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

Yoshimi HIROKAWA,* Tamaki HORIKAWA, and Shiro KATO

Discovery Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Enoki 33–94, Suita, Osaka 564–0053, Japan.
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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 D_2 and D_3 and serotonin-3 (5-HT_3) 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 CH_2Cl_2 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-HT_3 receptor; dopamine D_2; dopamine D_3; antiemetic agent; regioselective synthesis

Potent and selective serotonin-3 (5-HT_3) receptor antagonists, such as DAT-582[1] [(*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 D_2 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 D_2 receptor antagonistic activity along with a potent 5-HT_3 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 D_2 and D_3 and 5-HT_3 receptors antagonistic activity. AS-8112 was finally selected as a promising broad antiemetic agent.[6] In order to obtain a large mount 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-

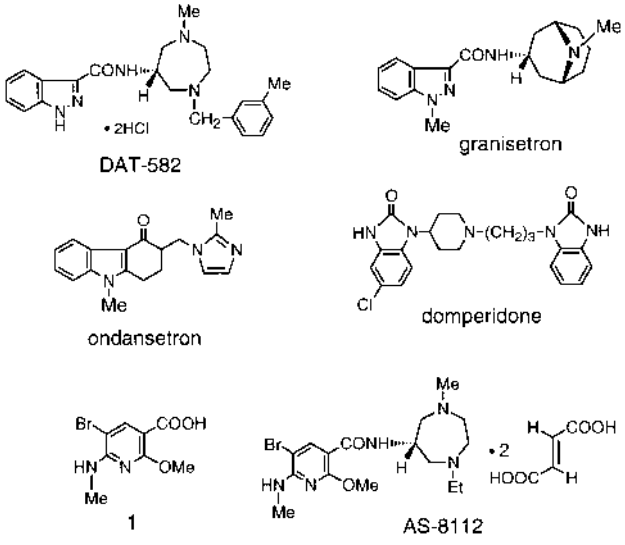
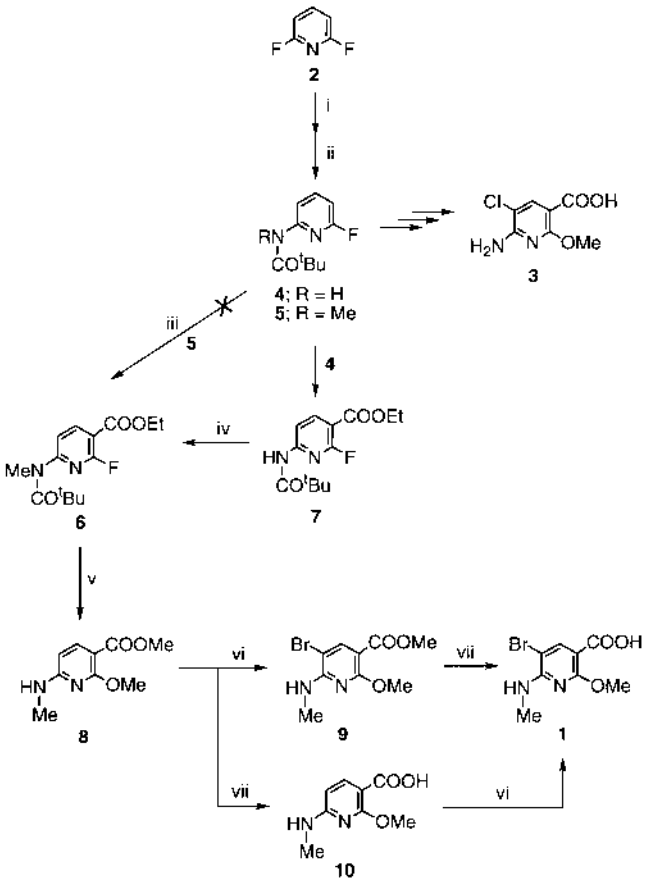


Fig. 1

* To whom correspondence should be addressed. e-mail: yoshimi-hirokawa@dainippon-pharm.co.jp



Reagents and conditions: i, $MeNH_2$, EtOH, 140 °C; ii, *tert*-BuCOCl, Et_3N, CH_2Cl_2, 0 °C; iii, *n*-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

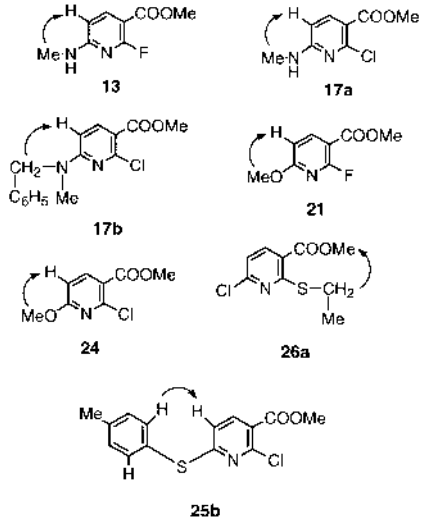
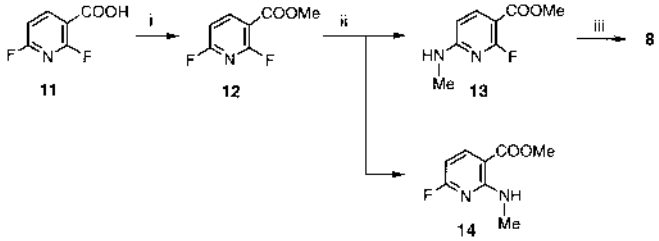


Fig. 2. Significant NOE Signals Observed upon Irradiation of the Methyl Group, Methylene Moiety, or Aromatic Proton of **13**, **17a**, **17b**, **21**, **24**, **25b**, **26a**



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

Chart 2

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-Dihalogenopyridine-3-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 chromatography 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 ^{1}H-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-

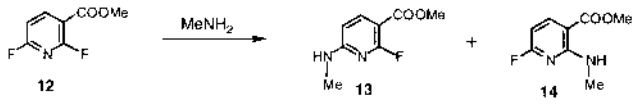
sary. Ester **16** prepared by esterfication of the commercially available 2,6-dichloropyridine-3-carboxylic acid (**15**) was treated with methylamine in THF and DMF at 5 °C for 3 h to afford the 2-methylaminopyridine-3-carboxylic ester **18a** as main product together with the regioisomer **17a** and the amide derivative **19** (runs 1, 2). In a similar reaction in MeOH, the main product was *N*-methyl-2,6-dichloropyridinecarboxamide (**19**) (run 3). Although the reaction of **16** with the secondary amine, *N*-benzylmethylamine, in THF showed good selectivity, the main product was the undesired 2-substitution product **18b** (run 4). Confirmation of the structure of **17a**, **b** was provided by differential NOE experiments; irradiation at δ 2.98 (*N*-Me) of **17a** and δ 4.82 (the methylene proton of *N*-CH_2Ph) of **17b** enhanced signal intensity of the pyridine 5-proton (δ 6.29) of **17a** and (δ 6.38) of **17b**, respectively (Fig. 2).

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 the 3-position with sodium ethoxide in xylene gives 2-ethoxypyridine derivatives as major products.[9] As an extension to our nucleophilic substitution reaction of the 2,6-difluoro and 2,6-dichloropyridine-3-carboxylic esters **12** and **16**, the reaction with methoxide anion was examined (Tables 3, 4). The reaction of **12** in CH_3CN, CH_2Cl_2 and THF at 5 °C gave the same results described above; regioselectivity for methoxide anion at the 2-position was enriched to give the 2-methoxypyridine-3-carboxylic ester **20** in spite of the reaction temperature (runs 1—5 in Table 3). Treatment in MeOH at 5 °C produced the 6-methoxypyridine-3-carboxylic ester **21** as main product (run 6 in Table 3). The reaction in DMF did not give a good result as the disubstituted product, methyl 2,6-dimethoxypyridine-3-carboxylate (**22**) was obtained as main product (run 7 in Table 3). Confirmation of the structure of **21** was provided by differential NOE experiment; irradiation at δ 3.92 (OMe) enhanced signal intensity of the pyridine 5-proton (δ 6.66) (Fig. 2).

Treatment of **16** with sodium methoxide in CH_2Cl_2 gave a good ratio of **23** and **24** (85 : 15) (run 1 in Table 4). The mixture of **23** and **24** was oil, and both products showed approximately the same *Rf* value on TLC with common solvent combinations. In a similar reaction in THF, the ratio of the 2-methoxypyridine-3-carboxylic ester **23**, the regioisomer **24** and **22** was 79 : 14 : 7 (run 2 in Table 4). Using DMF and MeOH, however, the 6-methoxypyridine-3-carboxylic ester **24** was obtained as main product (runs 3 and 4 in Table 4). In the reaction conditions of run 4, conversion of the sodium counter cation into potassium cation had no remarkable influence on the reaction (run 5 in Table 4). Confirmation of the structure of **24** was provided by differential NOE experiment; irradiation at δ 3.91 (OMe) enhanced signal intensity of the pyridine 5-proton (δ 6.70) (Fig. 2).

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

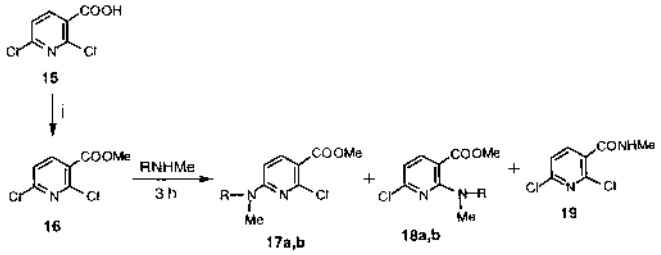
Table 1. Reaction of Methyl 2,6-Difluoropyridine-3-carboxylate **12** with Methylamine



Run	Conditions	Ratio (%)[a]	
		13	**14**
1	MeOH, 5 °C, 10 min	46	54
2	MeOH, −78 °C, 3 h	No reaction	
3	DMF, 5 °C, 10 min	55	45
4	DMF, −30 °C, 1 h	64	36
5	DMF, −60 °C, 3 h[b]	53	32
6	CH_3CN, 5 °C, 10 min	40	60
7	THF, 5 °C, 10 min	39	61
8	CH_2Cl_2, 5 °C, 10 min	25	75

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

Table 2. Reaction of Methyl 2,6-Dichloropyridine-3-carboxylate **16** with Methylamine

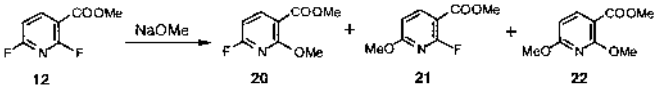


Reagents and conditions: i, MeOH, H_2SO_4, reflux. **a**: R=H **b**: R=CH_2Ph

Run	R	Conditions	Ratio (%)[a]			
			17a, **b**	**18a**, **b**	**19**	**16**
1	H	THF, 5 °C	12	49	12	27
2	H	DMF, 5 °C	32	51	7	10
3	H	MeOH, 5 °C	4	9	37	50
4	CH_2Ph	THF, −20 °C	14	86	N.D.	N.D.

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

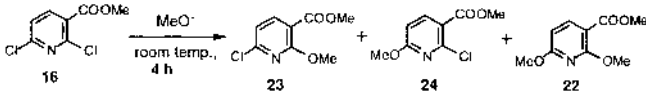
Table 3. Reaction of Methyl 2,6-Difluoropyridine-3-carboxylate **12** with Sodium Methoxide



Run	Conditions	Ratio (%)[a]			
		20	**21**	**22**	**12**
1	CH_3CN, 5 °C, 10 min	61	19	10	10
2	CH_2Cl_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 ^{1}H-NMR spectroscopy. See Experimental section. N.D.: Not detected.

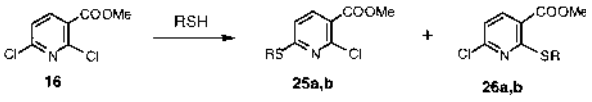
Table 4. Reaction of Methyl 2,6-Dichloropyridine-3-carboxylate **16** with Methoxide Anion



Run	Conditions	Ratio (%)[a]			
		23	**24**	**22**	**16**
1	NaOMe in CH_2Cl_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	*tert*-BuOK/MeOH	20	72	N.D.	8

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

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



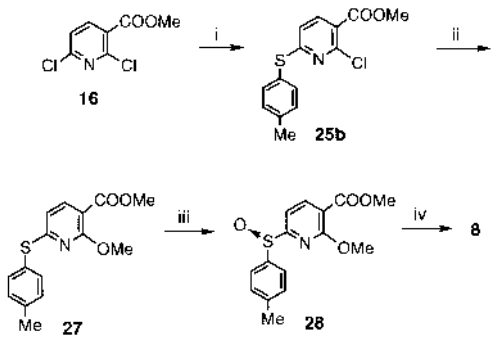
a; R = Et
b; R = 4-MeC_6H_4

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	*tert*-BuOK, DMF, −5 °C, 2 h	88	12	N.D.
3	Et	*tert*-BuOK, THF, −5 °C, 1 h	50	50	N.D.
4	Et	*tert*-BuOK, THF, −30 °C, 1 h	50	50	N.D.
5	4-MeC_6H_4	NaH, DMF, room temp., 15 min	52	48	N.D.
6	4-MeC_6H_4	*tert*-BuOK, DMF, room temp., 45 min	93.7	6.3	N.D.
7	4-MeC_6H_4	*tert*-BuOK, DMF, 5 °C, 30 min	94.1	5.9	N.D.
8	4-MeC_6H_4	*tert*-BuOK, DMF, −5 °C, 1 h	95.2	4.8	N.D.
9	4-MeC_6H_4	*tert*-BuOK, DMF, −30 °C, 1 h	97.0	3.0	N.D.
10	4-MeC_6H_4	*tert*-BuOK, THF, room temp., 1 h	65	22	13

a) An almost quantitative yield was obtained. The ratio was determined by ^{1}H-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 CH_3CN, CH_2Cl_2 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 CH_3CN have higher dielectric constant,[10] 32.6, 37.7 and 37.5, respectively, and CH_2Cl_2 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-MeC_6H_4SH, *tert*-BuOK, DMF, −30 °C; ii, NaOMe, THF, reflux; iii, MCPBA, CH_2Cl_2, room temperature; iv, $MeNH_2$, DMF, 60 °C.

Chart 3

more polar and better ionizing solvents having higher dielectric constants afforded predominantly the 6-isomers except for CH_3CN. 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. CH_3CN behaves as if it was a solvent with low dielectric constant. The detailed mechanism of reactions using CH_3CN 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 ^{1}H-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 ^{1}H-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 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, CH_2Cl_2 and CH_3CN 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. ^{1}H-NMR spectra were recorded on a Varian Gemini-200 (200 MHz) or a JEOL JNM-LA300 (300 MHz) apparatus using dilute solution in $CDCl_3$ 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 $MgSO_4$ unless otherwise specified. Solvents were evaporated under reduced pressure. Flash chromatography was carried out on 60 μm 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 K_2CO_3 was added the residue, and the mixture was extracted with $CHCl_3$. The extract was dried over anhydrous K_2CO_3 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 Et_3N (96.8 g, 0.96 mol) in CH_2Cl_2 (1500 ml) at *ca.* 0 °C. The reaction mixture was stirred at room temperature overnight and then washed successively with water, 2 M aqueous H_2SO_4, water and brine. The solvent was evaporated, and the residue was purified by flash chromatography ($CHCl_3$ to $CHCl_3$–MeOH, 10 : 1) to afford 59.6 g (65%) of **5** as an oil. ^{1}H-NMR δ: 1.15 (9H, s, CMe_3), 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 ($CHCl_3$) to give 6.4 g (17%) of **6** as an oil. ^{1}H-NMR δ: 1.27 (9H, s, CMe_3), 1.40 (3H, t, J=7.0 Hz, $CH_2\underline{Me}$), 3.42 (3H, s, NMe), 4.41 (2H, q, J=7.0 Hz, $C\underline{H}_2Me$), 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 H_2SO_4 (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 $CHCl_3$. 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}H-NMR δ: 3.96 (3H, s, CO_2Me), 6.93 (1H, ddd, J_{2F-5H}=3.0 Hz, J_{6F-5H}=3.0 Hz, J_{5H-4H}=8.2 Hz, 5-H), 8.52 (1H, ddd, J_{2F-4H}=8.3 Hz, J_{6F-4H}=8.3 Hz, J_{5H-4H}=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—159 °C. ^{1}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_{F-5H}=2.0 Hz, J_{4H-5H}=8.5 Hz, 5-H), 8.09 (1H, dd, J_{F-4H}=9.5 Hz, J_{5H-4H}=8.5 Hz, 4-H). MS *m/z*: 185 (MH^+). IR ν cm^{-1}: 3271, 3134, 1701, 1630, 1319. *Anal.* Calcd for $C_8H_9FN_2O_2$: 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—56 °C (hexane). ^{1}H-NMR δ: 3.03 (3H, d, *J*=4.8 Hz, NHMe), 3.85 (3H, s, CO_2Me), 6.07 (1H, dd, J_{F-5H}=2.7 Hz, J_{4H-5H}=8.2 Hz, 5-H), 8.18 (1H, dd, J_{F-4H}=8.2 Hz, J_{5H-4H}=8.2 Hz, 4-H). MS *m/z*: 185 (MH^+). IR ν cm^{-1}: 3373, 1699, 1620, 1583, 1261. *Anal.* Calcd for $C_8H_9FN_2O_2$: 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—54 °C (hexane) [lit.[9] 56.0—56.5 °C (MeOH)]. ^{1}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 $C_7H_5Cl_2NO_2$: 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—94 °C. ^{1}H-NMR δ: 2.42 (3H, s, C_6H_4Me), 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 $C_{15}H_{15}NO_3S$: 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-methylbenzenesulfinyl)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—107 °C. ^{1}H-NMR δ: 2.37 (3H, s, C_6H_4Me), 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 $C_{15}H_{15}NO_4S$: 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}H-NMR δ: 2.44 (3H, s, C_6H_4Me), 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—121.5 °C (diethyl ether–hexane). ^{1}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 $C_9H_{12}N_2O_3$: 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}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—138 °C (diethyl ether–hexane). ^{1}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 $C_9H_{11}BrN_2O_3$: 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—168.5 °C (EtOH). ^{1}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 $C_8H_{10}N_2O_3$: 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—225 °C (EtOH). ^{1}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 $C_8H_9BrN_2O_3$: 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}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 ^{1}H-NMR spectra.

Methyl 2-Chloro-6-methylaminopyridine-3-carboxylate (**17a**): ^{1}H-NMR δ: 2.98 (3H, d, J=4.8 Hz, NHMe), 3.87 (3H, s, CO_2Me), 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**): ^{1}H-NMR δ: 3.12 (3H, s, NMe), 3.86 (3H, s, CO_2Me), 4.82 (2H, s, CH_2Ph), 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**): ^{1}H-NMR δ: 3.05 (3H, d, J=4.8, NHMe), 3.96 (3H, s, CO_2Me), 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**): ^{1}H-NMR δ: 2.83 (3H, s, NMe), 3.81 (3H, s, CO_2Me), 4.79 (2H, s, CH_2Ph), 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**): ^{1}H-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**): ^{1}H-NMR δ: 3.90 (3H, s, OMe), 4.04 (3H, s, CO_2Me), 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**): ^{1}H-NMR δ: 3.92 (3H, s, OMe), 3.98 (3H, s, CO_2Me), 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**): ^{1}H-NMR δ: 3.86 (3H, s, OMe), 3.97 (3H, s, OMe), 4.05 (3H, s, CO_2Me), 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**): ^{1}H-NMR δ: 3.90 (3H, s, OMe), 4.06 (3H, s, CO_2Me), 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**): ^{1}H-NMR δ: 3.91 (3H, s, OMe), 4.00 (3H, s, CO_2Me), 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**): ^{1}H-NMR δ: 1.39 (3H, t, J=7.3 Hz, CH_2Me), 3.21 (2H, q, J=7.3 Hz, CH_2Me), 3.92 (3H, s, CO_2Me), 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**): ^{1}H-NMR δ: 1.37 (3H, t, J=7.5 Hz, CH_2Me), 3.17 (2H, q, J=7.5 Hz, CH_2Me), 3.92 (3H, s, CO_2Me), 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**): ^{1}H-NMR δ: 2.43 (3H, s, C_6H_4Me), 3.92 (3H, s, CO_2Me), 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**): ^{1}H-NMR δ: 2.40 (3H, s, C_6H_4Me), 3.97 (3H, s, CO_2Me), 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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