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RESEARCH ARTICLE

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Synthesis of Functionalized 2-Aminohydropyridines and 2-Pyridinones via Domino Reactions of Arylamines, Methyl Propiolate, Aromatic Aldehydes, and Substituted Acetonitriles

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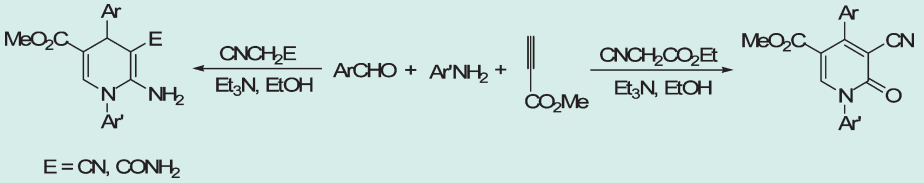
Supporting Information

ABSTRACT:



E = CN, $CONH_2$

An efficient and practical synthetic method for the functionalized 2-amino hydropyridines and 2-pyridinones was successfully developed via the domino reactions of arylamines, methyl propiolate, aromatic aldehydes and the substituted acetonitriles with triethylamine as base catalyst. Reactions involving malononitrile and cyanoacetamide gave exclusively the 2-aminohydropyridines. On the other hand ethyl cyanoacetate resulted in the 2-pyridinones as main products.

KEYWORDS: dihydropyridine, 2-pyridinone, electron-deficient alkyne, β-enamino ester, domino reaction

INTRODUCTION

1,4-Dihydropyridines present ubiquitous structural motifs, which are frequently found in natural products and in compounds for the pharmaceutical, agrochemical, and other chemical industries.[1,2] Traditional methods for synthesis of 1,4-dihydropyridines involve Hantzsch reaction,[3,4] cycloaddition reactions,[5,6] Michael condensation,[7] and others.[8,9] In the past few years, the Lewis acid-induced cyclization of enamines has become an attractive alternative method for 1,4-dihydropyridine synthesis. Vohra et al used the Lewis acid-catalyzed condensation of enamines and α,β-unsaturated aldehydes to prepare dihydropyridines.[10,11] Kikuchi et al. found the formation of 1,4-dihydropyridine derivatives from the reaction of aniline with ethyl propiolate in the presence of $Sc(OTf)_3$.[12] Under the catalysis of $TiCl_4$ β-enamino esters also cyclized to give 1,4-dihydropridines.[13] Recently, we found that the four-component reactions of aromatic aldehydes, arylamines, acetylenedicarboxylate, and acetonitrile derivatives provided an efficient method for the polysubstituted 1,4-dihydropyridines.[14] However the substrate scope and limitation of this novel domino reaction have not fully developed yet. In this text we wish to report the efficient synthesis of structurally diverse 1,4-dihydropyridine and 2-pyridinone derivatives via the domino reactions of arylamines, methyl propiolate, aromatic aldehydes, and the substituted acetonitriles.

RESULTS AND DISCUSSION

At first we carried out the reaction of methyl propiolate in four-component manner according to the previously reported procedure for the reactions of dimethyl acetylenedicarboxylate.[14] The four-component mixture of benzaldehyde, *p*-toluidine, methyl propiolate, and malononitrile with triethylamine as base catalyst in ethanol at room temperature resulted in a complicate mixture of products, which is not worthy for separation. The reason is that the addition reaction of aniline to methyl propiolate to give the adduct 3-arylaminoacrylates need more than twelve hours for completion,[15] while the addition of aniline to dimethyl acetylenedicarboxylate could be finished in 5−10 min.[16] Thus we decided first to let *p*-toluidine and methyl propiolate reacted in ethanol at room temperature for overnight. TLC analysis indicated that the addition reaction has finished and nearly merely the desired β-enamino ester existed in solution. Then benzaldehyde and malononitrile, as well as triethylamine, were added to the system, and the mixture was stirred at room temperature for additional ten hours. After workup, we are pleased to find that the expected 2-aminohydropyridine **1a** was obtained in 70% yields. Thus methyl propiolate has been successfully utilized in a one-pot domino four-component reaction. Subsequently, various aromatic aldehydes and amines were used in the reactions under the similar reaction conditions. The results are summarized in Table 1. From these results, we could see that all reactions proceeded smoothly to afford the corresponding *N*-aryl-2-aminohydropyridines **1b**−**1m** in high yields (70−88%) (Table 1). The substituents with different electronic effects on aromatic ring showed marginal effect to the reactivity and all aromatic aldehydes and arylamines reacted efficiently to give the desired products. To extend the scope of the domino reactions further, benzylamine and β-phenylethylamine were also utilized in the reaction

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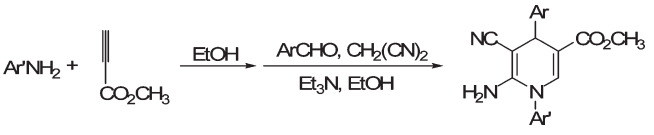
Table 1. Synthesis of Polysubstituted 2-Aminohydropyridines



entry	compd	Ar	Ar′	yield (%)
1	**1a**	C_6H_5	p-$CH_3C_6H_4$	70
2	**1b**	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	85
3	**1c**	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$	80
4	**1d**	p-$(CH_3)_2CHC_6H_4$	p-$CH_3C_6H_4$	82
5	**1e**	p-ClC_6H_4	p-$CH_3C_6H_4$	87
6	**1f**	m-$NO_2C_6H_4$	p-$CH_3C_6H_4$	80
7	**1g**	p-$CH_3C_6H_4$	C_6H_5	86
8	**1h**	p-$CH_3C_6H_4$	p-ClC_6H_4	88
9	**1i**	p-$CH_3C_6H_4$	o-$CH_3C_6H_4$	85
10	**1j**	p-$CH_3C_6H_4$	p-$CH_3OC_6H_4$	85
11	**1k**	p-$CH_3C_6H_4$	m-ClC_6H_4	70
12	**1l**	p-$CH_3C_6H_4$	m-$CH_3C_6H_4$	70
13	**1m**	p-$CH_3C_6H_4$	α-Naph	82
14	**1n**	p-$CH_3C_6H_4$	$C_6H_5CH_2$	83
15	**1o**	p-$(CH_3)_2CHC_6H_4$	$C_6H_5CH_2$	88
16	**1p**	p-$CH_3OC_6H_4$	$C_6H_5CH_2$	65
17	**1q**	p-ClC_6H_4	$C_6H_5CH_2$	87
18	**1r**	p-$CH_3C_6H_4$	$C_6H_5CH_2CH_2$	81
19	**1s**	p-$CH_3OC_6H_4$	$C_6H_5CH_2CH_2$	75
20	**1t**	C_6H_5	$C_6H_5CH_2CH_2$	78
21	**1u**	p-ClC_6H_4	$C_6H_5CH_2CH_2$	82
22	**1v**	p-BrC_6H_4	$C_6H_5CH_2CH_2$	88

and the corresponding *N*-benzyl-2-aminohydropyridines **1n**−**1q** and *N*-phenyl-2-aminoethylhydropyridines **1r**−**1v** were also prepared in satisfactory yields (65−88%). These results demonstrated that this domino reaction has a wide variety of substrates. The structures of twenty-two prepared 2-aminohydropyridines were fully characterized by elemental analysis, ^{1}H and ^{13}C NMR, MS, IR spectra, and were further confirmed by single-crystal studies performed for three representative compounds **1f**, **1k** (Figure 1), and **1t**. As observed in the molecular structure of **1k** the five carbon atoms and one nitrogen atom in hydropyridine ring exist nearly in one plane with the small degree of ring distortion from planarity. The 4-*p*-methylphenyl group is perpendicular to the hydropyridine ring and *N*-*m*-chlorophenyl exists nearly coplane to hydropyridine ring.

To explore the generality and scope of this domino reaction other substituted acetonitriles, such as ethyl cyanoacetate was also utilized in the reaction. The reaction of *p*-chlorobenzaldehyde, ethyl cyanoacetate and *β*-enamino ester derived from *p*-toluidine and methyl propiolate in ethanol with triethylamine as base catalyst resulted in the two products. After separation with thin-layer chromatography the expected 2-aminohydropyridine **2a** was obtained only in 30% yield. Another product was successfully separated in 53% yield, and its structure was assigned as 2-pyridinone **3a** after analysis. At the similar reaction conditions, various aromatic aldehydes and arylamines were used in the reactions. In some cases 2-aminohydropyridines **2b**−**2e** were obtained in lower yields and in most cases very lower yields of 2-aminohydropyridines were formed, which are not worthy to separate. But in each case the polysubstituted 2-pyridinones

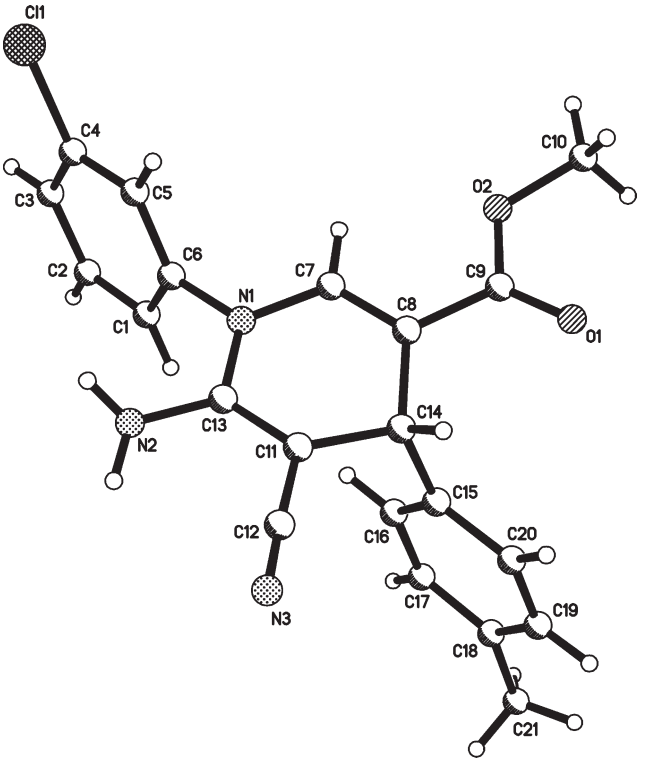


Figure 1. Molecular structure of 2-aminohydropyridine **1k**.

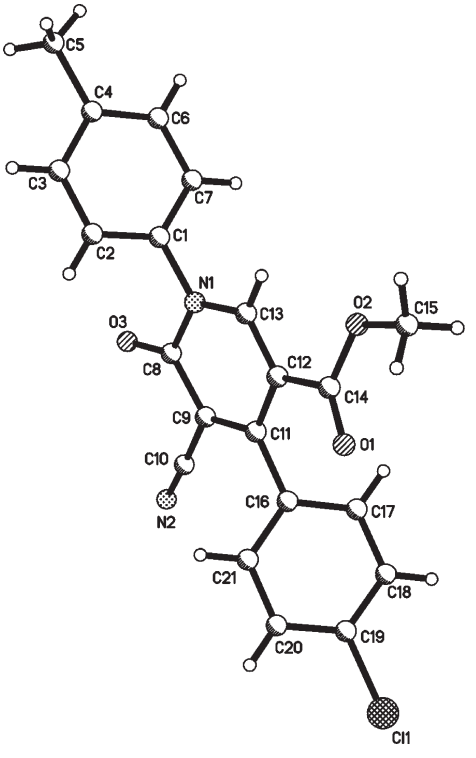


Figure 2. Molecular structure of 2-pyridinone **3a**.

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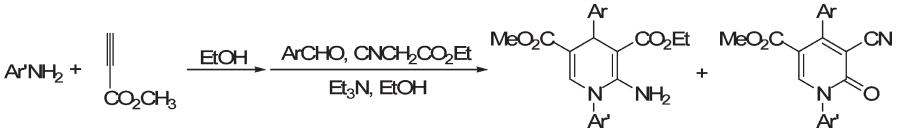
Table 2. Synthesis of Polysubstituted 2-Aminohydropyridines and 2-Pyridinones



entry	Ar	Ar′	compd **2**	yield (%)	compd **3**	yield (%)
1	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	**2a**	28	**3a**	53
2	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	**2b**	30	**3b**	51
3	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	**2c**	19	**3c**	55
4	*m*-$NO_2C_6H_4$	*p*-$CH_3C_6H_4$	**2d**	23	**3d**	43
5	*p*-$(CH_3)_2CHC_6H_4$	C_6H_5	**2e**	15	**3e**	53
6	C_6H_5	*p*-$CH_3OC_6H_4$	**2f**		**3f**	55
7	*p*-$(CH_3)_2CHC_6H_4$	*p*-$CH_3OC_6H_4$	**2g**		**3g**	56
8	*p*-ClC_6H_4	$C_6H_5CH_2$	**2h**		**3h**	58
9	*m*-$NO_2C_6H_4$	$C_6H_5CH_2$	**2i**		**3i**	50
10	*p*-$CH_3OC_6H_4$	$C_6H_5CH_2CH_2$	**2j**		**3j**	61
11	*p*-$(CH_3)_3CC_6H_4$	$C_6H_5CH_2CH_2$	**2k**		**3k**	63
12	*p*-ClC_6H_4	$C_6H_5CH_2CH_2$	**2l**		**3l**	66
13	*m*-$NO_2C_6H_4$	$C_6H_5CH_2CH_2$	**2m**		**3m**	60

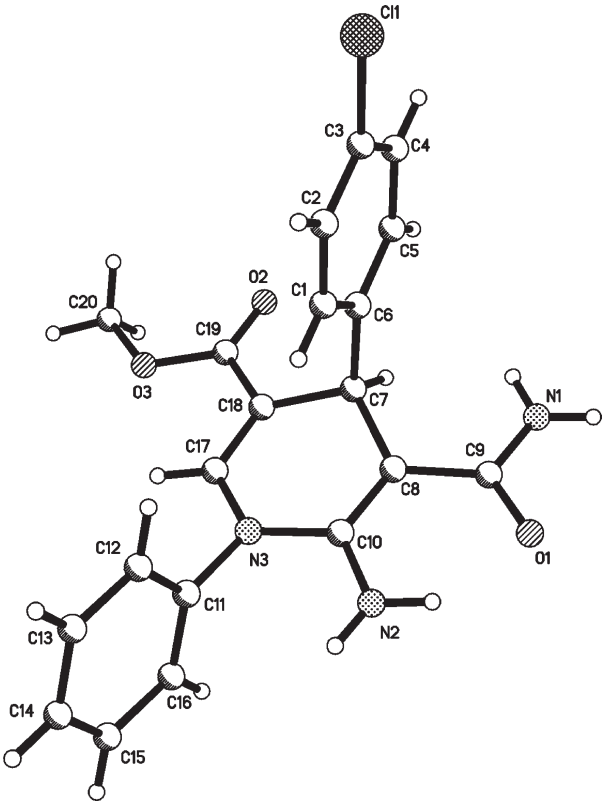
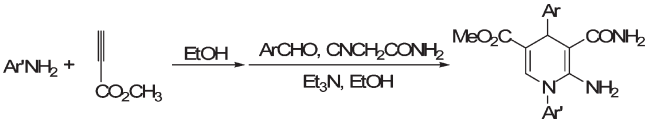


Figure 3. Molecular structure of 2-aminohydropyridine **4a**.

3b−**3m** were formed as the main products, which were separated in moderate to good yields (43−78%) (Table 2). The structures of the prepared 2-aminohydropyridines **2a**−**2e** and 2-pyridinones **3a**−**3m** were also fully characterized by spectroscopic methods and confirmed by X-ray diffraction determination of three

Table 3. Synthesis of 2-Aminohydropyridines from Reactions of Cyanoacetamide



entry	compd	Ar	Ar′	yield (%)
1	**4a**	*p*-ClC_6H_4	C_6H_5	80
2	**4b**	*m*-$NO_2C_6H_4$	C_6H_5	78
3	**4c**	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	76
4	**4d**	*m*-$NO_2C_6H_4$	*p*-$CH_3C_6H_4$	86
5	**4e**	*p*-ClC_6H_4	*m*-$CH_3C_6H_4$	76
6	**4f**	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	82
7	**4g**	*m*-ClC_6H_4	*p*-$CH_3OC_6H_4$	82
8	**4h**	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	80
9	**4i**	*p*-$(CH_3)_3CC_6H_4$	*p*-$CH_3OC_6H_4$	84

compounds **2t**, **3a** (Figure 2), and **3h**. These results indicated that ethyl cyanoacetate showed different reactivity to that of malononitrile. Formation of 2-aminohydropyridine in this reaction clearly indicated the cyano group took part in the reaction, while the formation of 2-pyridinone showed the esteric group transferred to cyclic amido group. Thus the selective synthesis of 2-aminohydropyridine and 2-pyridinone could be finished in this domino reaction.

Encouraged by the above interesting results and to shine more light on the formation mechanism of two kinds of products, cyanoacetamide was also introduced in this domino reaction. At the same conditions the reaction of aromatic aldehydes, cyanoacetamide and the in situ formed β-enamino ester proceeded smoothly to give the polysubstituted 2-aminohydropyridines

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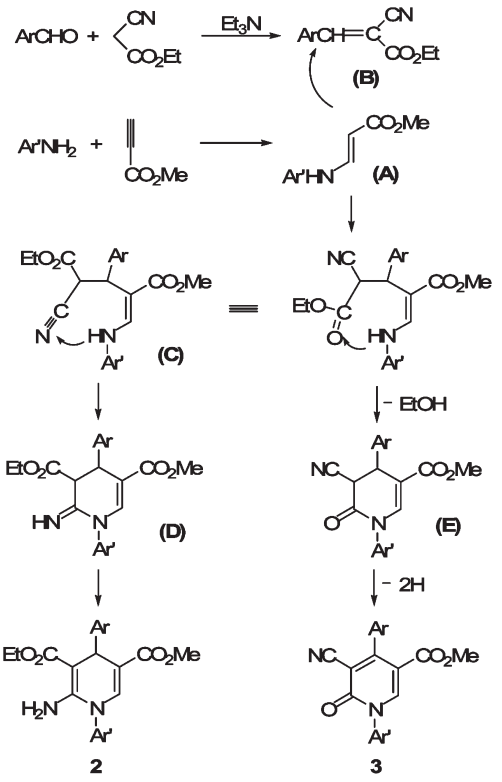
Scheme 1. Proposed Formation Mechanism of 2-Aminohydropyridine and 2-Pyridinone



(**4a**−**4i**) in 76−86% yields (Table 3). It should be pointed that the four-component reaction of aldehyde, arylamine, cyanoacetamide and dimethyl acetylenedicarboxylate is very sluggish even in refluxing ethanol and the expected 2-aminohydropyridines were only prepared in lower yields.[14] Here the reaction of methyl propiolate gave much better results. The structures of the prepared 2-aminohydropyridines (**4a**−**4i**) were fully established by spectroscopic method and confirmed by the X-ray diffraction of the single crystal **4a** (Figure 3).

To explain the mechanism of this one-pot multicomponent reaction, a plausible reaction course was proposed to account for the different products based on the reaction containing ethyl cyanoacetate, which is illustrated in Scheme 1. At first, addition of arylamine to methyl propiolate gave the key intermediate β-enamino ester **A**. Second, under the catalysis of triethylamine Knoevenagel condensation of aromatic aldehyde with ethyl cyanoacetate resulted in arylidene cyanoacetate **B**. Third, Michael addition of β-enamino ester intermediate **A** to arylidene cyanoacetate **B** yielded the addition intermediate **C**. Then, in intermediate **C**, the intramolecular nucleophilic addition of amino group to C−N triple band formed the cyclic intermediate **D**. At last the tautomerization of imino group to amino group resulted in the final product 2-aminohydropyridine **2**. On the other hand, in intermediate **C**, the amino group could also attack the ester group to give cyclic amide **E** with the elimination of ethanol, which in turn was dehydrogenated in air to give the 2-pyridinone **3** as the product. In the cases of reactions of malononitrile and cyanoacatoamide, the polysubstituted hydropyridine **1** and **4** were formed as products due to only cyano group could be attacked by amino group in the similar intermediate **C**. In this reaction course, the easily formation and high reactivity of β-enamino ester played a key factor.

CONCLUSION

In summary, we have developed a domino reaction of arylamine, methyl propiolate, aromatic aldehydes, and substituted acetonitrile based on easily formation and novel reactivity of β-enamino ester. Furthermore, we established the scope and limitation of this domino reaction and found two types of reaction modes in the reactions of ethyl cyanoacetate, which enabled further modification of the reaction to give more molecular diversity. This reaction provides a convenient and selective procedure for the preparation of functionalized 2-aminohydropyridines and 2-pyridinones. The potential uses of the reaction in synthetic and medicinal chemistry might be quite significant.

EXPERIMENTAL PROCEDURES

1. Typical Procedure for the Domino Reactions of Aromatic Aldehydes, Malononitrile, Arylamines, and Methyl Propiolate. In a round-bottom flask a mixture of arylamine (2.0 mmol) and methyl propiolate (2.0 mmol, 0.168 g) in 5.0 mL of ethanol was stirred at room temperature for 8−12 h. Then aromatic aldehyde (2.0 mmol), malononitrile (2.0 mmol, 0.144 g), and triethylamine (2.0 mmol, 0.202 g) in 5.0 mL of ethanol were added to it. The solution was stirred at room temperature for additional ten hours. The solvent was removed by rotary evaporator. The resulting oil was titrated by ethanol to give the solid product, which was collected by filtration and washed with cold alcohol to give the pure product **1a**: white solid, 70%, m.p.198−199 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.31 (m, 7H, ArH, CH), 7.22 (d, J = 6.0 Hz, 3H, ArH), 4.64 (s, 1H, CH), 4.15 (s, 2H, NH_2), 3.60 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 149.8, 145.5, 139.8, 138.6, 136.2, 131.0, 128.6, 127.3, 127.2, 126.9, 121.2, 107.4, 62.6, 51.5, 39.1, 21.2; IR (KBr) υ 3427, 3235, 3225, 3028, 2948, 2884, 2178, 1709, 1661, 1614, 1561, 1510, 1428, 1331, 1271, 1214, 1145, 1089, 1025, 828, 763 cm^{-1}; MS (m/z) 346.30 ([M + 1]$^+$) 100%. Anal. Calcd for $C_{21}H_{19}N_3O_2$: C 73.03, H 5.54, N 12.17; Found C 72.64, H 5.49, N 11.88.

2. Typical Procedure for the Domino Reaction of Aromatic Aldehydes, Ethyl Cyanoacetate, Arylamines, and Methyl Propiolate. A mixture of arylamine (2.0 mmol) and methyl propiolate (2.0 mmol, 0.168 g) in 5.0 mL of ethanol was stirred at room temperature for 8−12 h. Then aromatic aldehyde (2.0 mmol), ethyl cyanoacetate (2.0 mmol, 0.226 g), and triethylamine (2.0 mmol, 0.202 g) in 5.0 mL ethanol were added to it. The whole solution was stirred at room temperature for about ten additional hours. The solvent was removed by rotary evaporator. The resulting oil was subjected to thin-layer column chromatography with ethyl acetate and light petroleum (V/V = 1:4) as developing solvent to give the products **2** and **3** for analysis. **2a**: white solid, 28%, m.p.167−170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (brs, 4H, ArH), 7.29 (s, 1H, CH), 7.25 (brs, 2H, ArH), 7.22 (d, J = 7.2 Hz, 2H, ArH), 6.32 (brs, 2H, NH_2), 4.94 (s, 1H, CH), 4.05 (brs, 2H, CH_2), 3.62 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3), 1.19 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 167.0, 151.4, 146.4, 139.5, 138.4, 136.3, 131.5, 130.9, 129.4, 127.9, 127.5, 109.6, 80.0, 59.3, 51.3, 37.2, 21.2, 14.4; IR (KBr) υ 3729, 3458, 3233, 2980, 2353, 1704, 1672, 1595, 1505, 1438, 1370, 1340, 1303, 1238, 1197, 1084, 1034, 907, 831, 804, 760 cm^{-1}; MS (m/z) 427.23 ([M + 1]$^+$) 100%. Anal. Calcd for $C_{23}H_{23}ClN_2O_4$: C 64.71, H 5.43, N 6.56; Found C 64.57, H 5.68, N 6.27. **3a**: white solid, 53%,

m.p.234−236 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.57 (s, 1H, CH), 7.59 (d, J = 7.8 Hz, 2H, ArH), 7.45−7 0.42 (m, 4H, ArH), 7.39 (d, J = 7.8 Hz, 2H, ArH), 3.56 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 133.6, 129.2, 128.8, 127.8, 125.8, 114.4, 108.9, 104.5, 51.5, 20.2; IR (KBr) υ 3066, 2952, 2221, 1730, 1671, 1596, 1493, 1436, 1346, 1297, 1218, 1181, 1133, 1089, 990, 931, 815, 788 cm^{-1}; MS (m/z) 379.21 ($[M + 1]^+$) 100%. Anal. Calcd for $C_{21}H_{15}ClN_2O_3$: C 66.58, H 3.99, N 7.40; Found C 66.45, H 4.37, N 7.21.

3. Typical Procedure for the Domino Reactions of Aromatic Aldehydes, Cyanoacetamide, Arylamines, and Methyl Propiolate. A mixture of arylamine (2.0 mmol) and methyl propiolate (2.0 mmol, 0.168 g) in 5.0 mL of ethanol was stirred at room temperature for 8−12 h. Then aromatic aldehyde (2.0 mmol), cyanoacetamide (2.0 mmol, 0.208 g), and trietylamine (2.0 mmol, 0.202 g) in 5.0 mL of ethanol were added to it. The whole solution was stirred at room temperature for additional about ten hours. The solvent was removed by rotary evaporator. The resulting oil was titrated by ethanol to give the solid product, which was recystallized in ethanol to give the pure product **4a**: white solid, 80%, mp 202−204 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, J = 6.6 Hz, 2H, ArH), 7.48 (t, J = 6.6 Hz, 1H, ArH), 7.41 (d, J = 6.6 Hz, 2H, ArH), 7.38 (d, J = 7.2 Hz, 2H, ArH), 7.29 (d, J = 7.2 Hz, 2H, ArH), 7.23 (s, 1H, CH), 6.79 (brs, 2H, NH_2), 4.95 (s, 2H, NH_2), 4.73 (s, 1H, CH), 3.65 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3), 2.31 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.4, 166.9, 151.1, 144.7, 138.9, 132.5, 130.4, 129.3, 129.1, 128.8, 128.7, 127.8, 108.6, 79.7, 51.4, 38.4; IR (KBr) υ 3454, 3351, 3219, 2952, 1669, 1573, 1483, 1405, 1253, 1182, 1094, 1024, 900, 844, 812, 773 cm^{-1}; MS (m/z) 384.16 ($[M + 1]^+$) 100%, 386.19 ($[M + 3]^+$) 50%. Anal. Calcd for $C_{20}H_{18}ClN_3O_3$: C 62.58, H 4.73, N 10.95; Found C 62.24, H 5.11, N 10.67.

■ ASSOCIATED CONTENT

Supporting Information. Additional figures, tables, and procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

Crystallographic data (**1f**, CCDC 802248; **1k**, CCDC 802249; **1t**, CCDC 802318; **2d**, CCDC 802250; **3a**, CCDC 802251; **3h**, CCDC 802252; **4a**, CCDC 802319) have been deposited at the Cambridge Crystallographic Database Centreand is available on request from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (Fax +44-1223-336033; e-mail deposit@ccdc.cam.ac.uk or http//www.ccdc.cam.ac.uk).

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