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One-Step Synthesis of Pyrido[1,2-*a*]benzimidazole Derivatives by a Novel Multicomponent Reaction of Chloroacetonitrile, Malononitrile, Aromatic Aldehyde, and Pyridine

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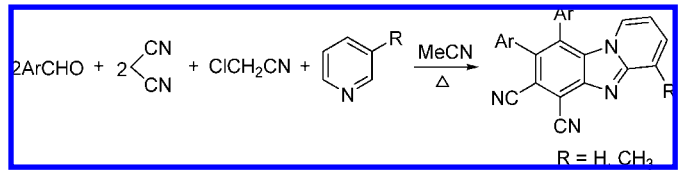

Polysubstituted pyrido[1,2-*a*]benzimidazole derivatives are efficiently produced in moderate yields in a novel one-pot, four-component reaction from pyridine or 3-picoline, chloroacetonitrile, malononitrile, and aromatic aldehyde in refluxing acetonitrile. The mechanism of this novel reaction was believed involving the formation of polysubstituted benzenes with subsequent substitution and annulation reaction of pyridine. All pyrido[1,2-*a*]benzimidazoles, polysubstituted benzenes, polysubstituted indoles, and some key reaction intermediates are characterized by ^{1}H and ^{13}C NMR, MS, IR spectra, and elemental analysis as well as X-ray crystallography.

Introduction

Ammonium ylides, which are often generated by deprotonation of the corresponding quaternary ammonium salts, are prone to be potential synthons and undergo versatile reactions, especially in the enantioselective catalytic cyclopropanation process. [1,2] As one kind of heterocyclic ammonium salts, the special nature of pyridinium salts allows them to be used to a great variety of synthetic reactions.[3,4] Due to the aromatic character and basicity of the pyridine heterocycle, and to the electron-attracting influence of the nitrogen atom, pyridinium cations in combination with strongly electron-withdrawing substituents like carbonyl, cyano, or nitro groups increase the activity, and hence the synthetic utility, of methylene groups.[5] The typical Kröhnke synthesis of pyridines is readily achieved by heating pyridinium salt with α,β-unsaturated ketones.[6] On the other hand, malononitrile is an exceptionally versatile compound; therefore, it is used extensively as a reactant or reaction intermediate. It exhibits unique reactivity since the strongly electron-withdrawing cyano groups activate the methylene groups ($pK_a = 11.2$), whose polar multiple bond is suitable for nucleophilic addition and is also a good leaving group for substitution.[7] The methylene group and either one or both cyano groups can take part in condensation reactions to give a variety of addition products and heterocyclic compounds.[8] This exceptional behavior makes malononitrile an important

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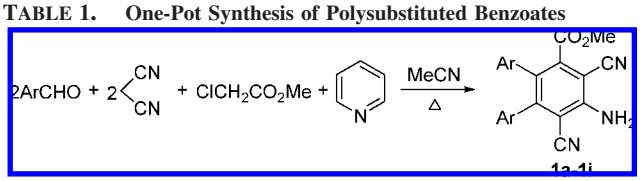
TABLE 1. One-Pot Synthesis of Polysubstituted Benzoates



entry	compd	Ar	time (h)	yield (%)
1	**1a**	Ph	18	37
2	**1b**	*p*-ClC_6H_4	12	38
3	**1c**	*p*-BrC_6H_4	12	54
4	**1d**	*p*-$CH_3C_6H_4$	24	27
5	**1e**	*m*-BrC_6H_4	12	27
6	**1f**	*p*-FC_6H_4	12	44
7	**1g**	*p*-EtC_6H_4	24	38
8	**1h**	*m*-$CH_3C_6H_4$	24	30
9	**1i**	*p*-$CH_3OC_6H_4$	24	29

candidate for the design of new practical multicomponent reaction procedures in research and in medicinal, industrial, and agricultural chemistry. In fact, there are a lot of multicomponent reaction procedures with malononitrile to prepare carbocyclic and heterocyclic compounds.[9−11] Recently, we found that polysubstituted benzene derivatives with an unprecedented substitution pattern could be produced in a one-pot multicomponent cyclization reaction of pyridine, ethyl α-bromoacetate, malononitrile, and aromatic aldehyde in refluxing acetonitrile.[12] In continuation of our efforts to investigate new one-pot multicomponent reactions, we developed this kind of reaction to other reactive α-halogenato-substituted carbonyl compounds and found very intriguing results of a new multicomponent reaction which involves malononitrile, aromatic aldehydes, pyridine, and chloroacetonitrile.

Results and Discussion

With the initial success of the one-pot multicomponent cyclization reaction of ethyl α-bromoacetate, pyridine, malononitrile, and aromatic aldehyde in refluxing acetonitrile to yield polysubstituted benzene derivatives with an unprecedented substitution pattern, [12] we tried to screen the reactivity of other reactive α-halogenato-substituted carbonyl compounds and use this four-component reaction to prepare cyclopropane derivatives. At first, we used methyl α-chloroacetate to replace ethyl α-bromoacetate in the reaction, and the respected polysubstituted methyl benzoates **1a**−**i** were produced as main products in similar yields (Table 1, entries 1−9). The polysubstituted benzoates **1a**−**i** were fully characterized by ^1H and ^{13}C NMR and IR spectra and elemental analysis, and their structures were also confirmed by single-crystal X-ray diffraction determination of **1a** (Figure 1). Thus, we could conclude that α-halogenato esters behave similarly in this component reaction and this reaction is a convenient synthetic procedure for the preparing some polysubstituted benzene derivatives.

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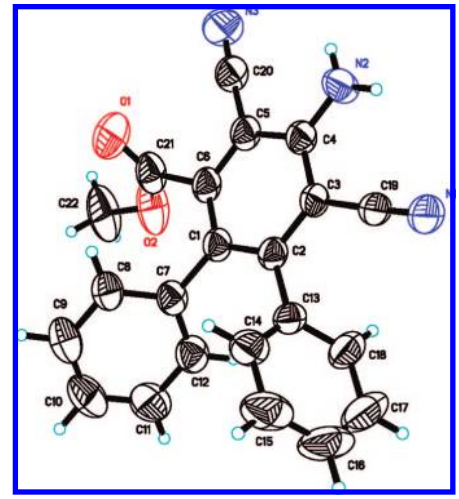
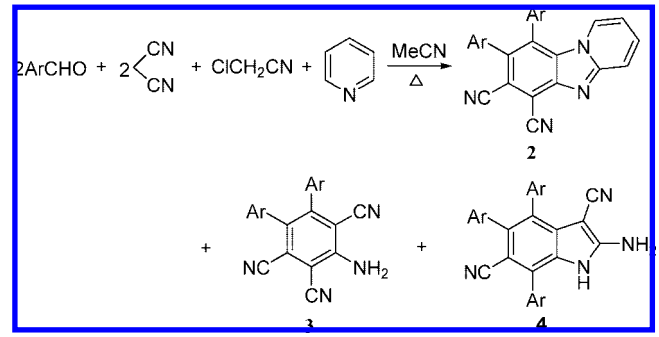


FIGURE 1. Molecular structure of **1a** in crystal.

TABLE 2. Results of One-Pot, Four-Component Reactions of Chloroacetonitrile

				yield (%)		
entry	compd	Ar	time (h)	**2a**−**l**	**3a**−**l**	**4a**−**l**
1	**a**	Ph	12	35		
2	**b**	*p*-$CH_3C_6H_4$	24	20	17	15
3	**c**	*p*-ClC_6H_4	6	33		17
4	**d**	*m*-ClC_6H_4	12	46		
5	**e**	*p*-BrC_6H_4	6	28		
6	**f**	*m*-BrC_6H_4	6	26		
7	**g**	*p*-$CH_3OC_6H_4$	24	34	10	
8	**h**	*m*-$CH_3C_6H_4$	18	32		
9	**i**	*p*-$C_2H_5C_6H_4$	24	31		
10	**j**	*p*-*i*-PrC_6H_4	24	51		14
11	**k**	*p*-*t*-BuC_6H_4	12	40		
12	**l**	*p*-FC_6H_4	12	35	14	

SCHEME 1. One-Pot, Four-Component Reactions Affording Three Kinds of Products 2−4



When a mixture of chloroacetonitrile, malononitrile, benzaldehyde, and an excess of pyridine was heated in acetonitrile for several hours, the unexpected nitrogen-containing heterocyclic compound pyrido[1,2-*a*]benzimidazole **2a** was isolated in 35% yield after workup. Similarly, various aromatic aldehydes were screened under the same conditions, and the corresponding pyrido[1,2-*a*]benzimidazole **2a**−**l** were produced in moderate yields (Table 2). Besides affording pyrido[1,2-*a*]benzimidazole derivatives (**2**) as main products, the reactions of *p*-chloro- and *p*-isopropylbenzaldehyde also yield polysubstituted indole products **4c** (17%) (Table 2, entry 3) and **4j** (14%) (Table 2, entry 10) in lower yields. From the reaction mixture of *p*-methoxybenzaldehyde and *p*-fluorobenzaldehyde, another byproduct polysubstituted benzene derivative **3g** and **3l** could be separated

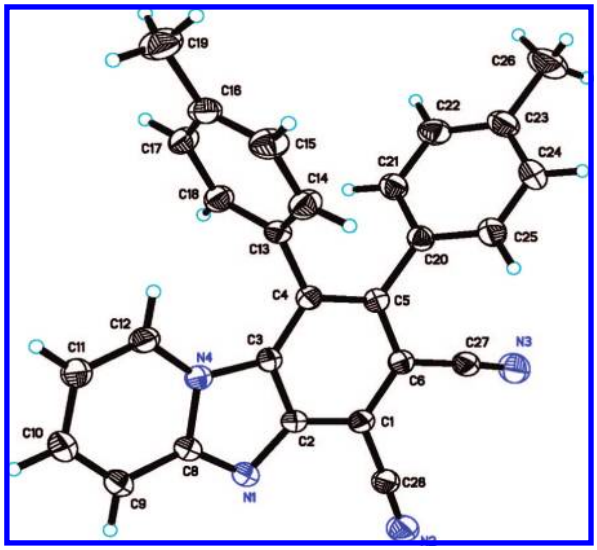


FIGURE 2. Molecular structure of **2b** in the crystal.

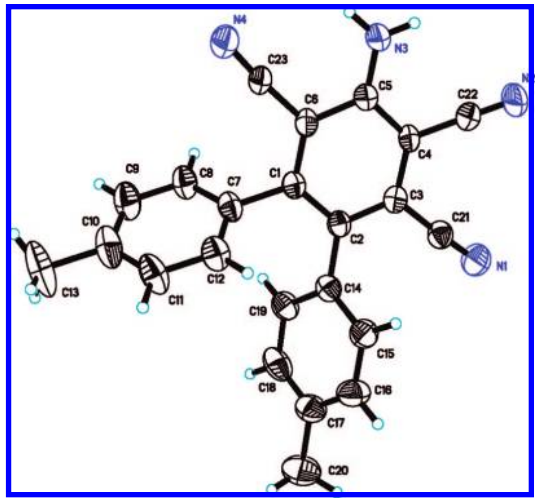


FIGURE 3. Molecular structure of **3b** in the crystal.

in 10% and 14% yields, respectively (Table 2, entries 7 and 12). The reaction of *p*-methylbenzaldehyde give all three products: **2b** (20%), **3b** (17%), and **4b** (15%). The results of the reaction are very interesting and show that three different kinds of products can be formed in the reactions. Theses four-component reactions of malononitrile, benzaldehyde, α-chloroacetonitrile, and pyridine are much more complicated than the similar multicomponent reactions of pyridine, ethyl α-bromoacetate, malononitrile, and aromatic aldehyde in refluxing acetonitrile, which were reported by us recently. The structures of all pyrido[1,2-*a*]benzimidazoles (**2a**−**2l**), polysubstituted benzenes (**3**), and polysusbtituted indoles (**4**) were fully characterized by ^{1}H and ^{13}C NMR, MS, and IR spectra and elemental analysis, and their structures were confirmed by single-crystal X-ray diffraction studies of **2b**, **2c**, **3b**, **4b**, **4c**, and **4j**. As examples, the structures of **2b**, **3b**, and **4b** are shown in Figures 2−4.

Formation of pyrido[1,2-*a*]benzimidazole (**2**) is also very interesting. In the structures of **2a**−**2l** there is one pyridine ring, which is clearly coming from the reaction of pyridine. Pyrido[1,2-*a*]benzimidazole motifs constitute various natural products, biologically active compounds, and synthetic intermediates.[13] The preparation of them often required lengthy steps and suffered from some drawbacks as well as lower yields.[14−16] The short reaction time and easiness of handling should render this new multicomponent reaction applicable to the synthesis of pyrido[1,2-*a*]benzimidazole derivatives. The special feature of the structure of **3** is that the two *p*-methylphenyl substituents are in the *ortho* position of the benzene ring, which has not been observed to date in any of the known cyclization reactions of malononitrile with formation of carbocyclic and heterocyclic compounds.[8−10] But the formation of **3** is reasonable according to our recent published work, in which a mixture of malononitrile, benzaldehyde, ethyl α-bromoacetate, and an excess of pyridine was heated in acetonitrile to give product with similar structure. By using chloroacetonitirle to replace ethyl α-bromoacetate in the reaction, the product is **3** in which the ester group is substituted by a cyano group. The formation of **4** is very intriguing. The most unusual feature of the structure of **4** is that there are three *p*-methylphenyl groups in the molecule, which means that at least three molecules of *p*-methylbenzaldehyde might take part in the reaction.

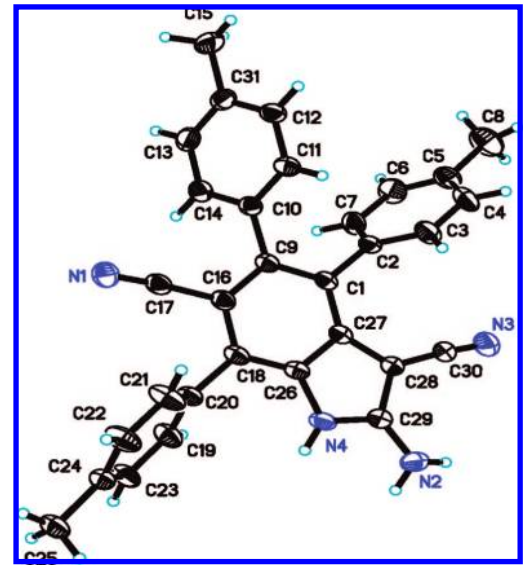


FIGURE 4. Molecular structure of **4b** in the crystal.

As shown in Table 2, benzaldehyde bearing moderate electronic influence substituents such as bromo, chloro, fluoro, alkyl, and methoxyl afforded three kinds of the desired products (Table 2). In some cases, compounds **3** and **4** were not separated because of low yields. In contrast, benzaldehydes with stronger electron-donating groups such as hydroxyl and dimethylamino or with stronger electron-withdrawing groups such as the nitro group as well as pyridinecarbaldehydes did not give one of the three kinds of products, affording only gummy materials whose structure could not be elucidated. To optimize the reaction conditions for the formation of pyrido[1,2-*a*]benzimidazole, the

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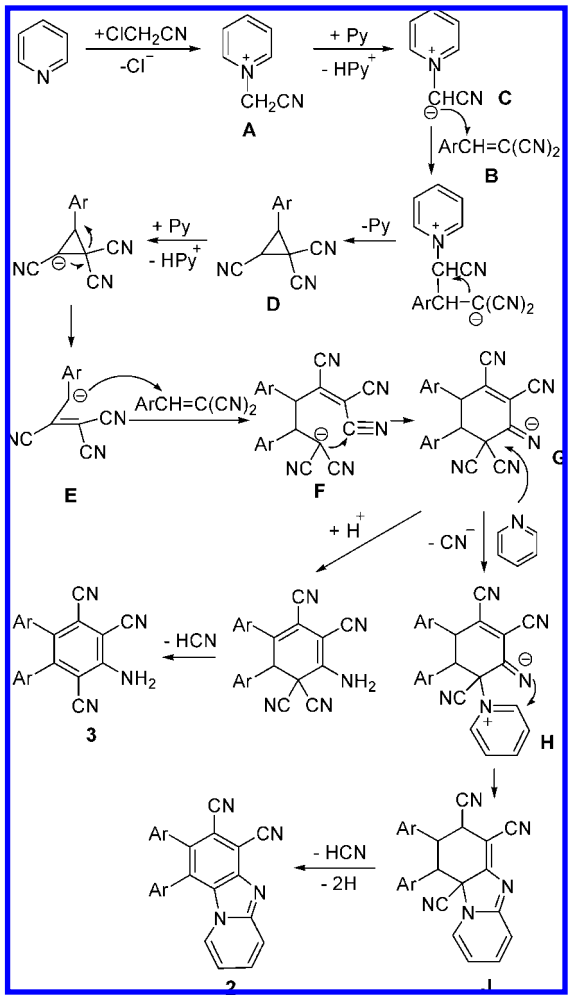
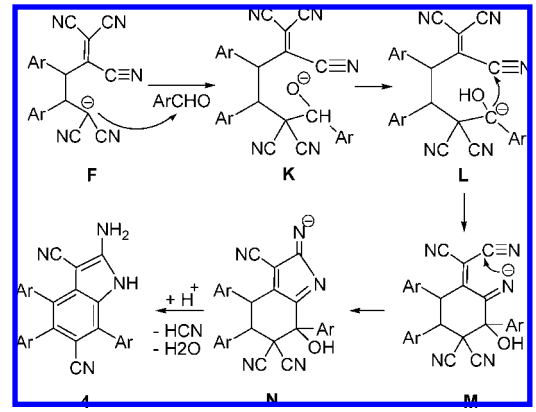
SCHEME 2. Proposed Mechanism for the Formation of Pyrido[1,2-*a*]benzimidazole (2) and Polysubstituted Benzenes (3)



SCHEME 3. Proposed Mechanism for the Formation of Polysubstituted Indoles (4)



influences of base catalyst, solvent, and the ratio of the components were investigated using the reaction of *p*-methoxybenzaldehyde as an example. If triethylamine, diethylamine, piperidine, morpholine, and potassium carbonate were used to replace pyridine as base, no anticipated products could be separated, which also indicate that pyridinium salt displays a crucial factor in the reaction. The reactions proceeds smoothly and moderate yields of pyrido[1,2-*a*]benzimidazole **2g** are produced in acetonitrile (34%), ethanol (29%), DMF (25%), and pyridine (24%). No pyrido[1,2-*a*]benzimidazoles can be separated from the reactions in dioxane and toluene.

To explain the mechanism of this one-pot multicomponent tandem reaction, we propose a plausible reaction course, which is illustrated in Scheme 2. The first step is the formation of the two reaction intermediates, namely the *N*-cyanomethylpyridinium salt (**A**) formed from the addition of chloroacetonitrile to pyridine and the arylidenemalononitrile (**B**) formed by the Knoevenagel condensation of the respective aromatic aldehyde with malononitrile. The second step is a Michael addition of a pyridinium ylide (**C**) which is formed by deprotonation of the *N*-cyanomethylpyridinium species (**A**) by excess pyridine to the arylidenemalononitrile (**B**) to afford a cyclopropane derivative (**D**). The third step is initiated by deprotonation and leads to the ring-opening of the activated cyclopropane (**D**) to form a allylic carbanionic intermediate (**E**), which in turn reacts with a second equivalent of arylidenemalononitrile (**B**) to form a new cyano-stabilized carbanionic intermediate (**F**). Then this cyano-stabilized carbanion concomitantly intramolecularly adds to one of the cyano groups to give a six-membered carbon ring system (**G**). This intermediate (**G**) reacts further according to two different paths to give different products. By elimination of one hydrocyanide molecule and aromatization the polysubtitute benzene derivative (**3**) was formed. On the other hand, the one cyano group in intermediate (**G**) can be substituted by excess pyridine to form a new pyridinium ion (**H**). In the resonance hybrid of this intermediate, an amino group attacks intramolecularly the ortho positive center of pyridine intermolecularly to yield a cyclic fused pyridine derivative (**J**) from which one hydrocyanide and two hydrogen atoms were eliminated to form pyrido[1,2-*a*]benzimidazole as the final product (**2**). This kind of the concerted substitution and annulation reaction pattern of pyridine have been encountered in several formation reactions of pyrido[1,2-*a*]benzimidazole.[14−16] In this proposed reaction mechanism, the unique properties of the two cyano groups in malononitrile are a crucial factor in the reaction sequence, especially in the final steps, where the cyano group acts as a strongly electron-withdrawing substituent, as a leaving group, and as a polar triple bond for nucleophilic addition. Pyridine also plays very important factor. It acts as a tertiary amine to form pyridinium cations, as a base to deprotonation to yield carbanium intermediate, and as a stronger nucleophilic reagent and so on. All these combinations result in this novel multicomponent reaction.

We also tentatively suggest one plausible mechanism for the formation of the minor polysubstituted indole product (Scheme 3). In the formation process of the products **2** and **3** (Scheme 2), the cyano-stabilized carbanionic intermediate (**F**) reacts with some additional aromatic aldehyde in solution to form a adduct intermediate (**K**). After a proton immigration from carbon atom to oxygen atom the new formed carbanion (**L**) intramolecularly adds to cyano group to form a cyclohexyl imine intermediate (**M**), which in turn adds to another cyano group to form a nitrogen-containing five-member ring species (**N**). The final polysubstituted indole (**4**) was produced by elimination of one molecule of water and hydrocyanide and aromatization process.

In order to probe the credibility of our proposed mechanistic scheme and shed more light on the formation of the pyrido[1,2-

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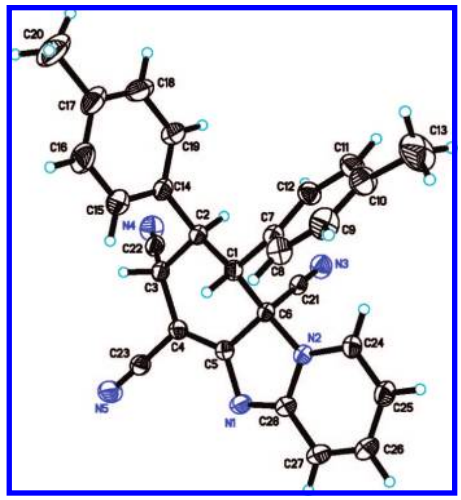
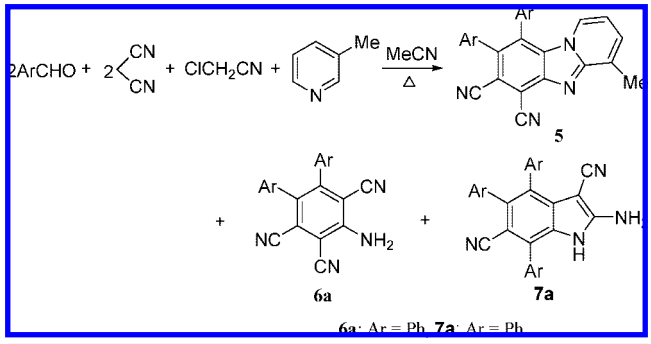


FIGURE 5. Molecular structure of intermediate **J1** in the crystal.

TABLE 3. Results of the One-Pot, Four-Component Reaction with 3-Picoline



entry	compd	Ar	yield (%)
1	**5a**	Ph	27
2	**5b**	*p*-$CH_3C_6H_4$	48
3	**5c**	*p*-ClC_6H_4	29
4	**5d**	*p*-BrC_6H_4	25
5	**5e**	*p*-FC_6H_4	29
6	**5f**	*p*-$CH_3OC_6H_4$	33
7	**5g**	*p*-$C_2H_5C_6H_4$	35
8	**5h**	*m*-$CH_3C_6H_4$	30
9	**5i**	*p*-*i*-PrC_6H_4	45

a]benzimidazole, further experiments were carried out. First, in the reaction of *p*-methylbezaldehyde and *p*-isopropylbenzadehyde the cyclic fused pyridine intermediates (**J1**: Ar = *p*-MeC_6H_4; **J2**: *p*-*i*-PrC_6H_4) could be isolated for their lower solubility, from which one hydrogen cyanide and two hydrogen atoms to be eliminated to give the final pyrido[1,2-*a*]benzimidazole derivatives. By prolonged heating in a mixture of acetonitrile and pyridine nearly quantitative conversion of this compound to final product proved to be possible. Fortunately, we have been able to obtain the crystal structures of two representative reaction intermediates (**J1**, **J2**). As an example, the structure of **J1** is shown in Figure 5. The mechanism proposed in Scheme 2 is strongly supported by the isolation of key intermediates, which were structurally characterized by X-ray diffraction.

Second, the reactivity of some pyridine derivatives such as picolines was tested in the reaction. The reactions of 3-picoline with various aromatic benzadehyde also give the corresponding methyl-substituted pyrido[1,2-*a*]benzimidazoles (**5a**−**i**) in moderate yields (Table 3). In the reaction of benzaldehyde, the other

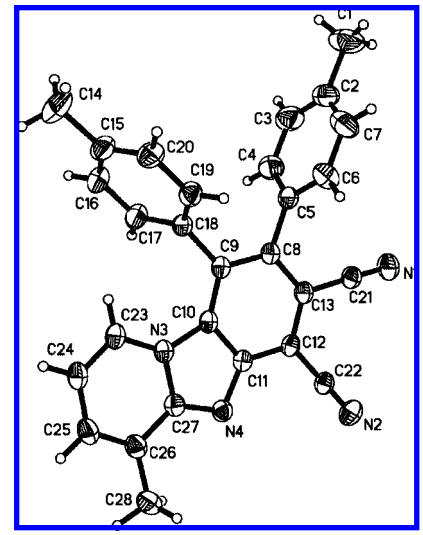


FIGURE 6. Molecular structure of intermediate **5b** in the crystal.

two minor products, polysubstituted benzene (**6a**) and polysubstituted indole (**7a**), are also separated in 6.6% and 8.6% yields respectively. In the reaction of other aldehydes the yields of these two minor products are too lower to separate. The structures of all pyrido[1,2-*a*]benzimidazoles (**5a**−**i**), polysubstituted benzene (**6a**) and polysusbtituted indoles (**7a**) were fully characterized by ^1H and ^{13}C NMR, MS, and IR spectra, and their structures were confirmed by single-crystal X-ray diffraction studies performed for **5a**, **5b**, **5c**, **5g**, and **5i**. As an example, the structure of **5b** is shown in Figure 6. It is worthy to mention that the *ortho*-position of methyl group rather than the relatively less crowded *para*-position in 3-picoline was attacked by imine anion to form a imidazole ring. The reactivities of 2-picoline and 4-picoline were also tested and they give much complicated results and no any pyrido[1,2-*a*]benzimidazole derivatives can be separated, which might due to stronger acidity of methyl group at the 2- and 4-positions of pyridine.

In conclusion, we have developed a new one-pot, four-component reaction involving pyridine or 3-picoline, chloroacetonitrile, malononitrile, and aromatic aldehyde in acetonitrile for the efficient synthesis of pyrido[1,2-*a*]benzimidazole derivatives in moderate yields. Even though the yield of product is a little lower, the short reaction time and easiness of handling should render this new multicomponent reaction applicable to the synthesis of pyrido[1,2-*a*]benzimidazole derivatives. The mechanism of this tandem reaction was investigated and some crucial reaction paths as well as some reaction intermediates have been observed. We are currently investigating the expansion of the scope of the reaction by other α-halogen-substituted carbonyl compounds and its application to the synthesis of other heterocyclic compounds.

Experimental Section

1. Typical Procedure of One-Pot Four-Component Reaction Involving Pyridine, Methyl Chloroacetate, Malononitrile, and Aromatic Aldehyde. A mixture of pyridine (20.0 mmol, 1.58 g), methyl α-chloroacetate (2.0 mmol, 0.217 g), aromatic aldehyde (4.0 mmol), and malononitrile (4.0 mmol, 0.264 g) in acetonitrile (20 mL) was refluxed for 12 h. The solvent was removed by evaporation, and the residue was titrated with ethanol (10 mL) to give the crude product, which was recrystallized in ethanol to give light yellow solid **1a**−**i**.

Methyl 5-amino-4,6-dicyano-2,3-diphenylbenzoate (1a): mp 210−211 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (s, 3H, C_6H_5), 7.14 (s, 3H, C_6H_5), 7.06 (s, 2H, C_6H_5), 6.91 (s, 2H, C_6H_5), 5.38 (s, 2H, NH_2), 3.60 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 149.7, 140.2, 134.7, 134.6, 128.7, 128.1, 127.7, 127.0, 126.7, 126.5, 113.7, 113.0, 98.7, 93.2, 51.8; IR (KBr) ν 3424 (s), 3353 (vs), 3254 (s), 2225 (m), 1731 (s), 1655 (s), 1565 (m), 1439 (m), 1366 (w), 1236 (s), 1019 (w), 754 (w), 703 (m) cm^{-1}. Anal. Calcd for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 75.67; H, 4.66; N, 11.68.

Methyl 5-amino-4,6-dicyano-2,3-di(*p*-chlorophenyl)benzoate (1b): mp 231−232 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (s, 2H, *p*-ClC_6H_4), 7.15 (d, J = 7.8 Hz, 2H, *p*-ClC_6H_4), 6.99 (d, J = 7.8 Hz, 2H, *p*-ClC_6H_4), 6.85 (d, J = 7.8 Hz, 2H, *p*-ClC_6H_4), 5.41 (s, 2H, NH_2), 3.66 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 149.3, 147.8, 139.9, 133.8, 132.6, 132.4, 132.3, 129.6, 129.0, 127.2, 126.9, 113.0, 112.3, 98.2, 93.3, 51.7; IR (KBr) ν 3241 (m), 2226 (m), 1749 (s), 1642 (s), 1562 (m), 1494 (m), 1444 (s), 1369 (m), 1221 (vs), 1090 (s), 1018 (m), 850 (m), 790 (m) cm^{-1}. Anal. Calcd for $C_{22}H_{13}Cl_2N_3O_2$: C, 62.58; H, 3.10; N, 9.95. Found: C, 62.33; H, 3.51; N, 9.73.

Methyl 5-amino-4,6-dicyano-2,3-di(*p*-bromophenyl)benzoate (1c): mp 252−253 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2H, *p*-BrC_6H_4), 7.31 (d, J = 7.8 Hz, 2H, *p*-BrC_6H_4), 6.92 (d, J = 6.6 Hz, 2H, *p*-BrC_6H_4), 6.78 (d, J = 8.4 Hz, 2H, *p*-BrC_6H_4), 5.40 (s, 2H, NH_2), 3.66 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 150.9, 149.3, 141.5, 134.4, 131.8, 131.4, 130.8, 128.4, 123.8, 122.4, 114.6, 113.9, 99.8, 95.0, 93.3, 29.7; IR (KBr) ν 3467 (m), 3345 (s), 3241(m), 2226 (m), 1749 (s), 1641 (s), 1564 (m), 1492 (m), 1443 (s), 1369 (m), 1220 (vs), 1072 (m), 1012 (m), 848 (m), 789 (m), 529 (w) cm^{-1}. Anal. Calcd for $C_{22}H_{13}Br_2N_3O_2$: C, 51.69; H, 2.56; N, 8.22. Found: C, 51.55; H, 2.89; N, 8.03.

Methyl 5-amino-4,6-dicyano-2,3-di(*p*-methylphenyl)benzoate (1d): mp 190−191 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.04 (d, J = 6.6 Hz, 2H, *p*-$CH_3C_6H_4$), 6.94 (d, J = 6.6 Hz, 4H, *p*-$CH_3C_6H_4$), 6.79 (d, J = 6.6 Hz, 2H, *p*-$CH_3C_6H_4$), 5.32 (s, 2H, NH_2), 3.63 (s, 3H, OCH_3), 2.29 (s, 3H, CH_3), 2.25 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 151.1, 150.8, 141.5, 138.8, 137.3, 133.1, 132.8, 129.8, 129.7, 129.2, 128.9, 128.7, 115.2, 114.3, 100.0, 94.0, 53.0, 21.3, 21.2; IR (KBr) ν 3465 (m), 3343 (s), 3239 (m), 2228 (m), 1744 (s), 1642 (s), 1562 (m), 1443 (m), 1369 (m), 1224 (vs), 1026 (m), 846 (m), 762 (m) cm^{-1}. Found: C, 75.33; H, 4.85; N, 10.75. $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02.

Methyl 5-amino-4,6-dicyano-2,3-di(*m*-bromophenyl)benzoate (1e): mp 187−188 °C; ^{1}H NMR ($CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 1H, *m*-BrC_6H_4), 7.33 (d, J = 7.8 Hz, 1H, *m*-BrC_6H_4), 7.21 (s, 1H, *m*-BrC_6H_4), 7.16 (t, J = 7.2 Hz, 1H, *m*-BrC_6H_4), 7.11 (s, 1H, *m*-BrC_6H_4), 7.05 (t, J = 7.2 Hz, 1H, *m*-BrC_6H_4), 7.04 (d, J = 7.2 Hz, 1H, *m*-BrC_6H_4), 6.84 (s, 1H, *m*-BrC_6H_4), 5.44 (s, 2H, NH_2), 3.69 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 150.3, 148.2, 140.6, 136.6, 131.5, 131.3, 130.4, 129.2, 128.8, 127.9, 127.3, 127.1, 121.6, 113.7, 113.1, 99.0, 94.3, 52.5; IR (KBr) ν 3458 (s), 3355 (vs), 2221 (m), 1742 (m), 1633 (s), 1563 (m), 1443 (m), 1384 (m), 1229 (s), 1023 (w), 848 (m), 772 (m) cm^{-1}. Anal. Calcd for $C_{23}H_{13}Br_2N_3O_2$: C, 51.69; H, 2.56; N, 8.22. Found: C, 51,48; H, 2.71; N, 8.38.

Methyl 5-amino-4,6-dicyano-2,3-di(*p*-fluorophenyl)benzoate (1f): mp 206 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03 (br, 2H, *p*-FC_6H_4), 6.97 (t, J = 7.8 Hz, 2H, *p*-FC_6H_4), 6.88 (br, 4H, *p*-FC_6H_4), 5.44 (s, 2H, NH_2), 3.65 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 163.6, 162.9, 162.0, 151.1, 149.9, 141.6, 131.7, 131.6, 131.3, 131.2, 128.6, 115.7, 115.6, 115.3, 115.2, 114.8, 114.1, 99.9, 94.6, 53.2; IR (KBr) ν 3475 (m), 3349 (s), 3245 (m), 2221 (w), 1742 (s), 1641 (s), 1605 (m), 1567 (m), 1513 (s), 1449 (s), 1227 (vs), 1161 (m), 1119 (w), 1023 (w), 849 (m), 806 (w) cm^{-1}. Anal. Calcd for $C_{23}H_{13}F_2N_3O_2$: C, 67.87; H, 3.37; N, 10.79. Found: C, 67.80; H, 3.63; N, 10.45.

Methyl 5-amino-4,6-dicyano-2,3-di(*p*-ethylphenyl)benzoate (1g): mp 192−193 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (d, J = 7.2 Hz, 2H, *p*-EtC_6H_4), 6.96 (d, J = 7.8 Hz, 4H, *p*-EtC_6H_4), 6.80 (d, J = 7.2 Hz, 2H, *p*-EtC_6H_4), 5.34 (s, 2H, NH_2), 3.61 (s, 3H, OCH_3), 2.59 (q, J = 7.2 Hz, 2H, CH_2), 2.55 (q, J = 7.2 Hz, 2H, CH_2), 1.18 (t, J = 7.2 Hz, 3H, CH_3), 1.15 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 150.4, 150.0, 144.2, 142.9, 140.7, 132.5, 129.2, 129.1, 128.6, 126.8, 126.6, 114.5, 113.6, 99.2, 93.3, 52.2, 27.8,27.7, 14.5, 14.3; IR (KBr) ν 3474 (s), 3366 (s), 3247 (m), 2967 (m), 2219 (m), 1744 (s), 1639 (s), 1566 (m), 1514 (w), 1449 (s), 1370 (w), 1234 (s), 1121 (w), 1027 (w), 852 (w), 792 (w) cm^{-1}. Anal. Calcd for $C_{26}H_{23}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.33; H, 4.85; N, 10.75.

Methyl 5-amino-4,6-dicyano-2,3-di(*m*-methylphenyl)benzoate (1h): mp 174−175 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.1−.95 (m, 4H, *m*-$CH_3C_6H_4$), 6.85 (t, J = 7.8 Hz, 2H, *m*-$CH_3C_6H_4$), 6.7−.70 (m, 2H, *m*-$CH_3C_6H_4$), 5.37 (s, 2H, NH_2), 3.63 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3), 2.17 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 151.1, 150.9, 141.3, 137.8, 137.4, 135.9, 135.7, 130.6, 129.9, 129.5, 128.3, 128.0, 127.7, 127.0, 126.4, 115.1, 114.3, 99.7, 94.1, 53.0, 21.3, 21.2; IR (KBr) ν 3465 (s), 3360 (s), 3240 (m), 2956 (w), 2222 (m), 1738 (s), 1634 (s), 1567 (m), 1444 (s), 1370 (w), 1310 (vw), 1239 (s), 1092 (vw), 1031 (w), 786 (w) cm^{-1}. Anal. Calcd for $C_{24}H_{19}N_3O_2$: C, 76.26; H, 5.66; N, 10.26. Found: C, 75.94; H, 5.81; N, 10.61.

Methyl 5-amino-4,6-dicyano-2,3-di(*p*-methoxyphenyl)benzoate (1i): mp 220−222 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (s, 2H, *p*-$OCH_3C_6H_4$), 6.8−6.9 (m, 6H, *p*-$OCH_3C_6H_4$), 5.35 (s, 2H, NH_2), 3.77 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 159.8, 158.9, 150.9, 150.7, 141.6, 131.1, 130.8, 129.6, 128.2, 128.0, 115.3, 114.3, 113.7, 113.5, 100.0, 93.9, 55.2, 55.1, 53.1; IR (KBr) ν 3457 (s), 3342 (s), 3240 (m), 2953 (w), 2841 (w), 2223 (m), 1740 (s), 1642 (s), 1612 (s), 1567 (m), 1516 (s), 1446 (s), 1371 (w), 1296 (m), 1247 (vs), 1179 (s), 1116 (w), 1031 (m), 844 (w) cm^{-1}. Anal. Calcd for $C_{24}H_{19}N_3O_4$: C, 69.72; H, 4.64; N, 10.16. Found: C, 79.45; H, 4.99; N, 9.67.

2. Typical Procedure for a One-Pot, Four-Component Reaction Involving Pyridine, Chloroacetonitrile, Malononitrile, and Aromatic Aldehyde. A mixture of pyridine (20.0 mmol, 1.58 g), chloroacetonitrile (2.0 mmol, 0.151 g), aromatic aldehyde (4.0 mmol), and malononitrile (4.0 mmol, 0.264 g) in acetonitrile (20 mL) was refluxed for 24 h. The solvent was removed by evaporation, and the residue was titrated with ethanol (10 mL) to give the crude product, which was purified by TLC thin-layer chromatography with chloroform and light petroleum as elute and then recrystallized from ethanol to give the pure product for analysis.

2a: Ar = C_6H_5; mp >300 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 1H, NC_5H_4), 7.54 (t, J = 7.8 Hz, 1H, NC_5H_4), 7.42 (s, 3H, C_6H_5), 7.34 (d, J = 6.6 Hz, 1H, NC_5H_4), 7.27 (s, 3H, C_6H_5), 7.20 (t, J = 6.6 Hz, 2H, C_6H_5), 7.16 (t, J = 6.6 Hz, 2H, C_6H_5), 6.64 (t, J = 6.6 Hz, 1H, NC_5H_4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.9, 144.5, 137.7, 134.9, 132.3, 132.5, 132.0, 129.9, 128.9, 128.8, 127.9, 127.6, 126.9, 118.2, 115.2, 113.6, 111.7, 105.3; IR (KBr) ν 3433 (m), 3355 (s), 3254 (m), 2986 (w), 2220 (m), 1726 (m), 1647 (m), 1565 (m), 1453 (m), 1374 (m), 1353 (w), 1304 (m), 1230 (s), 1123 (w), 1074 (m), 1034 (m), 865 (w), 790 (m), 755 (m), 702 (m) cm^{-1}. Anal. Calcd for $C_{25}H_{14}N_4$: C, 81.06; H,3.81; N, 15.13. Found: C, 79.83, H, 4.25; N, 15.80.

2b: Ar = *p*-$CH_3C_6H_4$; mp >300 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, J = 7.2 Hz, 1H, NC_5H_4), 7.55 (t, J = 7.2 Hz, 1H, NC_5H_4), 7.37 (d, J = 7.2 Hz, 1H, *p*-$CH_3C_6H_4$), 7.22 (d, J = 7.2 Hz, 2H, NC_5H_4), 7.0−.03 (m, 6H, *p*-$CH_3C_6H_4$), 2.41 (s, 3H, CH_3), 2.31 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.8, 144.4, 138.7, 137.9, 137.6, 132.7, 132.1, 131.8, 123.0, 129.8, 129.4, 129.2, 128.7, 128.3, 127.0, 118.1, 115.3, 113.8, 113.6, 111.5, 105.1, 20.9, 20.7; IR (KBr) ν 3425 (m), 3049 (m), 2228 (s), 1642 (s), 1489 (vs), 1444 (m), 1388 (s), 1358 (s), 1249 (s), 1148 (s), 841 (m), 785 (vs), 763 (m) cm^{-1}. Anal. Calcd for $C_{27}H_{18}N_4$: C, 81.39; H, 4.55; N, 14.06. Found: C, 81.24; H, 4.46; N, 13.87.

2c: Ar = *p*-ClC_6H_4; mp >300 °; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.95 (d, J = 8.4 Hz, 1H, NC_5H_4), 7.79 (t, J = 8.4 Hz, 1H,

NC_5H_4), 7.55 (d, J = 8.4 Hz, 2H, NC_5H_4), 7.4−7.39 (m, 5H, p-ClC_6H_4), 7.31 (d, J = 8.4 Hz, 2H, p-ClC_6H_4), 7.01 (t, J = 7.2 Hz, 1H, p-ClC_6H_4); IR (KBr) ν 3425 (w), 3123 (w), 2229 (m), 1640 (m), 1489 (s), 1444 (m), 1387 (m), 1359 (m), 1329 (m), 1313 (m), 1248 (m), 1199 (w), 1153 (w), 1091 (m), 1015 (m), 883 (w), 824 (m), 764 (m) cm^{-1}. Anal. Calcd for $C_{25}H_{12}Cl_2N_4$: C, 68.35; H, 2.76; N, 12.75. Found: C, 68.31, H, 3.10; N, 12.57.

2d: Ar = m-ClC_6H_4; mp >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.97 (b, 1H, NC_5H_4), 7.80 (b, 1H, NC_5H_4), 7.45−7.35 (m, 8H, m-ClC_6H_4), 7.01 (b, 2H, NC_5H_4). Anal. Calcd for $C_{25}H_{12}Cl_2N_4$: C, 68.35; H, 2.76; N, 12.75. Found: C, 68.08, H, 2.81; N, 12.64.

2e: Ar = p-BrC_6H_4; mp >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.94 (d, J = 9.6 Hz, 1H, NC_5H_4), 7.78 (t, J = 8.4 Hz, 1H, p-BrC_6H_4), 7.68 (d, J = 8.4 Hz, 2H, p-BrC_6H_4), 7.54 (d, J = 8.4 Hz, 2H, p-BrC_6H_4), 7.38 (d, J = 7.2 Hz, 1H, p-BrC_6H_4), 7.33 (d, J = 8.4 Hz, 2H, p-BrC_6H_4), 7.23 (d, J = 7.2 Hz, 2H, p-BrC_6H_4), 7.01 (t, J = 6.6 Hz, 1H, p-BrC_6H_4); IR (KBr) ν 3425 (w), 2226 (m), 1641 (m), 1488 (s), 1443 (m), 1384 (m), 1357 (m), 1329 (m), 1312 (m), 1247 (m), 1074 (m), 1011 (m), 849 (w), 821 (m), 763 (m) cm^{-1}. Anal. Calcd for $C_{25}H_{12}Br_2N_4$: C, 56.85; H, 2.29; N, 10.61. Found: C, 56.98, H, 2.47; N, 10.49.

2f: Ar = m-BrC_6H_4; mp >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.97 (d, J = 9.6 Hz, 1H, m-BrC_6H_4), 7.83 (t, J = 8.4 Hz, 1H, m-BrC_6H_4), 7.6−.28 (m, 9H, m-BrC_6H_4), 7.02 (t, J = 6.6 Hz, 1H, m-BrC_6H_4); IR (KBr) ν 3424 (m), 2229 (m), 1641 (m), 1560 (m), 1485 (s), 1387 (m), 1355 (w), 1328 (m), 1312 (m), 1245 (m), 1128 (m), 1065 (m), 900 (w), 841 (m), 783 (s), 758 (m), 740 (m) cm^{-1}. Anal. Calcd for $C_{25}H_{12}Br_2N_4$: C, 56.85; H, 2.29; N, 10.61. Found: C, 56.62, H, 2.38; N, 10.27.

2g: Ar = p-$CH_3OC_6H_4$; mp >300 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 1H, NC_5H_4), 7.55 (t, J = 6.6 Hz, 1H, NC_5H_4), 7.46 (d, J = 7.2 Hz, 1H, p-$CH_3OC_6H_4$), 7.08 (q, J = 8.4 Hz, 2H, p-$CH_3OC_6H_4$), 6.94 (d, J = 8.4 Hz, 2H, NC_5H_4), 6.80 (d, J = 8.4 Hz, 2H, p-$CH_3OC_6H_4$), 6.66 (t, J = 7.2 Hz, 1H, p-$CH_3OC_6H_4$), 3.86 (s, 3H, OCH_3), 3.79(s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 158.8, 151.8, 144.4, 132.6, 131.9, 131.2, 130.2, 129.4, 127.3, 127.0, 118.1, 115.4, 114.2, 113.1, 111.6, 105.0. Anal. Calcd for $C_{27}H_{18}N_4O_2$: C, 75.34; H, 4.21; N, 13.02. Found: C, 75.53; H, 4.67; N,12.75.

2h: Ar = m-$CH_3C_6H_4$; mp >300 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 1H, NC_5H_4), 7.53 (d, J = 7.8 Hz, 1H, NC_5H_4), 7.35 (d, J = 7.2 Hz, 1H, NC_5H_4), 7.29 (d, J = 7.8 Hz, 1H, m-$CH_3C_6H_4$), 7.22 (d, J = 7.2 Hz, 1H, m-$CH_3C_6H_4$), 7.14 (t, J = 7.2 Hz, 1H, m-$CH_3C_6H_4$), 7.06 (d, J = 7.8 Hz, 1H, m-$CH_3C_6H_4$), 6.9−.96 (m, 4H, m-$CH_3C_6H_4$), 6.63 (t, J = 7.2 Hz, 1H, NC_5H_4), 2.31 (s, 3H, CH_3), 2.26 (s, 3H, CH_3); IR (KBr) ν 3433 (s), 2921 (w), 2227 (w), 1641 (m), 1488 (vs), 1387 (m), 1323 (m), 1246 (m), 1134 (w), 834 (w), 749 (m), 701 (w) cm^{-1}. Anal. Calcd for $C_{27}H_{18}N_4$: C, 81.39; H, 4.55; N, 14.06. Found: C, 81.56; H, 4.71; N, 13.65.

2i: Ar = p-$C_2H_5C_6H_4$; mp >300 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 1H, NC_5H_4), 7.53 (d, J = 7.8 Hz, 1H, NC_5H_4), 7.39 (d, J = 7.2 Hz, 1H, NC_5H_4), 7.23 (d, J = 7.8 Hz, 2H, p- $C_2H_5C_6H_4$), 7.1−.04 (m, 6H, p-$C_2H_5C_6H_4$), 6.64 (t, J = 7.2 Hz, 1H, NC_5H_4), 2.70 (q, J = 7.8 Hz, 2H, CH_2), 2.60 (q, J = 7.8 Hz, 2H, CH_2), 1.26 (t, J = 7.8 Hz, 3H, CH_3), 1.18 (t, J = 7.8 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.3, 145.5, 144.8, 144.2, 138.4, 133.4, 132.7, 132.6, 130.5, 130.4, 123.0, 129.3, 128.7, 127.7, 127.5, 118.4, 115.9, 114.3, 114.0, 11.2, 105.2, 28.6, 28.5, 15.3, 15.1; IR (KBr) ν 2970 (m), 2225 (s), 1642 (s), 1486 (vs), 1394 (s), 1332 (vs), 1249 (s), 1146 (m), 1069 (m), 831 (m), 762 (s) cm^{-1}. Anal. Calcd for $C_{29}H_{22}N_4$: C, 81.66; H, 5.20; N, 13.14. Found: C, 81.53; H, 5.08; N, 12.77.

2j: Ar = p-i-PrC_6H_4; mp >300 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.82 (d, J = 8.4 Hz, 1H, NC_5H_4), 7.54 (d, J = 7.2 Hz, 1H, NC_5H_4), 7.48 (d, J = 7.2 Hz, 1H, NC_5H_4), 7.24 (d, J = 7.8 Hz, 2H, p-i-PrC_6H_4), 7.08 (d, J = 8.4 Hz, 4H, p-i-PrC_6H_4), 7.03 (d, J = 7.8 Hz, 2H, p-i-PrC_6H_4), 6.64 (t, J = 7.2 Hz, 1H, NC_5H_4), 2.9−2.92 (m, 1H, CH), 2.8−.82 (m, 1H, CH), 1.25 (d, J = 6.6 Hz, 6H, CH_3), 1.18 (d, J = 7.2 Hz, 6H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.3, 150.2, 148.8, 144.8, 138.6, 133.5, 132.8, 132.6, 130.7, 130.4, 129.6, 129.4, 127.7, 127.1, 125.9, 118.4, 115.9, 114.3, 113.8, 112.1, 105.2, 33.9, 33.1, 23.9, 23.8; IR (KBr) ν 3426 (w), 2960 (s), 2228 (s), 1642 (s), 1487 (vs), 1388 (s), 1360 (m),1310 (s), 1245 (s), 1202 (w), 1129 (m), 1053 (m), 854 (m), 761 (s), 740 (m), 647 (w), 616 (w), 503 (w) cm^{-1}. Anal. Calcd for $C_{31}H_{26}N_4$: C, 81.91; H, 5.77; N, 12.33. Found: C, 82.02; H, 5.83; N, 12.10.

2k: Ar = p-t-BuC_6H_4; mp >300 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 1H, NC_5H_4), 7.53 (d, J = 7.2 Hz, 2H, NC_5H_4), 7.36 (d, J = 8.4 Hz, 2H, p-t-BuC_6H_4), 7.18 (d, J = 8.4 Hz, 2H, p-t-BuC_6H_4), 7.03 (d, J = 8.4 Hz, 2H, p-t-BuC_6H_4), 6.99 (d, J = 8.4 Hz, 2H, p-t-BuC_6H_4), 6.64 (t, J = 7.2 Hz, 1H, NC_5H_4), 1.28 (s, 9H, CH_3), 1.22 (s, 9H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.9, 132.8, 130.2, 127.7, 125.9, 124.8, 118.5, 117.1, 116.0, 111.9, 114.1, 34.7, 31.2. Anal. Calcd for $C_{33}H_{30}N_4$: C, 82.13; H, 6.27; N, 11.60. Found: C, 82.37, H, 6.48; N, 11.54.

2l: Ar = p-FC_6H_4; mp >300 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 1H, NC_5H_4), 7.57 (t, J = 7.2 Hz, 1H, NC_5H_4), 7.40 (d, J = 6.6 Hz, 1H, NC_5H_4), 7.21−7.12 (m, 6H, p-FC_6H_4), 6.99 (t, J = 8.4 Hz, 2H, p-FC_6H_4), 6.71 (t, J = 6.6 Hz, 1H, NC_5H_4); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.3, 161.6, 161.3, 152.0, 144.6, 136.8, 132.3, 131.7, 131.5, 130.9, 130.8, 129.1, 128.8, 128.7, 126.7, 118.4, 116.4, 116.2, 115.1, 114.9, 113.6, 113.4, 112.1, 105.5; IR (KBr) ν 3484 (m), 3034 (m), 2226 (w), 2197 (m), 1643 (m), 1600 (s), 1514 (s), 1486 (vs), 1388 (m), 1358 (w), 1314 (m), 1238 (s), 1223 (s), 1160 (s), 1097 (m), 1066 (w), 850 (w), 838 (m), 775 (m). Anal. Calcd for $C_{25}H_{12}N_4F_2$: C, 73.88; H, 2.98; N, 13.79. Found: C, 73.76, H, 3.12; N, 13.76.

3b: Ar = p-$CH_3C_6H_4$; mp 136−137 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, J = 7.8 Hz, 2H, p-$CH_3C_6H_4$), 7.04 (d, J = 7.8 Hz, 2H, p-$CH_3C_6H_4$), 6.95 (d, J = 7.8 Hz, 2H, p-$CH_3C_6H_4$), 6.89 (d, J = 7.8 Hz, 2H, p-$CH_3C_6H_4$), 5.50 (s, 2H, NH_2), 2.31 (s, 3H, CH_3), 2.29 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.4, 150.9, 139.5, 138.6, 135.9, 132.2, 131.5, 129.9, 129.2, 129.1, 112.0, 114.9, 114.6, 113.6, 102.7, 98.3, 21.4, 21.3; IR (KBr) ν 3415 (m), 3347 (vs), 3248 (s), 2923 (w), 2222 (m), 1655 (vs), 1562 (vs), 1560 (w), 1451 (vs), 1268 (vs), 1188 (w), 1120 (w), 1023 (w), 847 (w), 820 (w), 765 (m) cm^{-1}. Anal. Calcd for $C_{23}H_{16}N_4$: C, 79.29; H, 4.63; N, 16.08. Found: C, 78.85; H, 4.48; N, 15.80.

3g: Ar = p-$CH_3OC_6H_4$; mp 125−126 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, J = 8.4 Hz, 2H, p-$CH_3OC_6H_4$), 6.93 (d, J = 8.4 Hz, 2H, p-$CH_3OC_6H_4$), 6.8−.77 (m, 4H, p-$CH_3OC_6H_4$), 5.46 (s, 2H, NH_2), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3); IR (KBr) ν 3442 (s), 2922 (w), 2221 (w), 1638 (m), 1609 (s), 1567 (w), 1516 (m), 1453 (m), 1293 (m), 1253 (vs), 1180 (s), 1129 (m), 841 (w). Anal. Calcd for $C_{23}H_{16}N_4O_2$: C, 72.62; H, 4.24; N, 14.73. Found: C, 72.49, H, 4.57; N, 14.47.

3l: Ar = p-FC_6H_4; mp 222−224 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.04−6.97 (m, 8H, p-FC_6H_4), 5.57 (s, 2H, NH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.4, 163.1, 161.8, 161.4, 150.4, 149.6, 134.1, 131.5, 131.4, 130.8, 130.7, 130.4, 129.7, 119.7, 115.6, 115.5, 115.4, 115.3, 113.9, 113.6, 112.7, 102.2, 98.4; IR (KBr) ν 3392 (vs), 3348 (vs), 3248 (vs), 2226 (m), 1661 (s), 1604 (m), 1568 (m), 1513 (s), 1454 (s), 1267 (s), 1229 (vs), 1160 (m), 1199 (w), 834 (m), 799 (w). Anal. Calcd for $C_{21}H_{10}N_4F_2$: C, 70.78; H, 2.83; N, 15.72. Found: C, 70.98, H, 2.95; N, 15.61.

4b: Ar = p-$CH_3C_6H_4$; mp 269−270 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.62 (s, 1H, NH), 7.48 (d, J = 7.8 Hz, 2H, p-$CH_3C_6H_4$), 7.40 (d, J = 7.8 Hz, 2H, p-$CH_3C_6H_4$), 7.03−6.97 (m, 8H, p-$CH_3C_6H_4$), 6.70 (s, 2H, NH_2), 2.42 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.23 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 107.8, 138.7, 138.2, 136.4, 136.1, 136.1, 134.3, 132.1, 131.0, 130.9, 130.8, 130.0, 127.9, 129.2, 128.5, 128.4, 127.0, 119.4, 115.8, 103.0, 65.1, 56.5, 21.4, 21.3, 21.2, 19.0; IR (KBr) ν 3452 (m), 3334 (s), 3026 (w), 2203 (vs), 1639 (vs), 1556 (vs), 1517 (m), 1485 (w), 1396 (m), 1308 (w), 1183 (w), 1115 (w), 1020 (w), 819 (m), 750 (m) cm^{-1}. Anal. Calcd for $C_{33}H_{30}N_4O(C_{31}H_{24}N_4 \cdot C_2H_5OH)$: C, 79.49; H, 6.06; N, 11.24. Found: C, 79.36; H, 5.72; N, 11.40.

4c: Ar = *p*-ClC_6H_4; mp 246−247 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.77 (s, 1H, NH), 7.54−6.71 (m, 12H, *p*-ClC_6H_4), 4.20 (s, 2H, NH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ 158.1, 137.4, 136.9, 135.6, 134.3, 133.6, 132.9, 132.7, 132.7, 132.5, 132.0, 131.1, 129.5, 128.7, 128.1, 128.0, 126.0, 119.0, 115.7, 102.6, 79.6, 65.0, 56.5, 19.0; IR (KBr) ν 3312 (s), 3187 (s), 2969 (m), 2208 (vs), 1643 (vs), 1554 (vs), 1498 (vs), 1448 (m), 1393 (s), 1315 (m), 1176 (w), 1090 (vs), 1044 (m), 1015 (s), 878 (w), 854 (s), 764 (s), 723 (w) cm^{-1}. Anal. Calcd for $C_{30}H_{21}N_4OCl_3(C_{28}H_{15}N_4Cl_3 \cdot C_2H_5OH)$: C, 64.36; H, 3.78; N, 10.01. Found: C, 64.14; H, 3.29; N, 9.87.

4j: Ar = *p*-*i*-PrC_6H_4; mp >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.51 (s, 1H, NH), 7.54 (d, J = 8.4 Hz, 2H, *p*-*i*-PrC_6H_4), 7.48 (d, J = 7.8 Hz, 2H, *p*-*i*-PrC_6H_4), 7.01 (d, J = 8.4 Hz, 6H, *p*-*i*-PrC_6H_4), 6.95 (d, J = 7.8 Hz, 2H, *p*-*i*-PrC_6H_4), 6.65 (s, 2H, NH_2), 2.99−3.06 (m, 1H, CH), 2.77−2.83 (m, 2H, CH), 1.30 (d, J = 7.2 Hz, 6H, CH_3), 1.12 (d, J = 6.6 Hz, 12H, CH_3); IR (KBr) ν 3422 (s), 3307 (s), 3187 (s), 2962 (s), 2212 (vs), 1644 (s), 1555 (s), 1460 (m), 1399 (m), 1040 (s), 877 (w), 834 (m), 555 (w) cm^{-1}. Anal. Calcd for $C_{37}H_{36}N_4$: C, 82.80; H, 6.76; N, 10.44. Found: C, 82.45; H, 6.92; N, 9.75.

3. Typical Procedure for a One-Pot, Four-Component Reaction Involving 3-Picoline, Chloroacetonitrile, Malononitrile, and Aromatic Aldehyde. A mixture of 3-picoline (20.0 mmol, 1.66 g), chloroacetonitrile (2.0 mmol, 0.151 g), aromatic aldehyde (4.0 mmol), and malononitrile (4.0 mmol, 0.264 g) in acetonitrile (20 mL) was refluxed for 24 h. The solvent was removed by evaporation, and the residue was titrated with ethanol (10 mL) to give the crude product, which was purified by TLC with chloroform and light petroleum as elute and then recrystallized from ethanol to give the pure product for analysis.

5a: Ar = C_6H_5; mp >300 °C; IR (KBr) 3432 (m), 3058 (w), 2225 (m), 1636 (m), 1575 (w), 1482 (vs), 1391 (s), 1312 (s), 1275 (w), 1250 (m), 1202 (w), 1160 (w), 1113 (vw), 1074 (m), 750 (s), 699 (s) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 6.6 Hz, 3H, NC_5H_3, C_6H_5), 7.32 (d, J = 6.6 Hz, 1H, NC_5H_3), 7.25 (br, 3H, C_6H_5), 7.20−7.15 (m, 5H, C_6H_5), 6.54 (t, J = 6.6 Hz, 1H, NC_5H_3), 2.75 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.6, 144.3, 137.5, 135.1, 133.0, 132.4, 130.0, 129.0, 128.7, 128.5, 127.8, 127.6, 124.5, 115.3, 113.9, 113.4, 111.6, 105.4, 17.1; MS (APCI+): m/z = 386.13.

5b: Ar = *p*-$CH_3C_6H_4$; mp >300 °C; IR (KBr) 3446 (w), 3123 (w), 2920 (w), 2225 (m), 1635 (m), 1571 (w), 1517 (w), 1482 (vs), 1388 (s), 1358 (w), 1326 (s), 1248 (m), 1192 (w), 1162 (w), 1111 (w), 1071 (m), 815 (s), 757 (w) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (d, J = 6.6 Hz, 1H, NC_5H_4), 7.22 (s, 1H, NC_5H_4), 7.20 (d, J = 7.8 Hz, 2H, *p*-$CH_3C_6H_4$), 7.06−7.02 (m, 6H, *p*-$CH_3C_6H_4$), 6.54 (t, J = 7.2 Hz, 1H, NC_5H_4), 2.74 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.30 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5, 144.8, 144.3, 143.6, 137.8, 132.8, 132.3, 130.2, 129.9, 129.8, 128.9, 128.3, 128.0, 126.9, 124.6, 115.5, 114.0, 113.4, 111.4, 28.1, 28.0, 17.0, 14.7, 14.6; MS (APCI+) m/z = 414.27.

5c: Ar = *p*-ClC_6H_4; mp >300 °C; IR (KBr) 3449 (w), 2226 (m), 1637 (m), 1486 (vs), 1385 (s), 1308 (s), 1249 (m), 1161 (w), 1091 (s), 1017 (m), 825 (m), 778 (m), 752 (m) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2H, NC_5H_3, *p*-ClC_6H_4), 7.36 (d, J = 6.6 Hz, 1H, NC_5H_3), 7.28 (d, J = 8.4 Hz, 3H, *p*-ClC_6H_4), 7.12 (d, J = 7.8 Hz, 2H, *p*-ClC_6H_4), 7.08 (d, J = 8.4 Hz, 2H, *p*-ClC_6H_4), 6.03 (t, J = 6.6 Hz, 1H, NC_5H_3), 2.76 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.8, 144.5, 136.0, 135.2, 134.4, 133.3, 131.2, 130.9, 130.3, 130.1, 129.2, 128.8, 128.2, 124.1, 114.9, 113.5, 113.3, 112.0, 106.1, 16.9; MS (APCI+) m/z = 454.27.

5d: Ar = *p*-BrC_6H_4; mp >300 °C; IR (KBr) 3423 (w), 3133 (w), 2226 (m), 1633 (m), 1575 (w), 1484 (vs), 1385 (s), 1310 (s), 1247 (m), 1199 (w), 1161 (w), 1109 (w), 1070 (s), 1009 (s), 822 (m), 777 (m), 753 (m) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 7.8 Hz, 2H, *p*-BrC_6H_4), 7.43 (d, J = 7.2 Hz, 2H, *p*-BrC_6H_4), 7.35 (d, J = 7.2 Hz, 1H, NC_5H_3), 7.24 (d, J = 7.8 Hz, 1H, NC_5H_3), 7.05 (d, J = 7.8 Hz, 2H, *p*-BrC_6H_4), 7.01 (d, J = 7.8 Hz, 2H, *p*-BrC_6H_4), 6.62 (t, J = 6.6 Hz, 1H, NC_5H_3), 2.75 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.8, 144.5, 135.9, 132.2, 131.7, 131.5, 131.1, 130.5, 130.1, 124.1, 123.4, 122.7, 114.9, 113.5, 112.0, 16.9; MS(APCI+) m/z = 543.60.

5e: Ar = *p*-FC_6H_4; mp >300 °C; IR (KBr): 3446 (m), 2228 (m), 1637 (m), 1605 (m), 1514 (vs), 1482 (vs), 1388 (s), 1361 (w), 1309 (s), 1237 (s), 1161 (s), 1073 (w), 1018 (w), 844 (m), 805 (w), 752 (m) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, J = 6.6 Hz, 1H, NC_5H_3), 7.24 (s, 1H, NC_5H_3), 7.17−7.11(m, 6H, *p*-FC_6H_4), 6.98 (t, J = 8.4 Hz, 2H, *p*-FC_6H_4), 6.60 (t, J = 6.6 Hz, 1H, NC_5H_3), 2.75 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2, 161.6, 152.7, 144.5, 136.5, 131.8, 131.7, 130.9, 130.8, 130.0, 128.8, 124.1, 116.2, 116.1, 115.0, 114.9, 113.5, 111.9, 105.8, 16.9; MS (APCI+) m/z = 422.13.

5f: Ar = *p*-$CH_3OC_6H_4$; mp 282−283 °C; IR (KBr) 3426 (w), 2933 (w), 2837 (w), 2225 (m), 1609 (s), 1516 (s), 1481 (m), 1456 (m), 1387 (m), 1291 (m), 1251 (vs), 1179 (s), 1112 (w), 1073 (w), 1028 (m), 840 (m), 792 (w), 752 (w) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, J = 6.0 Hz, 2H, NC_5H_3), 7.06 (d, J = 6.6 Hz, 4H, *p*-$CH_3OC_6H_4$), 6.92 (d, J = 7.8 Hz, 2H, *p*-$CH_3OC_6H_4$), 6.79 (d, J = 7.8 Hz, 2H, *p*-$CH_3OC_6H_4$), 6.56 (t, J = 6.6 Hz, 1H, NC_5H_3), 3.86 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.74 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 158.8, 152.5, 144.2, 137.7, 132.6, 131.2, 130.2, 129.9, 128.3, 127.5, 125.0, 124.6, 115.6, 114.1, 113.1, 111.5, 54.8, 54.7, 17.0; MS (APCI-) m/z = 444.80.

5g: Ar = *p*-$C_2H_5C_6H_4$; mp >300 °C; IR (KBr) 3424 (w), 3125 (w), 2967 (m), 2928 (m), 2225 (m), 1634 (m), 1573 (w), 1516 (w), 1481 (vs), 1387 (s), 1313 (s), 1248 (m), 1201 (w), 1161 (w), 1113 (w), 1071 (m), 832 (m), 754 (m) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (d, J = 6.6 Hz, 1H, NC_5H_4), 7.24 (d, J = 7.2 Hz, 1H, NC_5H_4), 7.21 (d, J = 7.2 Hz, 2H, *p*-$C_2H_5C_6H_4$), 7.05 (q, J = 7.2 Hz, 6H, *p*-$C_2H_5C_6H_4$), 6.54 (t, J = 7.2 Hz, 1H, NC_5H_4), 2.73 (s, 3H, CH_3), 2.69 (q, J = 7.2 Hz, 2H, CH_2), 2.60 (q, J = 7.2 Hz, 2H, CH_2), 1.25 (t, J = 7.8 Hz, 3H, CH_3), 1.19 (t, J = 7.8 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5, 149.5, 148.2, 144.3, 138.0, 132.8, 132.4, 130.4, 129.9,129.8, 129.7, 129.0, 128.3, 128.1, 126.9, 126.5, 125.4, 124.6, 115.5, 114.1, 113.2, 111.4, 105.0, 33.4, 33.2, 23.3, 23.2, 17.0; MS (APCI+) m/z = 442.33.

5h: Ar = *m*-$CH_3C_6H_4$; mp 276−277 °C; IR (KBr) 3435 (s), 3126 (w), 3041 (w), 2921 (w), 2225 (m), 1636 (m), 1482 (vs), 1389 (s), 1328 (s), 1276 (w), 1251 (m), 1164 (w), 1075 (w), 774 (m), 751 (s), 695 (w) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (s, 1H, NC_5H_3), 7.20 (br, 2H, NC_5H_3, *m*-$CH_3C_6H_4$), 7.13−6.97(m, 7H, *m*-$CH_3C_6H_4$), 6.55 (br, 1H, NC_5H_3), 2.74 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.26 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5, 144.2, 138.5, 137.7, 137.0, 135.0, 132.9, 132.7, 130.7, 130.0, 129.6, 129.4, 129.3, 128.5, 128.3, 127.3, 127.1, 125.9, 124.6, 115.4, 114.0, 113.2, 111.6, 104.9, 20.9, 20.8, 17.0; MS (APCI-) m/z = 413.40.

5i: Ar = *p*-*i*-PrC_6H_4; mp >300 °C; IR (KBr) 3425 (m), 3122 (w), 2960 (s), 2925 (m), 2225 (m), 1635 (m), 1481 (vs), 1388 (vs), 1309 (s), 1272 (w), 1249 (m), 1201 (w), 1161 (w), 1111 (w), 1053 (m), 788 (w), 755 (m) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (t, J = 7.8 Hz, 2H, NC_5H_4), 7.21 (d, J = 7.8 Hz, 2H, *p*-*i*-PrC_6H_4), 7.06 (d, J = 7.8 Hz, 2H, *p*-*i*-PrC_6H_4), 7.03 (t, J = 8.4 Hz, 4H, *p*-*i*-PrC_6H_4), 6.54 (t, J = 7.2 Hz, 1H, NC_5H_4), 2.95−2.90 (m, 1H, CH), 2.85−2.81 (m, 1H, CH), 2.74 (s, 3H, CH_3), 1.24 (d, J = 6.6 Hz, 6H, CH_3), 1.18 (d, J = 6.6 Hz, 6H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5, 144.2, 138.5, 137.8, 137.5, 132.6, 132.2, 130.0, 129.8, 129.4, 128.8, 128.3, 124.6, 115.5, 114.0, 113.5, 111.4, 105.1, 20.9, 20.8, 17.0; MS (APCI+) m/z = 470.33.

6a: mp 237 °C; IR (KBr) 3444 (m), 3336 (vs), 3238 (s), 2222 (m), 1651 (vs), 1555 (s), 1445 (s), 1268 (vs), 1075 (w), 1030 (w), 921 (vw), 779 (vw), 722 (s), 694 (s) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (d, J = 7.2 Hz, 1H, C_6H_5), 7.28−7.24 (m, 5H, C_6H_5), 7.06 (d, J = 7.8 Hz, 2H, C_6H_5), 7.01 (d, J = 7.2 Hz, 2H, C_6H_5), 5.54 (s, 2H, NH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.7, 150.4, 135.3, 134.6, 133.9, 129.6, 128.9, 128.7, 128.3, 127.9, 119.5, 114.1, 113.8, 113.0, 102.1, 98.1; MS(APCI-): m/z =320.13.

7a: mp >300 °C; IR (KBr) 3444 (s), 3355 (s), 3230 (s), 2204 (vs), 1638 (vs), 1559 (vs), 1497 (w), 1443 (w), 1404 (m), 1355 (w), 1315 (w), 1123 (w), 1074 (w), 1030 (w), 724 (w), 699 (m) cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 10.69 (s, 1H, NH), 7.63−7.60 (m, 4H, C_6H_5), 7.57−7.54 (m, 1H, C_6H_5), 7.20−7.16 (m, 8H, C_6H_5), 7.11−7.09 (m, 2H, C_6H_5), 6.75 (s, 2H, NH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ 157.5, 138.3, 137.7, 136.5, 134.5, 130.5, 130.4, 129.6, 129.0, 127.4, 127.3, 118.8, 115.2, 102.2; MS(APCI-): m/z = 410.40.

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Supporting Information Available: Single-crystal X-ray diffraction data have been deposited with the CCDC (deposition nos.: **1a**, 691943; **2b**, CCDC 691938; **3b**, CCDC 691936; **4b**, CCDC 691937; **2c**, CCDC 691941; **4c**, CCDC 691940; **2j**, 691934; **J1**, 691939; **J2**, CCDC 691935; **5a**, CCDC 703765; **5b**, CCDC703766; **5c**, CCDC 703767; **5g**, CCDC 703769 and **5i**, CCDC 703770). Experimental procedures and spectral data for all new compounds, including crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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