, 4H), 6.44 (s, 1H), 5.92 (d, *J* = 2.56 Hz, 1H), 5.54 (d, *J* = 2.56 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.28 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 167.18 (CO), 156.89, 154.35, 137.89, 134.91, 134.54, 132.86, 130.32, 129.59, 126.85, 123.77, 118.39, 114.66, 114.12, 106.40, 64.50, 55.61, 55.35, 21.15.

Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00. Found: C, 75.01; H, 5.98; N, 6.89.

5-(4-Chlorophenyl)-1-phenyl-3-(phenylamino)-1*H*-pyrrol-2(5*H*)-one (**3k**) [18].

This compound was obtained from ethyl acetate/petroleum as white solids in 87% yield; mp 222-224°; ir (potassium bromide): ν 3321, 1674 (CO), 1651, 1501, 1394, 840 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.37 (d, *J* = 7.89 Hz, 2H), 7.33-7.06 (m, 12H), 6.96 (t, *J* = 7.29 Hz, 1H), 6.67 (s, 1H), 6.05 (d, *J* = 2.39 Hz, 1H), 5.66 (d, *J* = 2.39 Hz, 1H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 167.07 (CO), 141.13, 136.93, 136.06, 133.92, 132.28, 129.42, 129.24, 129.02, 128.15, 125.19, 121.63, 121.43, 116.74, 107.49, 63.54.

Anal. Calcd for $C_{22}H_{17}ClN_2O$: C, 73.23; H, 4.75; N, 7.76. Found: C, 73.41; H, 4.82; N, 7.60.

3-(4-Chlorophenylamino)-1,5-bis(4-chlorophenyl)-1*H*-pyrrol-2(5*H*)-one (**3l**).

This compound was obtained from ethyl acetate/petroleum as white solids in 84% yield; mp 258-260°; ir (potassium bromide): ν 3325, 1669 (CO), 1652, 1538, 1516, 1392, 813 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.46 (dd, *J* = 8.92, 1.97 Hz, 2H), 7.29-7.24 (m, 6H), 7.12 (d, *J* = 8.41 Hz, 2H), 6.99 (d, *J* = 8.81 Hz, 2H), 6.64 (s, 1H), 6.00 (d, *J* = 2.48 Hz, 1H), 5.61 (d, *J* = 2.48 Hz, 1H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 166.80 (CO), 139.57, 135.43, 134.29, 132.07, 130.55, 129.43, 129.41, 129.15, 128.03, 126.43, 122.57, 117.97, 107.87, 77.21, 63.53.

Anal. Calcd for $C_{22}H_{15}Cl_3N_2O$: C, 61.49; H, 3.52; N, 6.52. Found: C, 61.38; H, 3.75; N, 6.47.

Procedure for the Reaction Mechanism.

4-Fluorobenzenamine (**1c**, 4.45 g, 40 mmol) and (*E*)-2-oxo-4-phenyl-but-3-enoic acid methyl ester (**2a**, 3.80 g, 20 mmol) was mixed together, flushed with atmospheric N_2, and then refluxed in 2 mL dichloromethane for 4 hours. Then the mixture was cooled to room temperature, and methyl 2,4-bis(4-fluorophenylamino)-4-phenylbut-2-enoate (**7c**, 16.56 mg, 0.21%) and 3-(4-fluoro-

phenylamino)-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrro (**3c**, 4.57 g, 63%) were isolated by flash chromatography (ethyl acetate: petroleum ether = 1:5, v/v) on silica gel (200-300 mesh) column.

(*E*)-Methyl 2,4-bis(4-fluorophenylamino)-4-phenylbut-2-enoate (**7c**).

This compound was obtained from ethyl acetate/petroleum as white solids in 0.21% yield; mp 157-160°; ir (potassium bromide): ν 3444, 3333, 2964, 1677 (CO), 1652, 1508, 1438, 1262, 1221, 1096, 1022, 803 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.86-6.97 (m, 14H), 6.58 (s, 1H), 6.00 (d, *J* = 2.60 Hz, 1H), 5.60 (d, *J* = 2.60 Hz, 1H), 3.94 (s, 3H); ^{13}C nmr (75 MHz, deuteriochloroform): δ 182.43 (CO), 167.07, 162.57, 158.24, 148.67, 137.39, 137.07, 134.00, 132.44, 131.71, 129.12, 129.08, 128.37, 126.77, 123.58, 123.47, 120.48, 118.29, 118.19, 116.16, 115.88, 115.86, 115.59, 107.35, 64.55, 53.04.

Anal. Calcd for $C_{23}H_{20}F_2N_2O_2$: C, 70.04; H, 5.11; N, 7.10. Found: C, 69.82; H, 5.37; N, 6.85.

7c (7.89 mg, 0.02 mmol) was flushed with atmospheric N_2, and then refluxed in 2 mL dichloromethane for 2 hours. Then the mixture was cooled to room temperature, and **3c** (6.67 mg, 92%) was isolated by flash chromatography (ethyl acetate: petroleum ether = 1:2, v/v) on silica gel (200-300 mesh) column.

Acknowledgement.

We thank the National Natural Science Foundation of China (No. 20232010, 20332030), Ministry of Science and Technology of China (No. 2002CCA03100), and the Chinese Academy of Sciences for financial support. We appreciate the suggestions and corrections from the reviewers.

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[26] Singlecrystal X-ray analysis of 3-(4-chlorophenylamino)-1-(4- chlorophenyl)-5-phenyl-1*H*-pyrrol-2 (5*H*)-one (**3d**): $C_{22}H_{16}Cl_2N_2O$, Mr = 395.27, Triclinic, P-1. *a* = 6.3462 (13), *b* = 12.223(2), *c* = 13.077(3) Å, V = 962.5(3) $Å^3$, Z = 2, Dx = 1.364 Mg/m^3. *T* = 293(2) K, reflections collected 6347, unique 3489 (R_{int} = 0.0582) which were used in all calculations. Data collection: Rapid Auto. Cell refinement: Rapid Auto. Data reduction: Rapid Auto. Program(s) used to solve structure: SHELXS-97. Program(s) used to refine structure: SHELXL-97. The data have been deposit with the Cambridge Crystallographic Data Center (Nr CCDC 270001). Selected bond lengths (Å): C(7)-C(8) = 1.509(5), C(8)-C(9) = 1.317(5), C(9)-C(10) = 1.487(5), N(2)-C(9) = 1.371(5), N(2)-C(17) = 1.392(5).

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