Synthesis of New Aminonicotinate Derivatives from Acetylated Baylis–Hillman Adducts and Enamino Esters via a Consecutive [3+3]-Annulation Protocol

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Abstract: A one-pot, consecutive [3+3]-annulation protocol is described for the synthesis of new aminonicotinate derivatives from acetylated Baylis–Hillman adducts and enamino esters.

Key words: Michael addition, cyclization, isomerization, hydrolysis, heterocycles

Multisubstituted pyridines represent molecular frameworks that serve as a platform for developing pharmaceutical agents for various applications. Among these, aminopyridine and nicotinate analogues constitute an important class of compounds in organic synthesis and drug discovery.[1] A large number of aminopyridine derivatives have been reported to exhibit antitumor,[2a,b] vasodilator[2c] and anti-inflammatory[2d] activities. A few aminopyridine derivatives have recently been screened as NCX inhibitors.[2e] Moreover, aminopyridine derivatives are the key intermediates in the synthesis of the corresponding 1,8-naphthyridines,[3] 7-azaindoles,[4] oxazolopyridines[5] and imidazopyridines.[6] In addition to pharmaceutical applications, aminopyridine derivatives have been used as ligands for transition-metal complexes,[7] as fluorescent dyes[8] and also for agricultural products.[9]

A survey of the literature shows that derivatization of a 2-unsubstituted pyridine moiety in a complex molecule to the corresponding 2-aminopyridine is often desired but only achieved in a long sequence and with low efficiency.[10] There are several methods available in the literature for the synthesis of 2-aminopyridine derivatives.[11] One of the most traditional approaches is amination of 2-halopyridines and analogues with ammonia or an equivalent under high temperature (150–250 °C) and pressure.[2e,12] The second approach is the Chichibabin reaction[1b,13] where 2-aminopyridines can be directly obtained from sodium amide and pyridines. There are some limitations, however, with the procedures for the synthesis of 2-aminopyridines suffering from the use of high reaction temperatures and prolonged reaction times, poor regioselectivity and low product yields. Due to the immense biological importance, the development of simple and convenient approaches to 2-aminopyridines from easily available starting materials is very much required.

In recent years the Baylis–Hillman reaction has attracted the attention of many organic chemists, because it is a simple, straightforward method for the generation of attractive densely functionalized molecules.[14] Recently, we have reported the synthesis of Baylis–Hillman adducts and have converted them into quinolines, 1,8-naphthyridines and 2-pyridones.[15] So far, no report exists in the literature on the synthesis of aminonicotinate derivatives from Baylis–Hillman adducts. In continuation of our research on the synthesis of heterocyclic compounds and applications of Baylis–Hillman chemistry,[15,16] we now describe a facile, one-pot synthesis of aminonicotinate derivatives via treatment of acetylated Baylis–Hillman nitriles with enamino esters by way of a [3+3]-annulation process.

The starting materials, acetylated Baylis–Hillman nitriles **1a**–**g** and enamines **2a**,**b** (Table 1), were synthesized according to literature procedures.[17] Enamino ester **2a** was treated with sodium hydride in anhydrous tetrahydrofuran at room temperature, and acetylated Baylis–Hillman nitrile **1a** was added. The reaction was completed in six hours and furnished the desired product **3a** in good yield (Table 1). We have examined this reaction by using different bases (K_2CO_3, Et_3N, *t*-BuOK, NaH) and varying the equivalents, from one to three, separately. Potassium carbonate and triethylamine failed to promote the reaction, whereas in the case of potassium *tert*-butoxide the yield was lower than when sodium hydride was used. So, finally, we concluded that three equivalents of sodium hydride are suitable to promote the reaction. Encouraged by this result, we have successfully transformed several representative acetylated Baylis–Hillman nitriles **1b**–**g** via treatment with enamino ester **2a** or **2b** into the desired substituted aminonicotinate derivatives **3b**–**j** in good yields (Table 1). All of the aminonicotinates synthesized were characterized by spectroscopic techniques and **3a** was additionally characterized by X-ray crystallographic studies (Figure 1).

A plausible mechanism for the formation of aminonicotinate derivative **3a** is shown in Scheme 1. The resonance-

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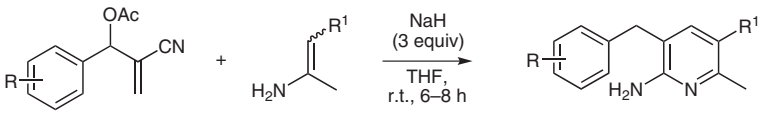
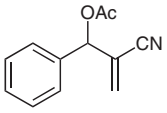
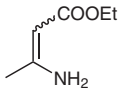
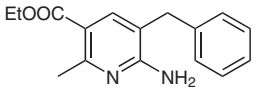
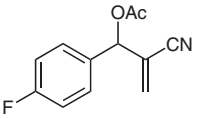
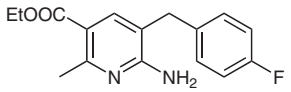
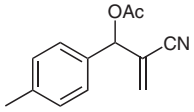
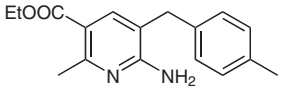
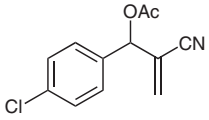
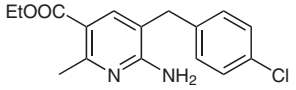
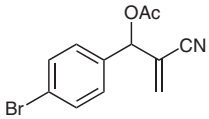
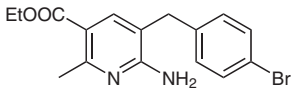
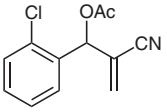
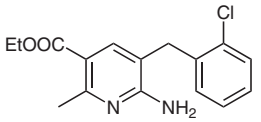
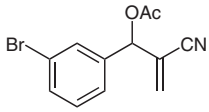
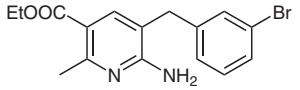
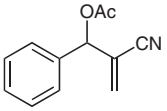
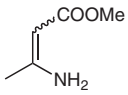
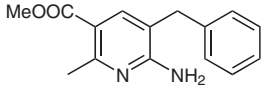
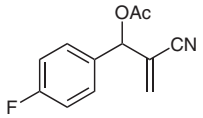
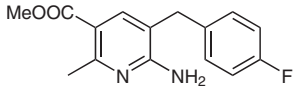
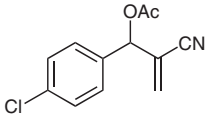
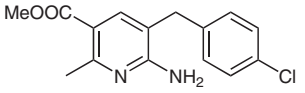
Table 1 One-Pot Synthesis of Aminonicotinate Derivatives from Acetylated Baylis–Hillman Nitriles and Enamino Esters



1a–g **2a, b** **3a–j**

Entry	Baylis–Hillman nitrile	Enamino ester	Product[a]	Yield[b] (%)
1	**1a** 	**2a** 	**3a** 	68
2	**1b** 	**2a**	**3b** 	65
3	**1c** 	**2a**	**3c** 	61
4	**1d** 	**2a**	**3d** 	70
5	**1e** 	**2a**	**3e** 	69
6	**1f** 	**2a**	**3f** 	68
7	**1g** 	**2a**	**3g** 	65
8	**1a** 	**2b** 	**3h** 	56
9	**1b** 	**2b**	**3i** 	55
10	**1d** 	**2b**	**3j** 	58

[a] All products were characterized by NMR, IR and mass spectroscopy.
[b] Yield of isolated product.

stabilized anion generated by the action of sodium hydride on the amino group of enamine **2a** attacks through its α-carbon (which is nucleophilic in nature) at the β-carbon of the external double bond of the acetylated Baylis–Hillman nitrile **1a** via an S_N2' mechanism, by which C–C bond formation takes place and subsequent migration of the double bond with elimination of the acetate group occurs simultaneously to give intermediate **I** which was not isolated during the reaction. Thus formed, intermediate **I** undergoes a proton shift as well as intramolecular cyclization to give the six-membered cyclic intermediate **II**. In this annulation protocol, the two-carbon and one-nitrogen source from the enamino ester with the three-carbon source from the acetylated Baylis–Hillman nitrile

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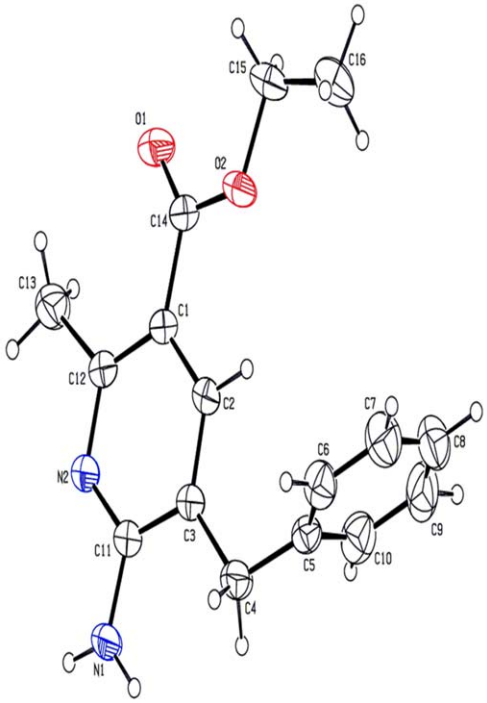


Figure 1 ORTEP diagram of compound **3a**

gives the [3+3]-cyclized product **II**. Subsequently, double-bond migration takes place and gives aminonicotinate **3a** in good yield after the usual workup. The beauty of this reaction is that three chemical transformations [i.e., addition, cyclization, isomerization (proton shifts)] take place in one pot leading to the aminonicotinate derivative.

In summary, we have developed a straightforward, convenient and practical synthesis of aminonicotinate derivatives from acetylated Baylis–Hillman nitriles and enamino esters, via a [3+3]-annulation protocol, in moderate to good yields. We believe this reaction has enough scope for further investigations.

Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded using a Thermo Nicolet Nexus 670 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance 300-MHz or a Varian Inova 400-MHz FT spectrometer, using TMS as an internal standard (chemical shift values in δ, *J* in Hz). HRMS (ESI) data were recorded on a QSTAR XL high-resolution mass spectrometer. GC-MS data were recorded on an Agilent 6890 series GC-MS system (column: Varian CP-Sil 8 CB, 5% phenyl, 95% PDMS, 30.0 m × 250 μm × 0.30 μm nominal).

Aminonicotinate Derivatives 3a–j; General Procedure

To a well-stirred solution of NaH (60% in paraffin oil; 240 mg, 6 mmol) in anhyd THF (15 mL) was added the enamino ester **2a** or **2b** (2 mmol) dissolved in anhyd THF (5 mL) at r.t. under N_2 atmosphere, and the mixture was stirred for 15 min at the same temperature. Then, an acetylated Baylis–Hillman nitrile **1a–g** (2.2 mmol) dissolved in anhyd THF (5 mL) was added slowly and the mixture was stirred at r.t. until the reaction was completed. After completion, the solvent was removed under reduced pressure and the residue was diluted with ice-cold H_2O (15 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (10 mL), dried (Na_2SO_4), concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc–hexane, 1:9 followed by 1:4) to afford pure compound **3a–j**.

Ethyl 6-Amino-5-benzyl-2-methylnicotinate (3a)

Yield: 68%; white solid; mp 137–139 °C.

IR (KBr): 3436, 3326, 3130, 1695, 1655, 1597, 1470, 1243 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (s, 1 H), 7.30–7.13 (m, 5 H), 4.71 (s, 2 H), 4.28 (q, *J* = 7.6 Hz, 2 H), 3.83 (s, 2 H), 2.65 (s, 3 H), 1.37 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 159.0, 158.2, 141.1, 137.5, 128.9, 128.2, 126.9, 115.5, 115.3, 60.4, 37.1, 24.2, 14.3.

GC-MS (EI, 70 eV): *m*/*z* (%) = 270 (100) [M$^+$], 254, 241, 225, 197, 180, 152, 127, 105, 91, 77, 43.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{19}N_2O_2$ [M + H]$^+$: 271.1446; found: 271.1456.

Ethyl 6-Amino-5-(4-fluorobenzyl)-2-methylnicotinate (3b)

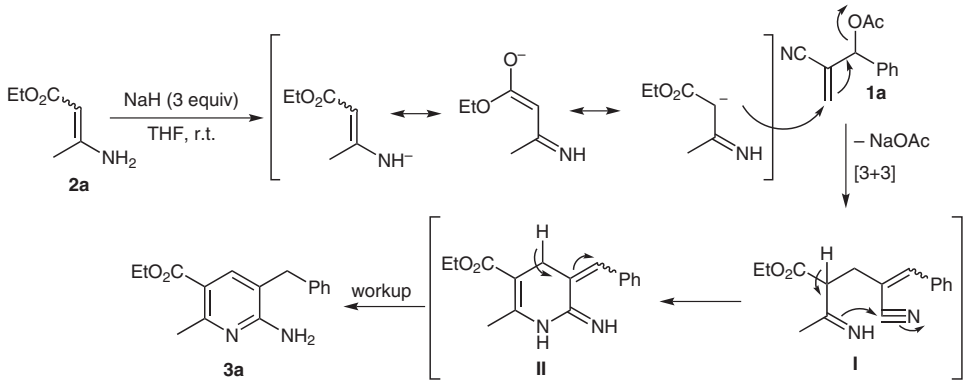
Yield: 65%; white solid; mp 131–133 °C.

IR (KBr): 3487, 3313, 3112, 2980, 1708, 1647, 1598, 1507, 1260 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (s, 1 H), 7.12 (q, *J* = 8.3 Hz, 2 H), 6.97 (t, *J* = 8.3 Hz, 2 H), 4.59 (br s, 2 H), 4.28 (q, *J* = 6.8 Hz, 2 H), 3.80 (s, 2 H), 2.65 (s, 3 H), 1.37 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 163.4, 160.1, 159.3, 158.1, 141.0, 133.2, 133.1, 129.8, 129.7, 115.9, 115.6, 115.2, 115.2, 60.4, 36.3, 24.4, 14.3.

GC-MS (EI, 70 eV): *m*/*z* (%) = 288 (100) [M$^+$], 273, 259, 243, 215, 198, 171, 146, 133, 120, 109, 100, 51.



Scheme 1

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HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}N_2O_2F$ [M + H]$^+$: 289.1352; found: 289.1342.

Ethyl 6-Amino-2-methyl-5-(4-methylbenzyl)nicotinate (3c)
Yield: 61%; white solid; mp 122–124 °C.

IR (KBr): 3483, 3299, 3105, 2985, 1705, 1642, 1559, 1261 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (s, 1 H), 7.10 (d, *J* = 8.1 Hz, 2 H), 7.04 (d, *J* = 8.1 Hz, 2 H), 4.61 (br s, 2 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 3.79 (s, 2 H), 2.66 (s, 3 H), 2.32 (s, 3 H), 1.37 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.9, 158.9, 157.6, 138.9, 135.9, 135.0, 128.9, 128.5, 116.1, 112.4, 59.5, 34.6, 24.1, 20.5, 14.1.

GC-MS (EI, 70 eV): *m*/*z* (%) = 284 (100) [M$^+$], 269, 255, 239, 211, 194, 178, 167, 152, 141, 119, 105, 91, 77, 51.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{21}N_2O_2$ [M + H]$^+$: 285.1603; found: 285.1604.

Ethyl 6-Amino-5-(4-chlorobenzyl)-2-methylnicotinate (3d)
Yield: 70%; pale yellow solid; mp 175–177 °C.

IR (KBr): 3477, 3308, 3141, 2982, 1714, 1643, 1561, 1258 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ = 7.69 (s, 1 H), 7.24 (d, *J* = 8.6 Hz, 2 H), 7.15 (d, *J* = 8.6 Hz, 2 H), 5.65 (s, 2 H), 4.21 (q, *J* = 7.0 Hz, 2 H), 3.77 (s, 2 H), 2.58 (s, 3 H), 1.33 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.8, 158.9, 158.0, 139.2, 138.2, 130.7, 130.4, 128.2, 115.4, 112.3, 59.6, 34.2, 24.2, 14.1.

GC-MS (EI, 70 eV): *m*/*z* (%) = 304 (100) [M$^+$], 289, 275, 259, 243, 231, 214, 196, 181, 167, 152, 125, 112, 99, 77, 52.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}N_2O_2Cl$ [M + H]$^+$: 305.1056; found: 305.1046.

Ethyl 6-Amino-5-(4-bromobenzyl)-2-methylnicotinate (3e)
Yield: 69%; pale yellow solid; mp 187–189 °C.

IR (KBr): 3475, 3307, 3141, 2982, 2931, 1712, 1642, 1562, 1256 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1 H), 7.42 (d, *J* = 8.3 Hz, 2 H), 7.04 (d, *J* = 8.3 Hz, 2 H), 4.54 (br s, 2 H), 4.28 (q, *J* = 6.8 Hz, 2 H), 3.78 (s, 2 H), 2.65 (s, 3 H), 1.37 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.9, 159.0, 158.0, 139.3, 138.6, 131.1, 130.8, 119.1, 115.3, 112.3, 60.0, 34.3, 24.2, 14.2.

GC-MS (EI, 70 eV): *m*/*z* (%) = 348 (100) [M$^+$], 319, 303, 275, 240, 224, 206, 195, 181, 169, 153, 127, 102, 90, 77, 52.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}N_2O_2Br$ [M + H]$^+$: 349.0551; found: 349.0540.

Ethyl 6-Amino-5-(2-chlorobenzyl)-2-methylnicotinate (3f)
Yield: 68%; white solid; mp 164–166 °C.

IR (KBr): 3479, 3312, 3141, 2981, 2929, 1711, 1647, 1563, 1254 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (s, 1 H), 7.39 (q, *J* = 5.3 Hz, 1 H), 7.20–7.13 (m, 2 H), 6.98 (q, *J* = 5.3 Hz, 1 H), 4.78 (br s, 2 H), 4.26 (q, *J* = 6.8 Hz, 2 H), 3.90 (s, 2 H), 2.65 (s, 3 H), 1.35 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 159.3, 158.1, 141.2, 135.2, 134.1, 129.8, 129.6, 128.3, 127.2, 115.6, 114.1, 60.4, 34.1, 24.4, 14.3.

GC-MS (EI, 70 eV): *m*/*z* (%) = 304 (49) [M$^+$], 269 (100), 259, 241, 225, 195, 181, 167, 152, 125, 112, 99, 77, 51.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}N_2O_2Cl$ [M + H]$^+$: 305.1056; found: 305.1049.

Ethyl 6-Amino-5-(3-bromobenzyl)-2-methylnicotinate (3g)
Yield: 65%; white solid; mp 124–126 °C.

IR (KBr): 3485, 3303, 3142, 2977, 1700, 1643, 1558, 1258 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (s, 1 H), 7.37 (d, *J* = 7.9 Hz, 1 H), 7.30 (s, 1 H), 7.16 (t, *J* = 7.7 Hz, 1 H), 7.07 (d, *J* = 7.5 Hz, 1 H), 4.65 (br s, 2 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 3.81 (s, 2 H), 2.65 (s, 3 H), 1.37 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 159.5, 158.0, 141.2, 140.0, 131.2, 130.4, 130.1, 126.8, 123.0, 115.6, 114.4, 60.4, 36.6, 24.4, 14.3.

GC-MS (EI, 70 eV): *m*/*z* (%) = 348 (100) [M$^+$], 319, 303, 275, 240, 226, 195, 181, 169, 153, 127, 115, 97, 77, 52.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}N_2O_2Br$ [M + H]$^+$: 349.0551; found: 349.0569.

Methyl 6-Amino-5-benzyl-2-methylnicotinate (3h)
Yield: 56%; white solid; mp 144–147 °C.

IR (KBr): 3482, 3307, 3133, 2946, 1709, 1646, 1559, 1262 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (s, 1 H), 7.30–7.12 (m, 5 H), 4.65 (br s, 2 H), 3.82 (s, 5 H), 2.65 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 159.4, 158.3, 141.0, 137.5, 128.9, 128.3, 126.9, 115.5, 115.1, 51.5, 37.2, 24.4.

GC-MS (EI, 70 eV): *m*/*z* (%) = 256 (100) [M$^+$], 241, 225, 195, 180, 153, 127, 115, 103, 91, 77, 51.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{17}N_2O_2$ [M + H]$^+$: 257.1290; found: 257.1296.

Methyl 6-Amino-5-(4-fluorobenzyl)-2-methylnicotinate (3i)
Yield: 55%; pale yellow solid; mp 151–154 °C.

IR (KBr): 3486, 3305, 3157, 2955, 1713, 1640, 1559, 1243 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.13 (q, *J* = 8.6 Hz, 2 H), 6.96 (t, *J* = 8.6 Hz, 2 H), 5.23 (s, 2 H), 3.79 (s, 3 H), 3.77 (s, 2 H), 2.75 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 163.4, 160.2, 159.5, 158.1, 140.9, 133.2, 133.1, 129.8, 129.7, 115.9, 115.6, 115.3, 115.2, 51.6, 36.3, 24.4.

GC-MS (EI, 70 eV): *m*/*z* (%) = 274 (100) [M$^+$], 259, 243, 213, 171, 147, 133, 109, 83, 52.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{16}N_2O_2F$ [M + H]$^+$: 275.1195; found: 275.1199.

Methyl 6-Amino-5-(4-chlorobenzyl)-2-methylnicotinate (3j)
Yield: 58%; pale yellow solid; mp 175–177 °C.

IR (KBr): 3476, 3310, 3118, 2941, 1720, 1645, 1563, 1257 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (s, 1 H), 7.28 (d, *J* = 8.3 Hz, 2 H), 7.10 (d, *J* = 8.3 Hz, 2 H), 4.60 (br s, 2 H), 3.83 (s, 3 H), 3.79 (s, 2 H), 2.66 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 159.6, 158.1, 141.1, 136.0, 132.8, 129.6, 129.0, 115.3, 114.9, 51.6, 36.4, 24.4.

GC-MS (EI, 70 eV): *m*/*z* (%) = 290 (100) [M$^+$], 275, 259, 231, 216, 196, 178, 152, 125, 97, 77, 52.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{16}N_2O_2Cl$ [M + H]$^+$: 291.0900; found: 291.0899.

X-ray Crystallography of Compound 3a[18]
A colorless cube crystal of compound **3a** was obtained from $CHCl_3$.

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$C_{16}H_{18}N_2O_2$, $M = 270.32$, monoclinic, space group *P21/n*, $a = 12.7513(2)$ Å, $b = 7.4527(1)$ Å, $c = 17.7352(3)$ Å, $\beta = 111.069(4)°$, $V = 1572.7(5)$ Å^3, $\rho = 1.142$ g/cm^3, F(000) = 576. X-ray diffraction data were collected using a Bruker SMART CCD area detector at 293 K, using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Integration and scaling of intensity data were accomplished using SAINT.[19a] The structure was solved by direct methods and refined by the full-matrix least-squares procedure based on F[19b] using the program SHELX-97.[19b] Non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms were included in the models at their calculated positions in a riding model approximation. The molecular geometry and graphics were computed using the programs PARST[19c] and ORTEP-3.[19d] The ORTEP view of the molecule is shown in Figure 1.

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