

An Efficient Synthesis of 5-Bromo-2-methoxy-6-methylaminopyridine-3-carboxylic Acid

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An efficient synthesis of 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid (**1**), a carboxylic acid moiety of a potent dopamine D₂ and D₃ and serotonin-3 (5-HT₃) receptors antagonist, (*R*)-5-bromo-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-2-methoxy-6-methylaminopyridine-3-carboxamide, is described. Reaction of methyl 2,6-difluoropyridine-3-carboxylate (**12**) with methylamine in EtOH at –25 °C gave a mixture of methyl 2-fluoro-6-methylaminopyridine-3-carboxylate (**13**) and the regioisomer **14** in a ratio of 57 : 43. On the other hand, reaction of **12** and methyl 2,6-dichloropyridine-3-carboxylate (**16**) with sodium methoxide in tetrahydrofuran (THF) and CH₂Cl₂ provided the 2-methoxypyridine-3-carboxylic esters **20** and **23**, respectively, as main products. Similar reaction of **16** in *N,N*-dimethylformamide (DMF) and MeOH proved to be highly regioselective for the 6-position. A much greater regioselectivity for substitution at the 6-position (>97%) was observed when **16** was treated with 4-methylbenzenethiolate anion in DMF (quantitative yield). After methoxylation of methyl 2-chloro-6-(4-methylbenzenethio)pyridine-3-carboxylate (**25b**) and successive oxidation of the 6-benzenethio moiety, nucleophilic substitution of the sulfoxide derivative **28** with methylamine gave the 6-methylamino derivative **8**. Finally, bromination of **8** and alkaline hydrolysis produced the desired product **1** in an overall yield of 67%.

Key words serotonin 5-HT₃ receptor; dopamine D₂; dopamine D₃; antiemetic agent; regioselective synthesis

Potent and selective serotonin-3 (5-HT₃) receptor antagonists, such as DAT-582¹⁾ [(*R*)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide dihydrochloride], discovered in our laboratories, granisetron and ondansetron are effective in the control of emesis induced by cancer chemotherapeutic agents.²⁾ The traditional antiemetic agent domperidone, a peripheral dopamine D₂ receptor antagonist, has been shown to be effective in the prevention of nausea and vomiting resulting from a variety of causes.³⁾ However, domperidone is only minimally effective against chemotherapy-induced nausea and vomiting.⁴⁾ In the course of our studies on the structure–activity relationships (SARs) of DAT-582,⁵⁾ benzamides with an alkyl group on the nitrogen atom in the hexahydro-1,4-diazepine ring, such as the 1-ethyl-4-methylhexahydro-1,4-diazepine ring were found to show dopamine D₂ receptor antagonistic activity along with a potent 5-HT₃ receptor antagonistic activity. This finding suggested that these compounds could be broad antiemetic agents, and led us to modify the benzene ring and prepare the optically active 6-aminohexahydro-1,4-diazepine ring, resulting in the discovery of (*R*)-5-bromo-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-2-methoxy-6-methylaminopyridine-3-carboxamide difumarate (originally AS-8112) with a potent dopamine D₂ and D₃ and 5-HT₃ receptors antagonistic activity. AS-8112 was finally selected as a promising broad antiemetic agent.⁶⁾ In order to obtain a large amount of AS-8112, an efficient synthesis of 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid (**1**) was essential. This paper describes the synthetic route to **1** from the 2,6-dichloropyridine-3-carboxylic ester **16**.

Results and Discussion

Synthesis of 5-Bromo-2-methoxy-6-methylaminopyridine-3-carboxylic Acid (1**) from 2,6-Difluoropyridine (**2**)**
For the success of preparation of **1**, introduction of nitrogen and oxygen functions at the 6- and 2-positions of the pyridine ring, respectively, is an important strategy. Coldwell *et*

al. reported the synthesis of 6-amino-5-chloro-2-methoxypyridine-3-carboxylic acid (**3**)⁷⁾ from 2,6-difluoropyridine (**2**) via 2-fluoro-6-pivaloylaminopyridine (**4**). However, the overall yield was poor. In our study we first prepared the key intermediate **8**, methyl 2-methoxy-6-methylaminopyridine-3-carboxylate, from ethyl 2-fluoro-6-(*N*-methyl-*N*-pivaloyl)aminopyridine-3-carboxylate (**6**) according to the method of Coldwell *et al.*⁷⁾ Selective displacement of one fluorine atom of **2** by methylamine in EtOH at *ca.* 140 °C and successive acylation with pivaloyl chloride afforded 2-fluoro-6-(*N*-methyl-*N*-pivaloyl)aminopyridine (**5**) in 65% yield. Unfortunately, ortho-directed lithiation of **5** with *n*-BuLi followed by treatment with ethyl chloroformate did not give the corresponding pyridine-3-carboxylic ester **6** and the starting **5** was recovered. We then examined *N*-methylation of ethyl 2-fluoro-6-pivaloylaminopyridine-3-carboxylate (**7**)⁷⁾ prepared from **4**. Reaction of **7** with MeI in the presence of NaH pro-

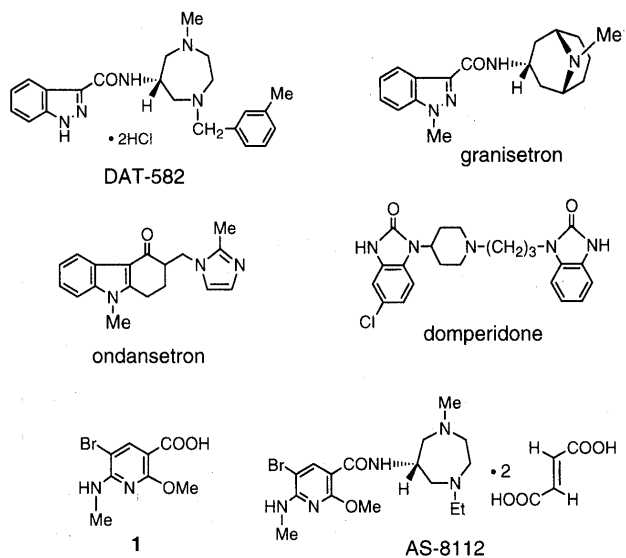
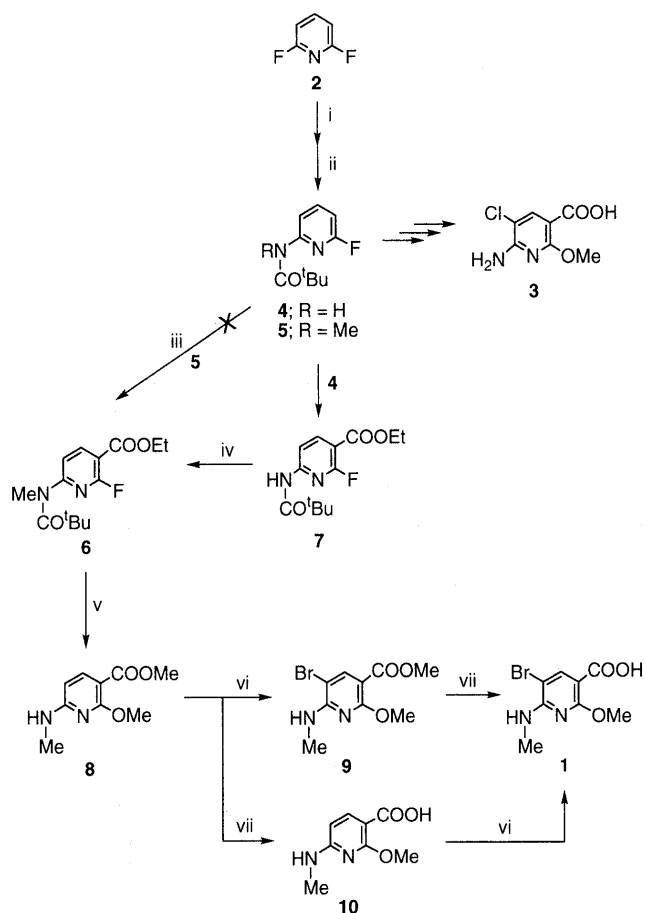


Fig. 1

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Reagents and conditions: i, MeNH_2 , EtOH, 140°C ; ii, tert-BuCOCl , Et_3N , CH_2Cl_2 , 0°C ; iii, $n\text{-BuLi}$, -78°C then ClCO_2Et ; iv, NaH then MeI , DMF, room temperature; v, tert-BuOK , MeOH, reflux; vi, NBS, DMF, 80°C ; vii, aq. NaOH, reflux.

Chart 1

vided the 6-(*N*-methyl-*N*-pivaloyl)aminopyridine-3-carboxylate **6** in only 17% yield. Displacement reaction of the fluorine atom of **6** by methoxide anion produced from potassium *tert*-butoxide and MeOH was accompanied by ester exchange and de-acylation to give **8** in 68% yield. Bromination of **8** with *N*-bromosuccinimide (NBS) followed by alkaline hydrolysis of the resulting **9** produced the desired pyridine-3-carboxylic acid **1** in 96% yield. On the other hand, after alkaline hydrolysis of **8**, bromination of 2-methoxy-6-methylaminopyridine-3-carboxylic acid (**10**) gave the 5-bromopyridine-3-carboxylic acid **1** in 88% yield along with 3,5-dibromo-2-methoxy-6-methylaminopyridine which was thought to be formed *via* decarboxylation of **10** in *ca.* 5% yield (Chart 1).

Nucleophilic Substitution Reaction of 2,6-Dihalo-3-pyridyl carboxylic Esters 12 and 16 In order to improve the overall yield of **1**, nucleophilic substitution reaction of methyl 2,6-difluoropyridine-3-carboxylate (**12**) prepared from 2,6-difluoropyridine-3-carboxylic acid (**11**)⁸⁾ with methylamine was carried out. Treatment of **12** with 20% methylamine in EtOH at -25°C gave a mixture of methyl 2-fluoro-6-methylaminopyridine-3-carboxylate (**13**) and the regioisomer of **13**, methyl 6-fluoro-2-methylaminopyridine-3-carboxylate (**14**). The mixture was separated into the less polar compound **14** (42%) as an oil and the more polar compound **13** (55%) as a solid by crystallization and flash chro-

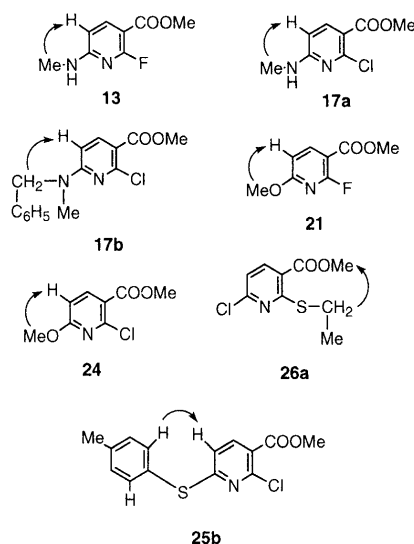
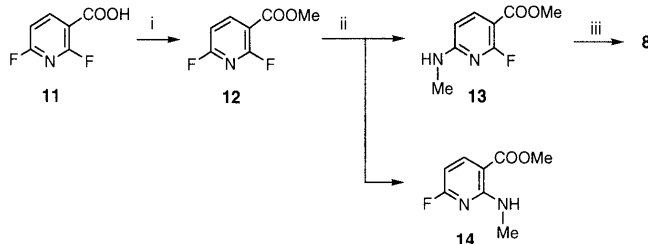


Fig. 2. Significant NOE Signals Observed upon Irradiation of the Methyl Group, Methylene Moiety, or Aromatic Proton of **13**, **17a**, **17b**, **21**, **24**, **25b**, **26a**



Reagents and conditions: i, MeOH, H_2SO_4 , reflux; ii, MeNH_2 , EtOH, -25°C ; iii, tert-BuOK , MeOH, reflux.

Chart 2

matography on silica gel. The position of the methylamino group of **13** was determined by differential nuclear Overhauser effect (NOE) experiment; irradiation at δ 2.98 (*N*-Me) enhanced signal intensity of the adjacent pyridine 5-proton (δ 6.23) (Fig. 2). Treatment of **13** with potassium *tert*-butoxide in MeOH afforded **8** in 97% yield (Chart 2). Next, the effects of solvents and temperature on the reaction of **12** with methylamine were examined (Table 1). The ratio of the mixture of 6- and 2-substituted pyridines **13** and **14** was determined by ^1H -NMR spectroscopy. The reaction in MeOH at 5°C for 10 min gave a mixture of **13** and **14** in a ratio of 46:54 in a quantitative yield (run 1). Similar reaction at -78°C did not proceed (run 2). The reaction in *N,N*-dimethylformamide (DMF) at 5°C and lower temperatures (-30°C , -60°C) afforded the 6-methylaminopyridine-3-carboxylic ester **13** as major product (runs 3—5). Using CH_3CN , tetrahydrofuran (THF) and CH_2Cl_2 as solvents at 5°C , the yield of the 6-methylaminopyridine-3-carboxylic ester **13** was poor compared with that observed in the reaction in DMF (runs 6—8). This indicates that the choice of solvent is important for the regioselective substitution reaction.

Similarly, the behavior of the more available methyl 2,6-dichloropyridine-3-carboxylate (**16**)⁹⁾ was then examined (Table 2). Since the reactivity towards a nucleophile of **16** is poor compared with that of **12**, longer reaction time is neces-

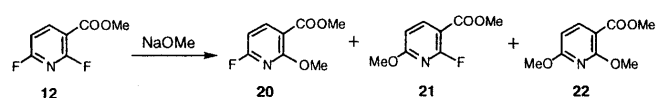
Kawato and Newkome reported that the reaction of 3-cyano-2,6-dichloropyridine and *N,N*-dimethyl-2,6-dichloropyridine-3-carboxamide with electron withdrawing groups at

On the basis of the results described above, the reaction of **16** with sulfur nucleophile in DMF was finally investigated (Table 5). Treatment of **16** with ethanethiol in DMF in the presence of NaH at 5 °C gave the 6-ethylthiopyridine derivative **25a** and the regioisomer **26a** in 91:9 ratio in a good yield (run 1). Potassium *tert*-butoxide used instead of NaH as

a) An almost quantitative yield was obtained. The ratio was determined by ^1H -NMR spectroscopy. See Experimental section. b) The presence of **12** was detected (15%).

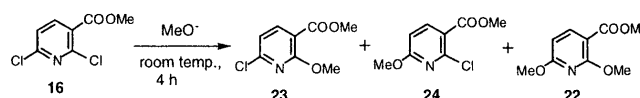
Reagents and conditions: i, MeOH, H₂SO₄, reflux. **a:** R=H
b: R=CH₂Ph

a) An almost quantitative yield was obtained. The ratio was determined by ^1H -NMR spectroscopy. See Experimental section. N.D.: Not detected.

Table 3. Reaction of Methyl 2,6-Difluoropyridine-3-carboxylate **12** with Sodium Methoxide

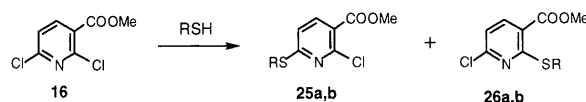
Run	Conditions	Ratio (%) ^{a)}			
		20	21	22	12
1	CH ₃ CN, 5 °C, 10 min	61	19	10	10
2	CH ₂ Cl ₂ , 5 °C, 10 min	74	10	8	8
3	THF, 5 °C, 10 min	77	14	4.5	4.5
4	THF, -30 °C, 1.5 h	67	18	N.D.	15
5	THF, -78 °C, 3 h	15	4	N.D.	81
6	MeOH, 5 °C, 10 min	18	80	2	N.D.
7	DMF, 5 °C, 10 min	15	27	29	2

a) An almost quantitative yield was obtained. The ratio was determined by ¹H-NMR spectroscopy. See Experimental section. N.D.: Not detected.

Table 4. Reaction of Methyl 2,6-Dichloropyridine-3-carboxylate **16** with Methoxide Anion

Run	Conditions	Ratio (%) ^{a)}			
		23	24	22	16
1	NaOMe in CH ₂ Cl ₂	85	15	N.D.	N.D.
2	NaOMe in THF	79	14	7	N.D.
3	NaOMe in DMF	28	69	3	N.D.
4	NaOMe in MeOH	24	74	2	N.D.
5	<i>tert</i> -BuOK/MeOH	20	72	N.D.	8

a) An almost quantitative yield was obtained. The ratio was determined by ¹H-NMR spectroscopy. See Experimental section. N.D.: Not detected.

Table 5. Reaction of Methyl 2,6-Dichloropyridine-3-carboxylate **16** with the Thiolate Anions

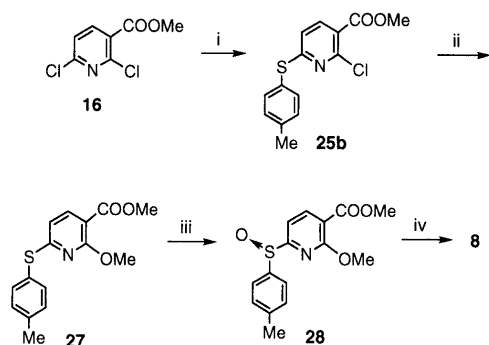
a: R = Et
b: R = 4-MeC₆H₄

Run	R	Conditions	Ratio (%) ^{a)}		
			25a, b	26a, b	16
1	Et	NaH, DMF, 5 °C, 1 h	91	9	N.D. ^{b)}
2	Et	<i>tert</i> -BuOK, DMF, -5 °C, 2 h	88	12	N.D.
3	Et	<i>tert</i> -BuOK, THF, -5 °C, 1 h	50	50	N.D.
4	Et	<i>tert</i> -BuOK, THF, -30 °C, 1 h	50	50	N.D.
5	4-MeC ₆ H ₄	NaH, DMF, room temp., 15 min	52	48	N.D.
6	4-MeC ₆ H ₄	<i>tert</i> -BuOK, DMF, room temp., 45 min	93.7	6.3	N.D.
7	4-MeC ₆ H ₄	<i>tert</i> -BuOK, DMF, 5 °C, 30 min	94.1	5.9	N.D.
8	4-MeC ₆ H ₄	<i>tert</i> -BuOK, DMF, -5 °C, 1 h	95.2	4.8	N.D.
9	4-MeC ₆ H ₄	<i>tert</i> -BuOK, DMF, -30 °C, 1 h	97.0	3.0	N.D.
10	4-MeC ₆ H ₄	<i>tert</i> -BuOK, THF, room temp., 1 h	65	22	13

a) An almost quantitative yield was obtained. The ratio was determined by ¹H-NMR spectroscopy. See Experimental section. N.D.: Not detected.

a base reduced the ratio of **25a** (run 2). Furthermore, replacement of DMF by THF caused a decrease in the ratio of **25a** regardless of the reaction temperature (runs 3, 4). Next, a similar reaction with more bulky 4-methylbenzenethiol in DMF in the presence of NaH at room temperature furnished approximately the same ratio of the products **25b** and **26b** (run 5). Surprisingly, treatment of **16** with 4-methylbenzenethiol in DMF in the presence of potassium *tert*-butoxide at room temperature gave **25b** and **26b** in a ratio of 93.7 : 6.3 (run 6). Lower temperatures resulted in an increase in the ratio of the product **25b** (runs 7–9). In particular, the reaction at -30 °C produced an excellent ratio of **25b**. Replacement of DMF by THF caused a decrease in the ratio of **25b**, and so did the reaction of **16** with ethanethiol (run 10). Confirmation of the structure of **25b** and **26a** was provided by differential NOE experiments; irradiation at δ 7.50 (aromatic H) of **25b** and δ 3.17 (methylene proton of ethyl group) of **26a** enhanced signal intensity of the pyridine 5-proton (δ 6.68) of **25b** and of the methyl ester group (δ 3.92) of **26a** (Fig. 2).

As shown in Tables 1–5, when MeOH and DMF were used as solvents, the selectivity for the 6-position of pyridine nucleus was high. On the other hand, in the case of CH₃CN, CH₂Cl₂ and THF, the main products were the 2-substituted pyridine derivatives. These interesting results can be explained as follows. The site of the initial nucleophilic attack is considered to be the halogen substituted carbon atom with strong inductive and electric field effects. When the carbon atoms at the 2- and 6-position were compared, the net charge of the carbon atom at the 2-position was more positive than that of the carbon atom at the 6-position. This is independent of the kind of solvent. The five solvents used above can be classified into two groups according to their polarity, namely MeOH, DMF and CH₃CN have higher dielectric constant,¹⁰⁾ 32.6, 37.7 and 37.5, respectively, and CH₂Cl₂ and THF have lower values 8.9 and 7.4, respectively. From their polarity and the reaction conditions shown in Tables 1–5, when solvents with lower polarity were used, the selectivity for the nucleophilic substitution reaction was found to be on the carbon atom at the 2-position. On the other hand, the use of



Reagents and conditions: i, 4-MeC₆H₄SH, *tert*-BuOK, DMF, -30 °C; ii, NaOMe, THF, reflux; iii, MCPBA, CH₂Cl₂, room temperature; iv, MeNH₂, DMF, 60 °C.

Chart 3

more polar and better ionizing solvents having higher dielectric constants afforded predominantly the 6-isomers except for CH₃CN. In general, the more dispersed the charge distribution of anionic transition state in a nucleophilic substitution reaction, the less solvated the transition state is. The result causes a slight decrease in reaction rates for substitution in higher polar solvent.¹¹⁾ All reactions described above simultaneously and competitively proceeded and involved the addition at the 2- and 6-position. Because the transition state is more solvated *via* the 6-adducts in more polar solvents compared with the 2-isomers, and the activation energy of the transition state in the reactions for the 6-isomers is lower than that of 2-isomers, the reaction in more polar solvents is considered to give the 6-substituted isomers as main product. In contrast, minor effect on the solvation in less polar solvents predominantly produced the 2-isomers as main products. CH₃CN behaves as if it was a solvent with low dielectric constant. The detailed mechanism of reactions using CH₃CN is still unknown. The significant selectivity at the 6-position of the 4-methylbenzenethiol shown in Table 5 was presumed to be the steric effect of nucleophile in addition to the solvent effect.

Synthesis of Methyl 2-Methoxy-6-methylaminopyridine-3-carboxylate (8) from Methyl 2,6-Dichloropyridine-3-carboxylate (16) Finally, a large scale synthesis of **8** using the reaction of **16** with 4-methylbenzenethiol was carried out (Chart 3). Treatment of **16** with 4-methylbenzenethiol in the presence of potassium *tert*-butoxide in DMF at -30 °C gave a mixture of **25b** and **26b** in a ratio of >97: <3 in a quantitative yield. The mixture was treated with sodium methoxide to afford the corresponding 2- and 6-methoxypyridine-3-carboxylates, which were purified by recrystallization from AcOEt to give the pure 2-methoxypyridine-3-carboxylate **27** in 87% yield. Oxidation of **27** with *m*-chloroperbenzoic acid (MCPBA) produced the sulfoxide **28** along with the corresponding sulfone derivative in a ratio of 11: 1 in an excellent yield. The ratio of the sulfoxide and sulfone was detected by ¹H-NMR spectroscopy and the mixture was purified by recrystallization to give **28**. Successively, treatment of **28**, which has a 4-methylbenzenesulfinyl group as a leaving group, with methylamine in DMF at *ca.* 60 °C gave methyl 2-methoxy-6-methylaminopyridine-3-carboxylate **8** in 90% yield. The product was identified with samples obtained from **6** or **13**, on the basis of TLC, IR and ¹H-NMR comparisons.

Conclusion

We examined a large scale synthesis of 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid (**1**). In order to ascertain the preferred site for nucleophilic attack on the pyridine nucleus, the reaction of the 2,6-difluoro and 2,6-dichloropyridine-3-carboxylic esters **12** and **16** with methylamine and methoxide anion was carried out under widely varied conditions. Although the reaction with methylamine did not result in a good selectivity, the reaction with methoxide anion, however, proved to be very selective as the preferred site for nucleophilic displacement in THF, CH₂Cl₂ and CH₃CN was found to be the 2-position. Reaction of **16** with methoxide and thiolate anions in DMF, on the other hand, afforded predominantly the 6-isomer. This indicates that the choice of solvent is very important in this reaction. It can therefore be concluded that the nucleophilic substitution reaction of **16** with 4-methylbenzenethiolate anion in DMF is a simple and efficient method for large scale synthesis of 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid (**1**) with an overall yield of 67% (**1** from **16** *via* **27**, **28**, **8** and **9**).

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Shimadzu FTIR-8200PC spectrometer with KBr disks. Atmospheric pressure chemical ionization mass spectra (APCI-MS) were obtained on a Hitachi M-1000 spectrometer. ¹H-NMR spectra were recorded on a Varian Gemini-200 (200 MHz) or a JEOL JNM-LA300 (300 MHz) apparatus using dilute solution in CDCl₃ unless otherwise stated. Chemical shifts are expressed as δ (ppm) values from tetramethylsilane as an internal standard and coupling constants (*J*) are given in Hz. Organic extracts were dried over anhydrous MgSO₄ unless otherwise specified. Solvents were evaporated under reduced pressure. Flash chromatography was carried out on 60 μ m mesh silica gel (Fuji Silysia FL60D).

2-Fluoro-6-(*N*-methyl-*N*-pivaloylamino)pyridine (5) A mixture of 2,6-difluoropyridine (**2**, 50.0 g, 0.43 mol) and methylamine (240 ml of *ca.* 30% EtOH) was heated at *ca.* 140 °C in a sealed tube for 8 h and cooled to room temperature. After evaporation of all volatiles, aqueous K₂CO₃ was added the residue, and the mixture was extracted with CHCl₃. The extract was dried over anhydrous K₂CO₃ and concentrated to dryness to give 59 g of crude 2-fluoro-6-methylaminopyridine as an oil. Pivaloyl chloride (78.6 g, 0.65 mol) was added dropwise to a solution of crude 2-fluoro-6-methylaminopyridine and Et₃N (96.8 g, 0.96 mol) in CH₂Cl₂ (1500 ml) at *ca.* 0 °C. The reaction mixture was stirred at room temperature overnight and then washed successively with water, 2 M aqueous H₂SO₄, water and brine. The solvent was evaporated, and the residue was purified by flash chromatography (CHCl₃ to CHCl₃-MeOH, 10:1) to afford 59.6 g (65%) of **5** as an oil. ¹H-NMR δ : 1.15 (9H, s, CMe₃), 3.33 (3H, s, NMe), 6.85 (1H, dd, *J*_{F-3H}=3.0 Hz, *J*_{4H-3H}=8.0 Hz, 3-H), 7.18 (1H, dd, *J*_{F-5H}=2.0 Hz, *J*_{4H-5H}=8.0 Hz, 5-H), 7.83 (1H, ddd, *J*_{3H-4H}=8.0 Hz, *J*_{F-4H}=8.0 Hz, *J*_{5H-4H}=8.0 Hz, 4-H). MS *m/z*: 211 (MH⁺).

Ethyl 2-Fluoro-6-(*N*-methyl-*N*-pivaloylamino)pyridine-3-carboxylate (6) NaH (8.1 g of 60% dispersion in oil, 0.20 mol) was added portionwise to a solution of **7** (36.0 g, 0.13 mol), prepared from **4** according to ref. 7 in DMF (360 ml) at *ca.* 0 °C. The mixture was stirred at room temperature for 4 h and then recooled at *ca.* 0 °C. After addition of MeI (17 ml, 0.27 mol), the whole was stirred at room temperature overnight. The mixture was poured into ice-water and extracted with AcOEt. The extract was washed with brine and evaporated, and the residue was purified by flash chromatography (CHCl₃) to give 6.4 g (17%) of **6** as an oil. ¹H-NMR δ : 1.27 (9H, s, CMe₃), 1.40 (3H, t, *J*=7.0 Hz, CH₂Me), 3.42 (3H, s, NMe), 4.41 (2H, q, *J*=7.0 Hz, CH₂Me), 7.37 (1H, dd, *J*_{F-5H}=1.5 Hz, *J*_{4H-5H}=8.2 Hz, 5-H), 8.33 (1H, dd, *J*_{F-4H}=9.5 Hz, *J*_{5H-4H}=8.2 Hz, 4-H). MS *m/z*: 283 (MH⁺).

Methyl 2,6-Difluoropyridine-3-carboxylate (12) Concentrated H₂SO₄ (5 ml) was added dropwise to a solution of **11**⁸⁾ (63.0 g, 0.40 mol) in MeOH (700 ml). The mixture was heated to reflux for 20 h and cooled to room temperature. After evaporation of the solvent, the oily residue was added to ice-water and extracted with CHCl₃. The extract was washed with brine and

concentrated to dryness, and the residue was purified by flash chromatography (CHCl_3) to give 64.0 g (93%) of **12** as an oil. $^1\text{H-NMR}$ δ : 3.96 (3H, s, CO_2Me), 6.93 (1H, ddd, $J_{2\text{F}-5\text{H}}=3.0$ Hz, $J_{6\text{F}-5\text{H}}=3.0$ Hz, $J_{5\text{H}-4\text{H}}=8.2$ Hz, 5-H), 8.52 (1H, ddd, $J_{2\text{F}-4\text{H}}=8.3$ Hz, $J_{6\text{F}-4\text{H}}=8.3$ Hz, $J_{5\text{H}-4\text{H}}=8.2$ Hz, 4-H). MS m/z : 174 (MH^+).

Methyl 2-Fluoro-6-methylaminopyridine-3-carboxylate (13) and Methyl 6-Fluoro-2-methylaminopyridine-3-carboxylate (14) Methylamine (72 g of ca. 20% EtOH solution, 0.46 mol) was added dropwise to a solution of **12** (38.0 g, 0.22 mol) in EtOH (500 ml) at ca. -25°C . The mixture was stirred at the same temperature for 5 h and then warmed to room temperature. After evaporation of all volatiles, ice-water was added to the residue. The resulting solid was collected by filtration, washed with water, dried, and recrystallized from diethyl ether–hexane to give 15.7 g (39%) of **13**, mp $156\text{--}159^\circ\text{C}$. $^1\text{H-NMR}$ δ : 2.98 (3H, d, $J=5.0$ Hz, NHMe), 3.87 (3H, s, CO_2Me), 5.50 (1H, br, NHMe), 6.23 (1H, dd, $J_{\text{F}-5\text{H}}=2.0$ Hz, $J_{4\text{H}-5\text{H}}=8.5$ Hz, 5-H), 8.09 (1H, dd, $J_{\text{F}-4\text{H}}=9.5$ Hz, $J_{5\text{H}-4\text{H}}=8.5$ Hz, 4-H). MS m/z : 185 (MH^+). IR ν cm^{-1} : 3271, 3134, 1701, 1630, 1319. *Anal.* Calcd for $\text{C}_8\text{H}_8\text{FN}_2\text{O}_3$: C, 52.17; H, 4.93; F, 10.32; N, 15.21. Found: C, 52.23; H, 4.89; F, 10.35; N, 15.05.

The filtrate was extracted with CHCl_3 , and the extract was washed with brine. The solvent was evaporated, and the residue was purified by flash chromatography (CHCl_3) to give 16.9 g (42%) of **14** as a viscous oil and 6.5 g (16%) of **13** as a solid.

14; mp $55\text{--}56^\circ\text{C}$ (hexane). $^1\text{H-NMR}$ δ : 3.03 (3H, d, $J=4.8$ Hz, NHMe), 3.85 (3H, s, CO_2Me), 6.07 (1H, dd, $J_{\text{F}-5\text{H}}=2.7$ Hz, $J_{4\text{H}-5\text{H}}=8.2$ Hz, 5-H), 8.18 (1H, dd, $J_{\text{F}-4\text{H}}=8.2$ Hz, $J_{5\text{H}-4\text{H}}=8.2$ Hz, 4-H). MS m/z : 185 (MH^+). IR ν cm^{-1} : 3373, 1699, 1620, 1583, 1261. *Anal.* Calcd for $\text{C}_8\text{H}_8\text{FN}_2\text{O}_3$: C, 52.17; H, 4.93; F, 10.32; N, 15.21. Found: C, 52.48; H, 4.81; F, 10.27; N, 14.88.

Methyl 2,6-Dichloropyridine-3-carboxylate (16) A mixture of 2,6-dichloropyridine-3-carboxylic acid (**15**, 400 g, 2.1 mol), MeOH (2000 ml) and concentrated H_2SO_4 (40 ml) was heated to reflux for 6 h and cooled to room temperature. The solvent was evaporated to leave an oily residue. After neutralization with saturated aqueous NaHCO_3 , the resulting solid was collected by filtration, washed with water and dried to give 414 g (96%) of **16**, mp $53\text{--}54^\circ\text{C}$ (hexane) [lit.⁹⁾ $56.0\text{--}56.5^\circ\text{C}$ (MeOH)]. $^1\text{H-NMR}$ δ : 3.96 (3H, s, CO_2Me), 7.36 (1H, d, $J=8.1$ Hz, 5-H), 8.16 (1H, dd, $J=8.1$ Hz, 4-H). MS m/z : 206 (MH^+). IR ν cm^{-1} : 1732, 1572, 1545, 1418. *Anal.* Calcd for $\text{C}_7\text{H}_5\text{Cl}_2\text{NO}_2$: C, 40.81; H, 2.45; Cl, 34.42; N, 6.80. Found: C, 40.63; H, 2.63; Cl, 34.32; N, 6.75.

Methyl 2-Methoxy-6-(4-methylbenzenethio)pyridine-3-carboxylate (27) Potassium *tert*-butoxide (30.7 g, 0.27 mol) was added portionwise to a solution of 4-methylbenzenethiol (32.5 g, 0.26 mol) in DMF (150 ml) at room temperature, and the mixture was stirred at the same temperature for 15 min. The resulting reaction mixture was added dropwise to a solution of **16** (51.4 g, 0.25 mol) in DMF (250 ml) at -30°C . The whole was stirred at the same temperature for 1 h, poured into ice-water and extracted with a mixture of AcOEt–hexane (2:1). The extract was washed with brine and evaporated to leave an oily residue (73.2 g, quantitative yield) containing methyl 2-chloro-6-(4-methylbenzenethio)pyridine-3-carboxylate **25b** and methyl 6-chloro-2-(4-methylbenzenethio)pyridine-3-carboxylate **26b** in the ratio of $>97: <3$.

NaOMe (50.0 g of ca. 28% MeOH solution, 0.26 mol) was added to a solution of the mixture of **25b** and **26b** (73.2 g, 0.25 mol) in THF (500 ml) at room temperature. The mixture was heated to reflux for 2 h and cooled to room temperature. The resulting deposited material was filtered off and washed with THF. The filtrate was concentrated to dryness, and the residue was dissolved in CHCl_3 and washed successively with water and brine. The solvent was evaporated to leave a solid (72.0 g), which was recrystallized from AcOEt to give 62.4 g (87%) of **27**, mp $92\text{--}94^\circ\text{C}$. $^1\text{H-NMR}$ δ : 2.42 (3H, s, $\text{C}_6\text{H}_4\text{Me}$), 3.85 (3H, s, OMe), 3.92 (3H, s, CO_2Me), 6.45 (1H, d, $J=8.0$ Hz, 5-H), 7.25 (2H, d, $J=8.0$ Hz, ArH), 7.50 (2H, d, $J=8.0$ Hz, ArH), 7.94 (1H, d, $J=8.0$ Hz, 4-H). MS m/z : 290 (MH^+). IR ν cm^{-1} : 1726, 1585, 1555, 1460, 1367, 1256. *Anal.* Calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_3\text{S}$: C, 62.47; H, 5.23; N, 4.90; S, 10.93. Found: C, 62.26; H, 5.23; N, 4.84; S, 11.08.

Methyl 2-Methoxy-6-(4-methylbenzenesulfonyl)pyridine-3-carboxylate (28) Ca. 60% MCPBA (248.5 g, 0.86 mol) was added to a solution of **27** (250 g, 0.87 mol) in CH_2Cl_2 (1250 ml) at ca. 5°C . The mixture was stirred at room temperature for 45 min and washed successively with 5% aqueous NaHCO_3 , water and brine. The solvent was evaporated to leave a mixture of **28** and methyl 2-methoxy-6-(4-methylbenzenesulfonyl)pyridine-3-carboxylate in a ratio of 11:1 as a solid (257 g, calculated yield of **28** is 89%). The pure **28** was obtained by recrystallization from AcOEt–hexane, mp $106\text{--}107^\circ\text{C}$. $^1\text{H-NMR}$ δ : 2.37 (3H, s, $\text{C}_6\text{H}_4\text{Me}$), 3.88 (3H, s, OMe), 3.97 (3H, s, CO_2Me), 7.27 (2H, d, $J=8.2$ Hz, ArH), 7.67 (2H, d, $J=8.2$ Hz,

ArH), 7.69 (1H, d, $J=7.7$ Hz, 5-H), 8.30 (1H, d, $J=7.7$ Hz, 4-H). MS m/z : 306 (MH^+). IR ν cm^{-1} : 1709, 1582, 1562, 1466, 1381, 1277. *Anal.* Calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_4\text{S}$: C, 58.87; H, 4.92; N, 4.60; S, 10.29. Found: C, 59.00; H, 4.95; N, 4.59; S, 10.50.

Methyl 2-Methoxy-6-(4-methylbenzenesulfonyl)pyridine-3-carboxylate: $^1\text{H-NMR}$ δ : 2.44 (3H, s, $\text{C}_6\text{H}_4\text{Me}$), 3.90 (3H, s, OMe), 3.96 (3H, s, CO_2Me), 7.34 (2H, d, $J=8.1$ Hz, ArH), 7.79 (1H, d, $J=7.6$ Hz, 5-H), 7.95 (2H, d, $J=8.1$ Hz, ArH), 8.29 (1H, d, $J=7.6$ Hz, 4-H). MS m/z : 322 (MH^+).

Methyl 2-Methoxy-6-methylaminopyridine-3-carboxylate (8) a) Potassium *tert*-butoxide (7.3 g, 65 mmol) was added portionwise to a solution of **6** (6.1 g, 22 mmol) in MeOH (250 ml) at ca. 0°C . The mixture was heated to reflux for 2 h and cooled to room temperature. The solvent was evaporated to leave a residue. After addition of cold aqueous NaHCO_3 , the resulting precipitates were collected by filtration, washed with water and dried to give 2.9 g (68%) of **8**, mp $120.5\text{--}121.5^\circ\text{C}$ (diethyl ether–hexane). $^1\text{H-NMR}$ δ : 2.97 (3H, d, $J=5.0$ Hz, NHMe), 3.82 (3H, s, OMe), 3.98 (3H, s, CO_2Me), 4.83 (1H, br, NHMe), 5.94 (1H, d, $J=8.5$ Hz, 5-H), 8.01 (1H, d, $J=8.5$ Hz, 4-H). MS m/z : 197 (MH^+). IR ν cm^{-1} : 3356, 2949, 1692, 1597, 1267, 1242. *Anal.* Calcd for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_3$: C, 55.09; H, 6.19; N, 14.28. Found: C, 55.05; H, 6.12; N, 14.17.

b) According to the same procedure as described on a), **8** (16.3 g, 97%) was obtained from **13** (15.7 g, 85 mmol), potassium *tert*-butoxide (19.1 g, 0.17 mol) and MeOH (400 ml).

c) A mixture of methylamine (4.2 g of 30% EtOH solution, 41 mmol) and DMF (10 ml) was added dropwise to a solution of **28** (2.5 g, 8.2 mmol) in DMF (30 ml) at room temperature. The mixture was stirred at ca. 60°C for 1 h, poured into ice-water, and extracted with a mixture of AcOEt–hexane (1:1). The extract was washed successively with 5% aqueous NaHCO_3 , water and brine and concentrated to give 1.4 g (90%) of **8** as a solid, which was identified with the sample obtained above, on the basis of TLC, IR and $^1\text{H-NMR}$ comparisons.

Methyl 5-Bromo-2-methoxy-6-methylaminopyridine-3-carboxylate (9) A mixture of **8** (7.3 g, 37 mmol), NBS (7.0 g, 39 mmol) and DMF (70 ml) was heated at 80°C for 4 h. The reaction mixture was poured into ice-water, and the resulting precipitates were collected by filtration, washed with water and dried to give 9.8 g (96%) of **9**, mp $136\text{--}138^\circ\text{C}$ (diethyl ether–hexane). $^1\text{H-NMR}$ δ : 3.08 (3H, d, $J=5.0$ Hz, NHMe), 3.82 (3H, s, OMe), 4.02 (3H, s, CO_2Me), 5.47 (1H, br, NHMe), 8.15 (1H, s, 4-H). MS m/z : 275, 277 (MH^+). IR ν cm^{-1} : 3393, 2949, 1709, 1597, 1566, 1263, 1236. *Anal.* Calcd for $\text{C}_9\text{H}_{11}\text{BrN}_2\text{O}_3$: C, 39.29; H, 4.03; Br, 29.05; N, 10.18. Found: C, 39.39; H, 3.96; Br, 29.35; N, 10.00.

2-Methoxy-6-methylaminopyridine-3-carboxylic Acid (10) A mixture of **8** (2.4 g, 12 mmol), 2 M aqueous NaOH (6.8 ml, 14 mmol) and MeOH (10 ml) was heated to reflux for 1.5 h and cooled to room temperature. After evaporation of MeOH, the residue was diluted with water (20 ml) and washed with diethyl ether. The aqueous solution was acidified with concentrated HCl, and the resulting precipitates were collected by filtration, washed with water and dried to give 2.1 g (94%) of **10** as a solid, mp $168\text{--}168.5^\circ\text{C}$ (EtOH). $^1\text{H-NMR}$ (dimethylsulfoxide- d_6) δ : 2.84 (3H, d, $J=5.0$ Hz, NHMe), 3.87 (3H, s, OMe), 6.03 (1H, d, $J=8.0$ Hz, 5-H), 7.25 (1H, br q, $J=5.0$ Hz, NHMe), 7.81 (1H, d, $J=8.0$ Hz, 4-H), 11.67 (1H, s, CO_2H). MS m/z : 183 (MH^+). IR ν cm^{-1} : 3319, 1699, 1601, 1497, 1364. *Anal.* Calcd for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.77; H, 5.62; N, 15.47.

5-Bromo-2-methoxy-6-methylaminopyridine-3-carboxylic Acid (1) a) A mixture of **9** (20.0 g, 73 mmol), MeOH (100 ml) and aqueous NaOH [NaOH 3.1 g (78 mmol) in H_2O (200 ml)] was heated to reflux for 1.5 h and cooled to room temperature. After evaporation of MeOH, the aqueous solution was acidified with concentrated HCl. The resulting solid was collected by filtration, washed with water, and dried to give 18.9 g (quantitative yield) of **1**, mp $224\text{--}225^\circ\text{C}$ (EtOH). $^1\text{H-NMR}$ (DMSO- d_6) δ : 2.92 (3H, d, $J=5.0$ Hz, NHMe), 3.88 (3H, s, OMe), 7.08 (1H, br q, $J=5$ Hz, NHMe), 7.98 (1H, s, 4-H), 12.08 (1H, s, CO_2H). MS m/z : 261, 263 (MH^+). IR ν cm^{-1} : 3412, 1674, 1589, 1560, 1229. *Anal.* Calcd for $\text{C}_8\text{H}_8\text{BrN}_2\text{O}_3$: C, 36.80; H, 3.47; Br, 30.61; N, 10.73. Found: C, 36.83; H, 3.43; Br, 30.40; N, 10.68.

b) A solution of NBS (10.8 g, 61 mmol) in DMF (50 ml) was added dropwise to a mixture of **10** (11.0 g, 60 mmol) and DMF (110 ml) kept at ca. 10°C . The mixture was stirred at the same temperature for 5 min, and cold water (220 ml) was added. The resulting precipitates were collected by filtration, washed with water and dried to give 14.6 g (88%) of **1** containing 3,5-dibromo-2-methoxy-6-methylaminopyridine (ca. 5%) as a pale pink solid.

3,5-Dibromo-2-methoxy-6-methylaminopyridine: $^1\text{H-NMR}$ δ : 3.00 (3H, d, $J=6.0$ Hz, NHMe), 3.96 (3H, s, OMe), 4.9 (1H, br, NHMe), 7.63 (1H, s, 4-H). MS m/z : 295, 263 (MH^+), 299.

General Procedure (Tables 1–5): Reaction of 12 or 16 with Methy-

lamine, *N*-Benzylmethylamine and Methoxide and Thiolate Anions
Methylamine (30% MeOH solution, 2 mol eq), *N*-benzylmethylamine (2 mol eq), sodium methoxide (ca. 28% MeOH solution, ca. 1 mol eq), potassium *tert*-butoxide (ca. 1 mol eq) in MeOH (10 ml) or ethanethiol and 4-methylbenzenethiol (ca. 1 mol eq) in the presence of a base was added to a solution of **12** or **16** (1.0 g) in an appropriate solvent (10 ml), and the mixture was stirred at an appropriate temperature for an appropriate reaction time. After dilution of the reaction mixture with water, the solution was extracted with AcOEt. The extract was washed with brine and concentrated to dryness. The residue was analyzed using ¹H-NMR spectra.

Methyl 2-Chloro-6-methylaminopyridine-3-carboxylate (**17a**): ¹H-NMR δ: 2.98 (3H, d, *J*=4.8 Hz, NHMe), 3.87 (3H, s, CO₂Me), 5.20 (1H, br), 6.29 (1H, d, *J*=8.7 Hz, 5-H), 8.04 (1H, d, *J*=8.7 Hz, 4-H).

Methyl 6-(*N*-Benzyl-*N*-methyl)amino-2-chloropyridine-3-carboxylate (**17b**): ¹H-NMR δ: 3.12 (3H, s, NMe), 3.86 (3H, s, CO₂Me), 4.82 (2H, s, CH₂Ph), 6.38 (1H, d, *J*=9.0 Hz, 5-H), 8.01 (1H, d, *J*=9.0 Hz, 4-H), 7.2—7.4 (5H, m, ArH).

Methyl 6-Chloro-2-methylaminopyridine-3-carboxylate (**18a**): ¹H-NMR δ: 3.05 (3H, d, *J*=4.8, NHMe), 3.96 (3H, s, CO₂Me), 6.50 (1H, d, *J*=8.7 Hz, 5-H), 8.01 (1H, d, *J*=8.7 Hz, 4-H).

Methyl 2-(*N*-Benzyl-*N*-methyl)amino-6-chloropyridine-3-carboxylate (**18b**): ¹H-NMR δ: 2.83 (3H, s, NMe), 3.81 (3H, s, CO₂Me), 4.79 (2H, s, CH₂Ph), 6.65 (1H, d, *J*=8.0 Hz, 5-H), 7.87 (1H, d, *J*=8.0 Hz, 4-H), 7.2—7.4 (5H, m, ArH).

2,6-Dichloro-*N*-methylpyridine-3-carboxamide (**19**): ¹H-NMR δ: 3.06 (3H, d, *J*=4.8 Hz, NHMe), 6.56 (1H, br), 7.38 (1H, d, *J*=8.1 Hz, 5-H), 8.13 (1H, d, *J*=8.1 Hz, 4-H).

Methyl 6-Fluoro-2-methoxypyridine-3-carboxylate (**20**): ¹H-NMR δ: 3.90 (3H, s, OMe), 4.04 (3H, s, CO₂Me), 6.53 (1H, dd, *J*_{F-5H}=3.0 Hz, *J*_{4H-5H}=8.1 Hz, 5-H), 8.31 (1H, dd, *J*_{F-4H}=8.1 Hz, *J*_{5H-4H}=8.1 Hz, 4-H).

Methyl 2-Fluoro-6-methoxypyridine-3-carboxylate (**21**): ¹H-NMR δ: 3.92 (3H, s, OMe), 3.98 (3H, s, CO₂Me), 6.66 (1H, dd, *J*_{F-5H}=1.3 Hz, *J*_{4H-5H}=8.4 Hz, 5-H), 8.24 (1H, dd, *J*_{F-4H}=9.3 Hz, *J*_{5H-4H}=8.4 Hz, 4-H).

Methyl 2,6-Dimethoxypyridine-3-carboxylate (**22**): ¹H-NMR δ: 3.86 (3H, s, OMe), 3.97 (3H, s, OMe), 4.05 (3H, s, CO₂Me), 6.32 (1H, d, *J*=8.2 Hz, 5-H), 8.14 (1H, d, *J*=8.2 Hz, 4-H).

Methyl 6-Chloro-2-methoxypyridine-3-carboxylate (**23**): ¹H-NMR δ: 3.90 (3H, s, OMe), 4.06 (3H, s, CO₂Me), 6.96 (1H, d, *J*=7.8 Hz, 5-H), 8.13 (1H, d, *J*=7.8 Hz, 4-H).

Methyl 2-Chloro-6-methoxypyridine-3-carboxylate (**24**): ¹H-NMR δ: 3.91 (3H, s, OMe), 4.00 (3H, s, CO₂Me), 6.70 (1H, d, *J*=8.4 Hz, 5-H), 8.13 (1H, d, *J*=8.4 Hz, 4-H).

Methyl 2-Chloro-6-ethylthiopyridine-3-carboxylate (**25a**): ¹H-NMR δ:

1.39 (3H, t, *J*=7.3 Hz, CH₂Me), 3.21 (2H, q, *J*=7.3 Hz, CH₂Me), 3.92 (3H, s, CO₂Me), 7.12 (1H, d, *J*=8.3 Hz, 5-H), 7.97 (1H, d, *J*=8.3 Hz, 4-H).

Methyl 6-Chloro-2-ethylthiopyridine-3-carboxylate (**26a**): ¹H-NMR δ: 1.37 (3H, t, *J*=7.5 Hz, CH₂Me), 3.17 (2H, q, *J*=7.5 Hz, CH₂Me), 3.92 (3H, s, CO₂Me), 7.03 (1H, d, *J*=8.0 Hz, 5-H), 8.13 (1H, d, *J*=8.0 Hz, 4-H).

Methyl 2-Chloro-6-(4-methylbenzenethio)pyridine-3-carboxylate (**25b**): ¹H-NMR δ: 2.43 (3H, s, C₆H₄Me), 3.92 (3H, s, CO₂Me), 6.68 (1H, d, *J*=8.0 Hz, 5-H), 7.29 (2H, d, *J*=8.0 Hz, ArH), 7.50 (2H, d, *J*=8.0 Hz, ArH), 7.90 (1H, d, *J*=8.0 Hz, 4-H). MS *m/z*: 294 (MH⁺).

Methyl 6-Chloro-2-(4-methylbenzenethio)pyridine-3-carboxylate (**26b**): ¹H-NMR δ: 2.40 (3H, s, C₆H₄Me), 3.97 (3H, s, CO₂Me), 7.02 (1H, d, *J*=8.0 Hz, 5-H), 7.23 (2H, d, *J*=8.0 Hz, ArH), 7.42 (2H, d, *J*=8.0 Hz, ArH), 8.14 (1H, d, *J*=8.0 Hz, 4-H).

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