Thermal and Microwave-Assisted Rapid Syntheses of Substituted Imidazo[1,2-*a*]pyridines Under Solvent- and Catalyst-Free Conditions

Kaushik C. Chunavala, Girdhar Joshi, Eringathodi Suresh, Subbarayappa Adimurthy*

Central Salt and Marine Chemicals Research Institute (CSIR), G. B. Marg, Bhavnagar 364 002, Gujarat, India
Fax +91(278)2567562; E-mail: sadimurthy@yahoo.com

Received 15 November 2010; revised 23 November 2010

Abstract: Thermal and microwave-assisted rapid syntheses of highly substituted imidazo[1,2-*a*]pyridine derivatives by reaction of aminopyridines and α-bromo-β-keto esters under solvent-free conditions are described. Reactions carried out under microwave irradiation give the highest yields of products in reaction times of less than two minutes.

Key words: aminopyridines, α-bromo-β-keto esters, imidazo[1,2-*a*]pyridines, microwave irradiation, solvent-free, thermal

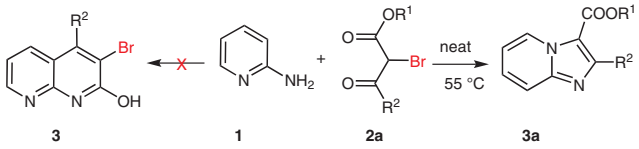
Imidazo[1,2-*a*]pyridines are an important class of molecules due to their wide spectrum of biological activity and clinical applications.[1] Derivatives of imidazo[1,2-*a*]pyridine have been shown to act as melatonin receptor ligands,[2] antiviral,[3] antiulcer,[4] antibacterial[5] and antifungal agents,[6] an agonist of the benzodiazepine receptor,[7] a calcium channel blocker,[8] an inhibitor of β-amyloid formation,[9] a ligand for detecting β-amyloid,[10] orally active non-peptide bradykinin B2 receptor antagonists,[11a] and an hypnotic agent.[11b]

Although a number of methods have been developed for the synthesis of this important framework, most are limited to the condensation of α-halocarbonyl compounds with 2-aminopyridines under harsh conditions, or the condensation of substituted imidazoles with unsaturated dicarboxylates, or α,β-unsaturated carbonyl compounds.[12] Other methods include copper- and palladium-catalyzed procedures,[13]and multicomponent reactions.[14] Clay- and alumina-supported, three-component, microwave-assisted reactions for the synthesis of imidazo[1,2-*a*]pyridines have been reported.[15]

To the best of our knowledge, there are no methods available for the rapid synthesis of imidazo[1,2-*a*] pyridines by either thermal or microwave reactions. We describe herein the unexpected synthesis of ethyl 2-methylimidazo[1,2-*a*]pyridine-3-carboxylate (**3a**), under solvent-free conditions, employing 2-aminopyridine (**1**) and ethyl 2-bromo-3-oxobutanoate (**2a**, R^1 = Et, R^2 = Me) (Scheme 1). This reaction was found by chance during our recent investigations on the synthesis of 3-bromo-4-methyl-1,8-naphthyridin-2-ol (**3**), which was of interest to us as a ligand and base for the copper(I)-catalyzed oxidative homocoupling of terminal alkynes in the presence of an oxidant.[16]

SYNTHESIS 2011, No. 4, pp 0635–0641
Advanced online publication: 12.01.2011
DOI: 10.1055/s-0030-1258405; Art ID: Z27510SS

Our initial studies focused on the development of an optimum set of reaction conditions for the synthesis of compound **3** from 2-aminopyridine (**1**) and ethyl 2-bromo-3-oxobutanoate (**2a**). Preliminary studies (after screening various solvents including methanol, ethanol, isopropyl alcohol, acetonitrile, dichloromethane and 1,2-dichloroethane) revealed that the best yield (87%) of product **3a**, and not the desired naphthyridin-2-ol **3**, was obtained under neat conditions at room temperature in 60 minutes. A similar yield of **3a** was achieved within 10 minutes when the same reaction was carried out at 55 °C.



Scheme 1 Reaction of 2-aminopyridine (**1**) with ethyl 2-bromo-3-oxobutanoate (**2a**)

Intrigued by this experimental observation, we decided to extend this strategy to the synthesis of substituted imidazo[1,2-*a*]pyridine-3-carboxylates **3b–e** using aminopyridine **1** and α-bromo-β-keto esters **2b–e** (Figure 1).

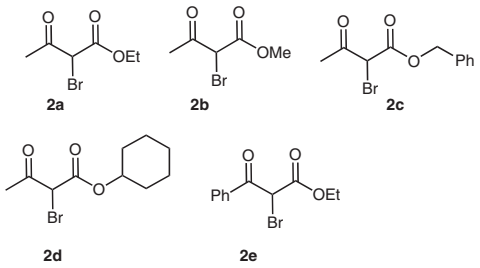
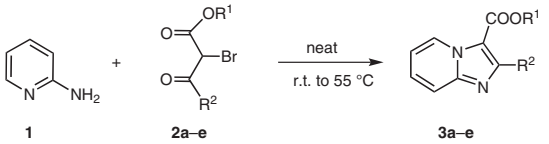


Figure 1 Structures of α-bromo-β-keto esters **2a–e**

The reactions of 2-aminopyridine (**1**) with α-bromo-β-keto esters **2b–e** were carried out in a similar manner to that described above to afford alkyl/benzyl 2-alkyl/phenylimidazo[1,2-*a*]pyridine-3-carboxylates **3b–e**. The yields and reaction times are summarized in Table 1. Ethyl 2-bromo-3-oxo-3-phenylpropanoate (**2e**) gave an 89% yield of ethyl 2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate (**3e**) (Table 1, entry 5). In the present studies, none of the corresponding 1,8-naphthyridin-2-ols of type **3** was formed.

Table 1 Synthesis of 2-Alkyl- or 2-Phenylimidazo[1,2-*a*]pyridine-3-carboxylates **3a–e**[a]



Entry	β-Keto ester	Time (min)	Product	Yield (%)[b]
1	**2a**	10	**3a**	87
2	**2b**	10	**3b**	89
3	**2c**	35	**3c**	84
4	**2d**	30	**3d**	84
5	**2e**	25	**3e**	89

[a] 2-Aminopyridine (**1**) (1.0 mmol), β-keto ester **2a–e** (1.0 mmol).
[b] Yield of isolated product.

Using the optimized reaction conditions, substituted 2-aminopyridines **4a–e** (Figure 2) were reacted with α-bromo-β-keto esters **2a**,**b**,**e** to afford the corresponding 2-alkyl/phenylimidazo[1,2-*a*]pyridine-3-carboxylates **5a–k**; the results are summarized in Table 2. In general, the reactions proceeded smoothly and were complete within 35 minutes giving the products in yields ranging from 80–89% (apart from imidazo[1,2-*a*]pyridine **5k** which was obtained in a moderate 58% yield).

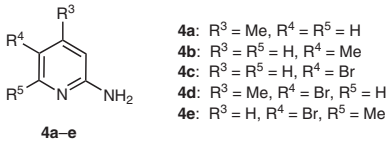


Figure 2 Structures of substituted 2-aminopyridines **4a–e**

The structure of product **5g** was confirmed unambiguously by single crystal X-ray diffraction (Figure 3).[17]

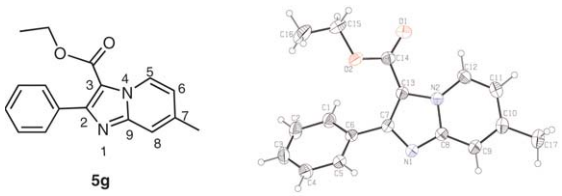
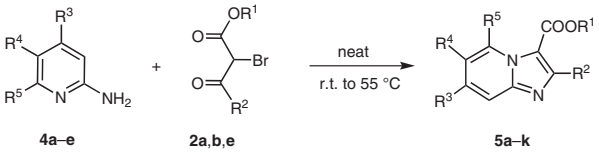


Figure 3 ORTEP diagram of compound **5g**

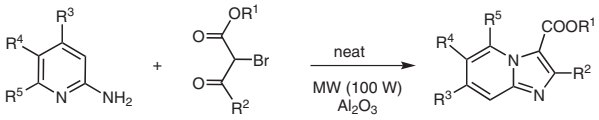
We also describe herein the microwave-assisted synthesis of representative substituted imidazo[1,2-*a*]pyridine-3-carboxylates under solvent-free conditions (Scheme 2). The reactions of 2-aminopyridines **1** and **4a–d** with α-bromo-β-keto esters **2a**,**b**,**e** were carried out on neutral alumina (Al_2O_3) as a solid support under microwave irradiation (100 W) for 50–90 seconds, with a five-second interval for every 15 seconds of reaction time. The results are summarised in Table 3. Under these conditions the reactions were very rapid and clean, and the substituted imidazo[1,2-*a*]pyridine products were isolated in 85–95% yields. The structures of the products prepared under microwave irradiation conditions were confirmed by comparing their ^{1}H NMR spectra with those of the same products prepared via traditional heating (see Tables 1 and 2).

Table 2 Synthesis of Substituted 2-Alkyl- or 2-Phenylimidazo[1,2-*a*]pyridine-3-carboxylates **5a–k**[a]



Entry	2-Aminopyridine	β-Keto ester	Time (min)	Product	Yield (%)[b]
1	**4a**	**2a**	15	**5a**	85
2	**4b**	**2a**	15	**5b**	87
3	**4c**	**2a**	20	**5c**	84
4	**4a**	**2b**	15	**5d**	84
5	**4b**	**2b**	15	**5e**	86
6	**4c**	**2b**	20	**5f**	86
7	**4a**	**2e**	20	**5g**	83
8	**4b**	**2e**	20	**5h**	85
9	**4c**	**2e**	20	**5i**	85
10	**4d**	**2e**	25	**5j**	84
11	**4e**	**2a**	30	**5k**	58

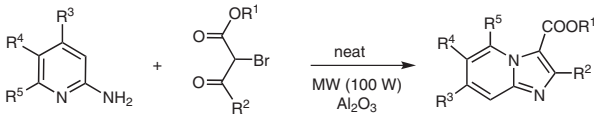
[a] Substituted 2-aminopyridine **4a–e** (1.0 mmol), β-keto ester **2a,b,e** (1.0 mmol).
[b] Yield of isolated product.



Scheme 2 Alumina-supported microwave reaction of 2-aminopyridines with α-bromo-β-keto esters

The advantages of our protocol include the use of commercially available and inexpensive 2-aminopyridines and α-bromo-β-keto esters, rapid reactions (less than two minutes using microwave irradiation and less than 35 minutes under thermal heating), mild conditions, a simple work-up, high yields of products and no contamination with by-products. The harsh conditions typically employed for the synthesis of substituted imidazo[1,2-*a*]pyridines[12c,18] are thus avoided. The present method does not require the use of expensive or corrosive re-

Table 3 Microwave-Assisted Synthesis of Substituted 2-Alkyl- or 2-Phenylimidazo[1,2-*a*]pyridine-3-carboxylates[a]



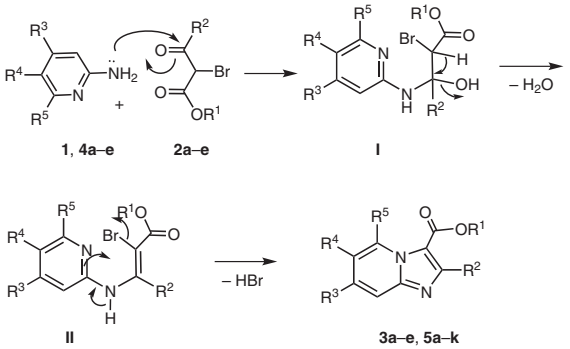
1,4a–d 2a,b,e 3,5

Entry	2-Amino-pyridine	β-Keto ester	Time (sec)	Product	Yield (%)[b]
1	**1**	**2e**	60	**3e**	95
2	**4a**	**2a**	60	**5a**	94
3	**4a**	**2b**	50	**5d**	92
4	**4a**	**2e**	50	**5g**	95
5	**4b**	**2e**	60	**5h**	93
6	**4c**	**2a**	70	**5c**	85
7	**4c**	**2b**	70	**5f**	92
8	**4d**	**2e**	90	**5j**	91

[a] 2-Aminopyridine **1**,**4a**–**d** (1.0 mmol), β-keto ester **2a**,**b**,**e** (1.0 mmol), MW (100 W).
[b] Yield of isolated product.

agents, or transition-metal catalysts, and no precautions need to be taken to exclude moisture.

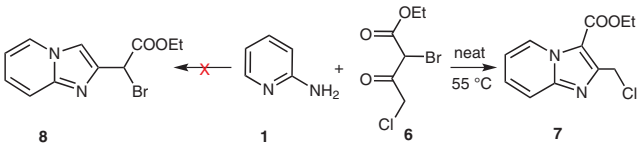
A possible mechanism for the formation of products **3a**–**e** and **5a**–**k** is illustrated in Scheme 3. It is rational to assume that intermediate **I** results from initial reaction of the 2-aminopyridine with α-bromo-β-keto esters **2a**–**e**. Next, elimination of a molecule of water leads to the more stable conjugated intermediate **II**. Finally, intramolecular cyclization of **II** with loss of hydrogen bromide yields the imidazo[1,2-*a*]pyridine-3-carboxylates.



1, 4a–e 2a–e I II 3a–e, 5a–k

Scheme 3 A possible mechanism for the formation of products **3a**–**e** and **5a**–**k**

We also prepared an imidazo[1,2-*a*]pyridine derivative possessing a reactive functionality on the imidazole moiety. Reaction of 2-aminopyridine (**1**) with ethyl 2-bromo-4-chloro-3-oxobutanoate (**6**) using the above-mentioned thermal conditions afforded ethyl 2-(chloromethyl)imidazo[1,2-*a*]pyridine-3-carboxylate (**7**) in 69% isolated yield (Scheme 4). As expected the highly reactive C-2 and C-3 carbons of the β-keto ester participated selectively in the cyclization to give the desired product **7**, and not compound **8** which would occur via reaction at carbons C-3 and C-4.



8 1 6 7

Scheme 4 Reaction of 2-aminopyridine (**1**) with ester **6**

In conclusion, we have developed a convenient, simple and rapid one-step approach for the direct synthesis of highly substituted imidazo[1,2-*a*]pyridine-3-carboxylates via thermal and microwave-assisted reactions of readily available 2-aminopyridines and various α-bromo-β-keto esters, under solvent-free conditions. All the reactions proceeded efficiently to provide the desired products in high yields, apart from **5k** which was obtained in a moderate 58% yield. This novel route also allows reactive functionalities to be installed on the imidazole moiety for the synthesis of promising pharmacophores that are found in many biologically active compounds.

All commercially available reagents were used without further purification unless otherwise indicated, and all reactions were carried out in air without any special precautions. Microwave-assisted reactions were accomplished using a Milstone Start S (Italy) programmable microwave oven (model no. Start S; Terminal T260; Line voltage 230 V; Magnetron SN131528; Frequency 50 Hz). Melting points were obtained using a Mettler Toledo FP62 melting point apparatus with open capillary tubes and are uncorrected. Column chromatography was carried out on basic alumina (Sisco Research Laboratory; 60–325 mesh). Analytical thin layer chromatography (TLC) was performed on precoated Aluchrosep silica gel 60/UV_{254} plates. ^1H and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, for compounds **3a–e** and 500 MHz and 125 MHz, respectively, for compounds **5a–k** and **7**, using $CDCl_3$ as the solvent. The ^1H and ^{13}C chemical shifts were referenced to the residual solvent signals at δ_H 7.26 and δ_C 77.28 ($CDCl_3$) relative to TMS as the internal standard. IR spectra were obtained using a Perkin Elmer GX-2000 FT-IR spectrometer. GC–MS analyses were recorded using a Shimadzu GCMS-QT2010 with an HP-5 column. Low-resolution mass spectra (ESI) were recorded in positive mode using a Waters Micromass Q-ToF instrument. Elemental analyses were obtained using a Perkin Elmer 2400 Series II CHNS/O analyzer.

Ethyl 2-Methylimidazo[1,2-*a*]pyridine-3-carboxylate (3a); Typical Thermal Procedure

Ethyl 2-bromo-3-oxobutanoate (**2a**) (1.11g, 5.32 mmol) was added slowly to 2-aminopyridine (**1**) (500 mg, 5.32 mmol), at r.t. under stirring. The mixture was heated at 55 °C for 10 min. The reaction progress was monitored by GC–MS. After completion, the mixture was made basic (pH 8–9) by the addition of sat. aq Na_2SO_3 soln. The product was extracted with EtOAc (3 × 10 mL), the combined organic layers washed with sat. aq Na_2SO_3 soln (2 × 10 mL) and dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was subjected to column chromatography over basic Al_2O_3 (eluent: EtOAc–hexane, 0.5:9.5) to afford pure **3a**.

White crystalline solid; yield: 965 mg (89%); mp 66–68 °C.

IR (KBr): 3407, 3146, 2996, 1679, 1595, 1490, 1412, 1292, 1222, 1094, 850, 761, 669 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.3 (d, *J* = 6.8 Hz, 1 H, H-5), 7.6 (d, *J* = 9.0 Hz, 1 H, H-8), 7.3 (dd, *J* = 7.4, 7.2 Hz, 1 H, H-7), 6.9 (dd, *J* = 6.8, 6.6 Hz, 1 H, H-6), 4.4 (q, *J* = 7.0 Hz, 2 H), 2.7 (s, 3 H), 1.4 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.8, 153.1, 147.2, 128.2, 127.6, 116.9, 113.7, 60.5, 16.8, 14.7.

ESI-MS: *m*/*z* = 205.1 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.73; H, 5.54; N, 13.78.

Ethyl 2-Phenylimidazo[1,2-*a*]pyridine-3-carboxylate (3e); Typical Microwave-Assisted Procedure

A mixture of 2-aminopyridine (**1**) (500 mg, 5.32 mmol) and ethyl 2-bromo-3-oxo-3-phenylpropanoate (**2e**) (1.11g, 5.32 mmol) was mixed thoroughly with neutral Al_2O_3 (1 g), and then irradiated in a microwave oven at 100 W for 60 sec with a time interval of 5 sec after every 15 sec of irradiation. The mixture turned brown, and after cooling to r.t., the residue was diluted with EtOAc (15 mL) and made basic (pH 8–9) by addition of sat. aq Na_2SO_3 soln. The organic layer was washed with sat. aq Na_2SO_3 soln (2 × 10 mL) and dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was subjected to column chromatography over basic Al_2O_3 (eluent: EtOAc–hexane, 5:95) to afford pure compound **3e**.

White crystalline solid; yield: 1.349 g (95%); mp 51–53 °C.

IR (KBr): 3144, 3038, 2979, 1679, 1496, 1475, 1402, 1383, 1334, 1221, 1161, 1047, 840, 755, 700 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.4 (d, *J* = 6.8 Hz, 1 H, H-5), 7.8–7.7 (m, 3 H), 7.4–7.3 (m, 4 H), 7.0 (dd, *J* = 7.2, 6.8 Hz, 1 H, H-6), 4.3 (q, *J* = 7.2 Hz, 2 H), 1.2 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.1, 153.5, 134.4, 130.1, 128.6, 128.3, 127.8, 127.5, 117.4, 114.0, 60.4, 13.9.

ESI-MS: *m*/*z* = 259.1 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.70; H, 5.36; N, 10.60.

Methyl 2-Methylimidazo[1,2-*a*]pyridine-3-carboxylate (3b)

White crystalline solid; mp 70–72 °C.

IR (KBr): 3389, 2955, 1688, 1495, 1446, 1401, 1330, 1224, 1130, 1093, 804, 762 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.3 (d, *J* = 7.0 Hz, 1 H, H-5), 7.6 (d, *J* = 9.0 Hz, 1 H, H-8), 7.4 (dd, *J* = 7.4, 6.8 Hz, 1 H, H-7), 6.9 (dd, *J* = 7.0, 6.8 Hz, 1 H, H-6), 3.9 (s, 3 H), 2.7 (s, 3 H, Me-2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.6, 152.8, 146.9, 127.8, 127.3, 116.6, 113.4, 50.9, 16.3.

ESI-MS: *m*/*z* = 191.1 $[M + H]^+$.

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.80; H, 5.42; N, 14.39.

Benzyl 2-Methylimidazo[1,2-*a*]pyridine-3-carboxylate (3c)

White crystalline solid; mp 85–87 °C.

IR (KBr): 3264, 3036, 2932, 2860, 1685, 1498, 1408, 1363, 1215, 1090, 1015, 758, 696 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.3 (d, *J* = 6.8 Hz, 1 H, H-5), 7.6 (dd, *J* = 9 Hz, 1 H, H-8), 7.4–7.3 (m, 6 H), 6.9 (dd, *J* = 6.8, 5.8 Hz, 1 H, H-6), 5.4 (s, 2 H), 2.7 (s, 3 H, Me-2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.0, 147.0, 128.6, 128.0, 127.81, 127.80, 126.9, 116.6, 113.7, 113.0, 66.0, 16.8.

ESI-MS: *m*/*z* = 267.1 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.85; H, 5.63; N, 10.59.

Cyclohexyl 2-Methylimidazo[1,2-*a*]pyridine-3-carboxylate (3d)

Colorless liquid.

IR (neat): 3408, 3118, 2933, 2859, 1683, 1499, 1447, 1408, 1336, 1291, 1218, 1091, 916, 764, 657 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.3 (dd, *J* = 7.1, 7.0 Hz, 1 H, H-5), 7.6 (d, *J* = 8.8 Hz, 1 H, H-8), 7.3 (dd, *J* = 8.9 Hz, 1 H, H-7), 6.9 (dd, *J* = 6.9, 6.8 Hz, 1 H, H-6), 5.1–5.0 (m, 1 H), 2.7 (s, 3 H, Me-2), 2.0–1.4 (m, 10 H, cyclohexyl).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.8, 152.4, 146.7, 127.8, 127.2, 116.5, 113.4, 72.4, 31.7, 25.4, 23.5, 16.7.

ESI-MS: *m*/*z* = 259.1 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 70.09; H, 7.07; N, 10.49.

Ethyl 2,7-Dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (5a)

White crystalline solid; mp 64–66 °C.

IR (KBr): 3419, 3075, 2982, 2909, 1685, 1492, 1410, 1316, 1219, 1142, 1096, 1035, 795, 749 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.1 (d, *J* = 7.0 Hz, 1 H, H-5), 7.3 (s, 1 H, H-7), 6.7 (d, *J* = 7.0 Hz, 1 H, H-6), 4.4 (q, *J* = 7.0 Hz, 2 H), 2.6 (s, 3 H, Me-2), 2.4 (s, 3 H, Me-7), 1.4 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5, 152.8, 147.3, 138.9, 127.1, 116.1, 115.3, 60.1, 21.3, 16.6, 14.4.

ESI-MS: *m*/*z* = 219.1 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.50; H, 6.45; N, 12.89.

Ethyl 2,6-Dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (5b)

White crystalline solid; mp 65–67 °C.

IR (KBr): 3406, 2987, 2931, 1683, 1539, 1421, 1395, 1244, 1162, 1136, 1087, 816, 770 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.1 (s, 1 H, H-5), 7.5 (d, *J* = 9.0 Hz, 1 H, H-8), 7.2 (d, *J* = 9.0 Hz, 1 H, H-7), 4.4 (q, *J* = 7.2 Hz, 2 H), 2.6 (s, 3 H, Me-2), 2.3 (s, 3 H, Me-6), 1.4 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.1, 153.0, 146.4, 131.0, 126.5, 124.0, 116.4, 112.9, 60.8, 19.0, 17.3, 15.1.

ESI-MS: *m*/*z* = 219.1 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.40; H, 6.68; N, 12.90.

Ethyl 6-Bromo-2-methylimidazo[1,2-*a*]pyridine-3-carboxylate (5c)

White crystalline solid; mp 120–122 °C.

IR (KBr): 3406, 2987, 2931, 1683, 1539, 1421, 1395, 1244, 1162, 1136, 1087, 816, 770 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.1 (s, 1 H, H-5), 7.5 (d, *J* = 9.0 Hz, 1 H, H-8), 7.2 (d, *J* = 9.0 Hz, 1 H, H-7), 4.4 (q, *J* = 7.2 Hz, 2 H), 2.7 (s, 3 H, Me-2), 1.4 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.7, 153.5, 145.7, 131.6, 128.7, 117.7, 113.5, 109.2, 61.2, 17.2, 15.1.

ESI-MS: *m*/*z* = 283.0 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{11}BrN_2O_2$: C, 46.66; H, 3.92; N, 9.89. Found: C, 46.27; H, 4.09; N, 9.64.

Methyl 2,7-Dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (5d)
White crystalline solid; mp 118–120 °C.

IR (KBr): 3130, 3034, 2947, 1686, 1513, 1493, 1466, 1435, 1395, 1267, 1221, 1170, 1138, 1087, 1024, 801, 769, 751 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.10 (d, *J* = 7.0 Hz, 1 H, H-5), 7.3 (s, 1 H, H-8), 6.8 (d, *J* = 7.0 Hz, 1 H, H-6), 3.9 (s, 3 H), 2.6 (s, 3 H, Me-2), 2.4 (s, 3 H, Me-7).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.8, 153.0, 147.5, 138.9, 127.1, 115.9, 115.4, 50.9, 21.1, 16.3.

ESI-MS: *m*/*z* = 205.1 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.76; H, 6.15; N, 13.43.

Methyl 2,6-Dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (5e)
White crystalline solid; mp 72–74 °C.

IR (KBr): 3358, 2930, 1685, 1512, 1449, 1395, 1370, 1271, 1246, 1198, 1163, 1092, 1035, 810, 766 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.1 (s, 1 H, H-5), 7.5 (d, *J* = 8.4 Hz, 1 H, H-8), 7.2 (d, 1 H, H-7), 3.9 (s, 3 H), 2.6 (s, 3 H, Me-2), 2.3 (s, 3 H, Me-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.6, 153.3, 146.6, 131.2, 126.6, 124.2, 116.5, 112.8, 51.9, 19.0, 17.3.

ESI-MS: *m*/*z* = 205.1 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.50; H, 5.84; N, 13.40.

Methyl 6-Bromo-2-methylimidazo[1,2-*a*]pyridine-3-carboxylate (5f)
White crystalline solid; mp 113–115 °C.

IR (KBr): 3134, 3064, 3001, 2951, 1685, 1517, 1490, 1445, 1391, 1364, 1338, 1286, 1212, 1143, 1165, 1019, 858, 816, 765 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.4 (s, 1 H, H-5), 7.5 (d, *J* = 9.4 Hz, 1 H, H-8), 7.4 (d, *J* = 9.6 Hz, 1 H, H-7), 3.9 (s, 3 H), 2.6 (s, 3 H, Me-2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.2, 153.8, 146.0, 131.7, 128.8, 117.8, 113.5, 109.2, 52.2, 17.2.

ESI-MS: *m*/*z* = 269.0 $[M + H]^+$.

Anal. Calcd for $C_{10}H_9BrN_2O_2$: C, 44.63; H, 3.37; N, 10.41. Found: C, 44.32; H, 3.10; N, 10.30.

Ethyl 7-Methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate (5g)
White crystalline solid; mp 88–90 °C.

IR (KBr): 3431, 3056, 2992, 2915, 1678, 1644, 1486, 1401, 1377, 1224, 1162, 1050, 796, 751, 701 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.2 (d, *J* = 7.2 Hz, 1 H, H-5), 7.7 (m, 2 H), 7.48 (s, 1 H, H-8), 7.4–7.3 (m, 3 H), 6.8 (d, *J* = 7.2 Hz, 1 H, H-6), 4.3 (q, *J* = 7.2 Hz, 2 H), 2.4 (s, 3 H, Me-7), 1.2 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1, 147.5, 139.2, 134.0, 130.1, 128.5, 127.4, 116.4, 116.0, 60.3, 21.4, 14.0.

ESI-MS: *m*/*z* = 281.1 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.56; H, 6.00; N, 10.11.

Ethyl 6-Methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate (5h)
White crystalline solid; mp 72–74 °C.

IR (KBr): 2979, 2925, 1672, 1501, 1387, 1332, 1241, 1167, 1044, 811, 756, 700 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.2 (s, 1 H, H-5), 7.7 (d, *J* = 3.6 Hz, 2 H), 7.6 (d, *J* = 9.0 Hz, 1 H, H-8), 7.4 (d, *J* = 3.4 Hz, 3 H), 7.30 (s, 1 H, H-7), 4.2 (q, *J* = 7.0 Hz, 2 H), 2.4 (s, 3 H, Me-6), 1.2 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.1, 146.1, 134.8, 130.6, 130.1, 128.4, 127.4, 126.1, 123.8, 116.7, 60.2, 18.4, 13.9.

ESI-MS: *m*/*z* = 281.1 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.98; H, 5.70; N, 9.83.

Ethyl 6-Bromo-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate (5i)
White crystalline solid; mp 132–134 °C.

IR (KBr): 3132, 3028, 1680, 1486, 1379, 1336, 1212, 1072, 1038, 822, 764 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.6 (dd, *J* = 1.8 Hz, 1 H, H-5), 7.8–7.7 (m, 2 H), 7.65 (d, *J* = 9.4 Hz, 1 H, H-8), 7.60 (d, *J* = 9.5 Hz, 1 H, H-7), 7.5–7.4 (m, 3 H), 4.3 (q, *J* = 7.2 Hz, 2 H), 1.2 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5, 154.4, 146.1, 134.6, 132.0, 130.8, 129.5, 129.1, 128.3, 118.6, 109.6, 61.4, 14.6.

ESI-MS: *m*/*z* = 345.0 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{13}BrN_2O_2$: C, 55.67; H, 3.80; N, 8.12. Found: C, 55.74; H, 3.79; N, 8.21.

Ethyl 6-Bromo-7-methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate (5j)
White crystalline solid; mp 132–134 °C.

IR (KBr): 2979, 2925, 1672, 1501, 1387, 1332, 1241, 1167, 1044, 811, 756, 700 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.6 (s, 1 H, H-5), 7.7 (t, *J* = 3.2 Hz, 2 H), 7.5 (s, 1 H, H-8), 7.4 (d, *J* = 3.4 Hz, 3 H), 4.3 (q, *J* = 7.0 Hz, 2 H), 2.5 (s, 3 H, Me-7), 1.2 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.5, 130.1, 128.6, 128.0, 127.4, 126.0, 125.3, 120.3, 116.5, 107.1, 60.4, 22.6, 13.9.

ESI-MS: *m*/*z* = 359.0 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{15}BrN_2O_2$: C, 56.84; H, 4.21; N, 7.80. Found: C, 56.45; H, 4.12; N, 8.15.

Ethyl 6-Bromo-2,5-dimethylimidazo[1,2-*a*]pyridine-3-carboxylate (5k)
White crystalline solid; mp 91–93 °C.

IR (KBr): 3430, 2978, 2927, 1703, 1496, 1407, 1371, 1275, 1200, 1092, 1027, 811, 761, 685 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.5 (d, *J* = 9.4 Hz, 1 H, H-8), 7.3 (d, *J* = 9.4 Hz, 1 H, H-7), 4.4 (q, *J* = 7.2 Hz, 2 H), 2.7 (s, 3 H, Me-5), 2.6 (s, 3 H, Me-2), 1.4 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.9, 152.6, 147.0, 136.7, 152.0, 115.8, 114.8, 111.0, 61.1, 22.2, 16.0, 14.5.

ESI-MS: *m*/*z* = 297.0 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{13}BrN_2O_2$: C, 48.50; H, 4.41; N, 9.43. Found: C, 48.41; H, 4.11; N, 9.15.

Ethyl 2-(Chloromethyl)imidazo[1,2-*a*]pyridine-3-carboxylate (7)
Brown viscous liquid.

IR (neat): 3433, 2926, 2856, 1734, 1639, 1502, 1463, 1378, 1166, 1083, 1027, 911, 734, 648 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.3 (d, *J* = 6.8 Hz, 1 H, H-5), 7.7 (d, *J* = 9.0 Hz, 1 H, H-8), 7.4 (dd, *J* = 7.4 Hz, 1 H, H-7), 7.0 (dd, *J* = 6.8 Hz, 1 H, H-6), 5.0 (s, 2 H), 4.5 (q, *J* = 7.0 Hz, 2 H), 1.5 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 144.9, 128.9, 128.3, 125.7, 117.4, 115.4, 112.5, 61.2, 35.1, 14.4.

ESI-MS: *m/z* = 276.1 $[M + K]^-$ (recorded in negative mode).

Anal. Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74. Found: C, 54.98; H, 4.28; N, 11.41.

Acknowledgment

We thank Mr. Hitesh, Mr. A. K. Das, Mr. H. Brahmbhatt, Mr. V. Agrawal and Mr. Viral from our Analytical Division for providing IR, NMR, and mass spectra and elemental analyses. G.J. and K.C.C. are grateful to the Council of Scientific & Industrial Research, New Delhi, India for the awards of Senior Research Fellowship and Junior Research Fellowship, respectively.

References

(1) For a general review on the chemistry of imidazopyridine derivatives, see: Couty, F.; Evano, G. In *Comprehensive Heterocyclic Chemistry III*, Vol. 2; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Elsevier: Oxford, **2008**, 409–499.

(2) (a) Guillaumet, G.; Berteina-Raboin, S.; El Kazzouli, S.; Delagrange, P.; Caignard, D. H. WO2006027474, **2006**; *Chem. Abstr.* **2006**, *144*, 254132. (b) Song, G.; Zhang, Y.; Li, X. *Organometallics* **2008**, *27*, 1936. (c) Enguehard, C.; Fauvelle, F.; Debouzy, J.; Peinnequin, A.; Thery, I.; Dabouis, V.; Gueiffier, A. *Eur. J. Pharm. Sci.* **2005**, *24*, 219. (d) Gudmundsson, K. S.; John, B. A. *Org. Lett.* **2003**, *5*, 1369. (e) Hamdouchi, C.; Zhong, B.; Mendoza, J.; Collins, E.; Jaramillo, C.; Diego, J.; Robertson, D.; Spencer, C. D.; Anderson, B. D.; Watkins, S. A.; Zhang, F.; Brooks, H. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1943.

(3) (a) Elhakmoui, A.; Gueiffier, A.; Milhavet, J. C.; Blache, Y.; Chapat, P. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1937. (b) Gueiffier, A.; Lhassani, M.; Elhakmoui, A.; Snoeck, R.; Andrei, G.; Chavignion, O.; Teulade, J. C.; Kerbal, A.; Essassi, M.; Debouzy, J. C.; Witurowo, J. P.; Blache, Y.; Balzarini, J.; De Clercq, E.; Chapat, J. P. *J. Med. Chem.* **1996**, *39*, 2856. (c) Lhassani, M.; Chavignion, O.; Chezal, J. M.; Teulade, J. C.; Chapat, J. P.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E.; Gueiffier, A. *J. Med. Chem.* **1999**, *34*, 271. (d) Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. *J. Org. Chem.* **1997**, *62*, 3453. (e) Pan, S.; Wang, G.; Shinazi, R. F.; Zhao, K. *Tetrahedron Lett.* **1998**, *39*, 2695. (f) Hamdouchi, C.; de Blas, J.; del Prado, M.; Gruber, J.; Heinz, B. A.; Vance, L. *J. Med. Chem.* **1999**, *42*, 50. (g) Gudmundsson, K. S.; Williams, J. D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2003**, *46*, 1449.

(4) (a) Kaminski, J. J.; Doweyko, A. M. *J. Med. Chem.* **1999**, *40*, 427. (b) Kaminski, J. J.; Puchalski, C.; Solomon, D. M.; Rizvi, R. K.; Conn, D. J.; Elliot, A. J.; Lovey, R. G.; Guzik, H.; Chui, P. J. S.; Long, J. F.; McPhail, A. T. *J. Med. Chem.* **1989**, *32*, 1686.

(5) (a) Rival, Y.; Grassy, G.; Michael, G. *J. Med. Chem.* **1992**, *40*, 1170. (b) Rewankar, G. R.; Matthews, J. R.; Robins, R. K. *J. Med. Chem.* **1975**, *18*, 1253. (c) Ismail, M. A.; Arafa, R. K.; Wenzler, T.; Brun, R.; Tanious, F. A.; Wilson, W. D.; Boykin, D. W. *Bioorg. Med. Chem.* **2008**, *16*, 683. (d) Odell, L. R.; Nilsson, M. T.; Gising, J.; Lagerlund, O.; Muthas, D.; Nordqvist, A.; Karlen, A.; Larhed, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4790.

(6) (a) Beswick, P. J.; Campbell, I. B.; Naylor, A. WO9631509, **1996**; *Chem. Abstr.* **1997**, *126*, 8117j. (b) Abignente, E. *Acta Chim. Therap.* **1991**, *18*, 1253. (c) Gudmundsson, K. S.; Johns, B. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2735.

(7) (a) Tully, W. R.; Gardner, C. R.; Gillespie, R. J.; Westwood, R. *J. Med. Chem.* **1991**, *34*, 2060. (b) Trapani, G.; Franco, M.; Latrofa, A.; Ricciardi, L.; Carotti, A.; Serra, M.; Sanna, E.; Biggio, G.; Liso, G. *J. Med. Chem.* **1999**, *42*, 3934. (c) Trapani, G.; Franco, M.; Ricciardi, L.; Latrofa, A.; Genchi, G.; Sanna, E.; Tuveri, F.; Gagetti, E.; Biggio, G.; Liso, G. *J. Med. Chem.* **1997**, *40*, 3109.

(8) Sanfilippo, P. J.; Urbanski, M.; Press, J. B.; Dubinsky, B.; Moore, J. B. Jr. *J. Med. Chem.* **1991**, *34*, 2060.

(9) Fuchs, K.; Romig, M.; Mendla, K.; Briem, H.; Fechteler, K. WO0214313, **2002**; *Chem. Abstr.* **2002**, *136*, 183824r.

(10) Zhuang, Z.-P.; Kung, M.-P.; Wilson, A.; Lee, W.-C.; Plössl, K.; Hou, C.; Holtzman, D. M.; Kung, H. F. *J. Med. Chem.* **2003**, *46*, 237.

(11) (a) Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Imai, K. H. *J. Med. Chem.* **1998**, *41*, 564. (b) Holm, K. J.; Goa, K. L. *Drugs* **2000**, *59*, 865.

(12) (a) El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2003**, *44*, 6265. (b) El Kazzouli, S.; Berthaut, A.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Lett. Org. Chem.* **2005**, *2*, 184. (c) Koubachi, J.; El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *J. Org. Chem.* **2007**, *72*, 7650. (d) Kamal, A.; Devaiah, V.; Reddy, K. L.; Rajendar, R.; Shetti, V.; Shankaraiah, N. *J. Comb. Chem.* **2007**, *9*, 267. (e) Herath, A.; Dahl, R.; Cosford, N. D. P. *Org. Lett.* **2010**, *12*, 412. (f) Patel, H. S.; Linn, J. A.; Drewry, D. H.; Hillesheim, D. A.; Zuercher, W. J.; Hokstra, W. J. *Tetrahedron Lett.* **2003**, *44*, 4077. (g) Montgomery, J. A.; Secrist, J. A. In *Comprehensive Heterocyclic Chemistry*, Vol. 5; Katritzky, A. R.; Rees, C. W.; Potts, K. T., Eds.; Pergamon: Oxford, **1984**, 607.

(13) (a) Chernyak, N.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 2743. (b) Bakherad, M.; Nasr-Isfahani, H.; Keivanloo, A.; Doostmohammadi, N. *Tetrahedron Lett.* **2008**, *49*, 3819. (c) Bakherad, M.; Nasr-Isfahani, H.; Keivanloo, A.; Sang, G. *Tetrahedron Lett.* **2008**, *49*, 6188.

(14) (a) Davey, D. D. *J. Org. Chem.* **1987**, *52*, 1863. (b) Galons, H.; Bergerat, I.; Farnoux, C. C.; Miocque, M. *Synthesis* **1982**, 1103. (c) Knolker, H. J.; Boese, R.; Hitzemann, R. *Chem. Ber.* **1990**, *123*, 327. (d) Liu, P.; Fang, L.; Lei, X.; Lin, G. *Tetrahedron Lett.* **2010**, *51*, 4605. (e) Andaloussi, M.; Moreau, E.; Chavignon, O.; Teulade, J. C. *Tetrahedron Lett.* **2007**, *48*, 8392. (f) Yadav, J. S.; Subba Reddy, B. V.; Rao, Y. G.; Srinivas, M.; Narsaiah, A. V. *Tetrahedron Lett.* **2007**, *48*, 7717. (g) Adib, M.; Sheibani, E.; Zhu, L.-G.; Mirzaei, P. *Tetrahedron Lett.* **2008**, *49*, 5108. (h) Kercher, T.; Rao, C.; Bencsik, J. R.; Josey, J. A. *J. Comb. Chem.* **2007**, *9*, 1177. (i) Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 7665. (j) Katagiri, N.; Kato, T. *J. Heterocycl. Chem.* **1984**, *21*, 407. (k) Kondo, T.; Kotachi, S.; Ogino, S.; Watanabe, Y. *Chem. Lett.* **1993**, 1317.

(15) (a) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193. (b) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 435. (c) Vega, J. A.; Vaquero, J. J.; Builla, J. A.; Ezquerra, J.; Hamdouchi, C. *Tetrahedron* **1999**, *55*, 2317. (d) Dimauro, E. F.; Kennedy, J. M. *J. Org. Chem.* **2007**, *72*, 1013.

(16) Adimurthy, S.; Malakar, C. C.; Beifuss, U. *J. Org. Chem.* **2009**, *74*, 5648.

(17) X-ray crystal data for **5g**: empirical formula: $C_{17}H_{16}N_2O_2$, formula weight: 280.32, T = 293(2) K, λ = 0.71073, crystal system: monoclinic, space group: *P*21/*c*, unit cell dimensions: a = 11.419(3) Å, b = 14.292(4) Å, c = 9.001(2) Å, β = 99.912(4)°, V = 1447.1(6) Å^3, Z = 4, density (calcd) = 1.287 mg/m^3, absorption coefficient: 0.086 mm^{-1}, F(000) = 592, crystal size: 0.32 × 0.21 × 12 mm, reflections collected: 7540, independent reflections: 2813, $R_{(int)}$ = 0.0225, data/restraints/parameters: 2813/0/193, goodness-of-fit on F^2 = 1.151, final R indices [$I \geq 2\sigma(I)$], $R1$ = 0.0623, $wR2$ = 0.1392, R indices (all data): $R1$ = 0.0742, $wR2$ = 0.1456, largest diff. peak and hole: 0.204 and –0.219 eÅ^{-3}. CCDC 793451 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(18) (a) Byth, F. K.; Culshaw, J. D.; Green, S.; Oakes, S. E.; Thomas, A. P. *Bioorg. Med. Chem.* **2004**, *14*, 2245. (b) Katritzky, A. R.; Xu, Y. J.; Tu, H. *J. Org. Chem.* **2002**, *68*, 4935. (c) Kiselyov, A. S. *Tetrahedron Lett.* **2006**, *47*, 2941.