A Practical Preparation of Methyl 2-Methoxy-6-methylaminopyridine-3-carboxylate from 2,6-Dichloro-3-trifluoromethylpyridine

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An effective and practical synthetic route to methyl 2-methoxy-6-methylaminopyridine-3-carboxylate (7), the key intermediate of 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid (1), from 2,6-dichloro-3-trifluoromethylpyridine (12) was undertaken. Process improvements were highlighted by regioselectivity of 12 with a nitrogen nucleophile and conversion of the 3-trifluoromethyl group into the methoxycarbonyl group. The reaction of 12 with N-benzylmethylamine provided the 6-((N-benzyl-N-methyl)aminomethyl)pyridine 26a and the regioisomer 26b in >98 : <2 ratio in a quantitative yield. Treatment of 2-methoxy-6-methylaminopyridine-3-trifluoromethylpyridine (14a) with a large excess of sodium methoxide followed by acid hydrolysis gave the pyridine-3-carboxylic ester 7 in an excellent yield. The potential application of this reaction is also described.

**Key words** serotonin-3 receptor; dopamine D$_2$, D$_3$ receptor; antiemetic agent; 2-chloro-6-methylamino-3-trimethoxymethylpyridine; regioselective synthesis; 2,6-dichloro-3-trifluoromethylpyridine

Potent and selective serotonin-3 (5-HT$_3$) receptor antagonists such as DAT-582$^1$)$^{[(R)-N-[1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepin-6-yl]-1H-indazole-3-carboxamide dihydrochloride], granisetron and ondansetron are known to be effective for the control of emesis induced by cancer chemotherapeutic agents.$^{2}$ In addition, the traditional antiemetic agent domperidone, a peripheral dopamine D$_2$ receptor antagonist, has been shown to be effective for the treatment of symptoms of chronic upper gastrointestinal distress and for the prevention of nausea and vomiting resulting from a variety of causes.$^{3}$ However, domperidone is only minimally effective against chemotherapy- or radiation-induced nausea and vomiting.$^{4}$ In the course of our studies on the structure–activity relationships of DAT-582,$^5$ novel benzamides with an alkyl group at the nitrogen atom in the hexahydro-1,4-diazepine ring such as, 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 antagonist activity and to cause only weak central nervous system depression and extrapyramidal syndromes.$^6$ Thus, these compounds were expected to be broad antiemetic agents. These findings had led us to modify the benzoyl moiety and to prepare the optically active 6-aminohexahydro-1,4-diazepine ring, resulting in the optical 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), a potent dopamine D$_2$ and D$_3$, and 5-HT$_3$ receptors antagonist. AS-8112 was finally selected as a promising candidate in our search for broad antiemetic agents.$^{10}$ In order to obtain a large amount of AS-8112, an efficient synthesis of 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid (1) and 6-amino-1-ethyl-4-methylhexahydro-1,4-diazepine was essential. This paper describes the efficient synthetic route to methyl 2-methoxy-6-methylaminopyridine-3-carboxylate (7), the key intermediate of 1, from the commercially available 2,6-dichloro-3-trifluoromethylpyridine (12).

**Results and Discussion**

Large-Scale Synthesis of 5-Bromo-2-methoxy-6-methylaminopyridine-3-carboxylic Acid (1) from 2,6-Dichloro-3-trifluoromethylpyridine (12)

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Chart 1. Previous Route\(^7\) to the Preparation of I

eyield. Finally, 8 was hydrolyzed under alkaline conditions to afford the desired carboxylic acid 1 in a quantitative yield (Chart 1). This route to 1 is quite adequate for the preparation of a wide variety of 2-alkoxy-6-alkylaminopyridine-3-carboxylic acids. However, when carried out on a large-scale (few hundreds gram), the yield of 5 from 3 decreased remarkably (ca. 25% yield) compared with that in a small-scale reaction. In addition, in the reaction of 5 with methylamine the unexpected 2-methoxy-\(N\)-methyl-6-(4-methylbenzenesulfonyl)pyridine-3-carboxamide (9a) and/or the corresponding 6-methylaminopyridine 9b were isolated in ca. 20% yield, and the yield of 7 decreased (ca. 50% yield). In order to improve the overall yield of 1 in large-scale preparations, a novel and facile synthetic route to the key intermediate 7 with short steps was examined.

Previously, we reported that the nucleophilic substitution reaction of methyl 2,6-dichloro-3-carboxylate (2) with methylamine did not show good regioselectivity and gave the undesired 6-chloro-2-methylaminopyridine-3-carboxylic ester as a major product.\(^8\) On the other hand, Dainter et al.\(^9\) reported that treatment of 2,6-dichloro-3-trichloromethylpyridine (10) having strong electron-withdrawing trichloromethyl group at the 3 position of pyridine ring with 10 mol eq of piperidine as a nucleophile gave only the 2-chloro-6-piperidino-3-[tri(1-piperidinyl)methyl]pyridine 11, which underwent displacement of all three chlorine atoms from the trichloromethyl group as well as the ring chlorine atom in a good yield. We, therefore, expected that commercially available 2,6-dichloro-3-trifluoromethylpyridine (12), which is the starting material for the preparation of 2,6-dichloropyridine-3-carboxylic acid,\(^10\) undergoes the nucleophilic substitution reaction of the ring chlorine atom at the 6 position only (Chart 2). 3-Trifluoromethylpyridines show much less activation of the trifluoromethyl group on the nucleophilic substitution than do their trichloromethyl analogues, since the fluorine atom is a poorer leaving group than the chlorine atom. Thus, nucleophilic substitution reaction of 12 with methylamine was initially examined.

Treatment of 12 with 1.1 mol eq of methylamine generated from methylvamine hydrochloride and triethylamine at room temperature gave a mixture of the 2-chloro-6-methylamino-3-trifluoropyrididine (13a) as a solid and the regioisomer 13b as a viscous oil in a ratio of ca. 4:1 in >90% yield. The ratio was determined by \(^1\)H-NMR spectroscopy. As expected, the corresponding 3-tri(methylamino)methylpyridine was not detected by \(^1\)H-NMR spectrum. The reaction at ca. 60 °C afforded a similar result. The desired 6-methylaminopyridine 13a was found to be readily separable by washing with hexane. After washing of the mixture of 13a and b with hexane, the crystals obtained (60% yield) consisted only of the isomer 13a by \(^1\)H-NMR spectrum and HPLC. The position of methylamino group of 13a was determined by differential nuclear Overhauser effect (NOE) experiment; irradiation at \(\delta\) 2.97 (N-Me) enhanced signal intensity of the adjacent pyridine 5-proton (\(\delta\) 6.28). Conversion of 13a into 2-methoxy-6-methylamino-3-trifluoromethylpyridine (14a) was then attempted. Reaction of 13a with a large excess of sodium methoxide in MeOH at reflux temperature gave a mixture of unexpected two products instead of 14a in a good yield. \(^1\)H-NMR and mass spectra (MS) revealed these two products to be 2-chloro-6-methylamino-3-(trimethoxymethyl)pyridine (15a) and the 2-methoxy counterpart 15b. The ratio of 15a and b (ca. 0.9:1) was determined by \(^1\)H-NMR spectroscopy. Nucleophilic substitution reaction at the 2 position of 15a with methoxide anion did not proceed to recover the starting material 15a. The mixture of 15a and b was then hydrolyzed with a catalytic amount of aqueous hydrochloric acid or sulfuric acid solution to afford a mixture of the corresponding pyridine-3-carboxylic esters 16 and 7 in an excellent yield in a ratio of ca. 0.7:1. The structure of 16 was confirmed by \(^1\)H-NMR and MS, and 7 was identified with the sample obtained in a previously reported method,\(^16\) on the basis of TLC. \(^1\)H-NMR, mass and IR spectra and HPLC comparison. Once again, the mixture of 16 and 7 thus obtained was treated with sodium methoxide in MeOH. The 2-methoxylolation of 16 with methoxide anion smoothly proceeded, and the key intermediate 7 was obtained ultimately in an excellent yield (Chart 3). A large amount of methyl 2-
methoxy-6-methylaminopyridine-3-carboxylate (7) was converted into the target 1 via methyl 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylate (8) in an excellent yield without serious problems according to a method reported previously.8)

The speculated mechanism for transformation of the 3-trifluoromethylpyridine 13a into the corresponding 3-trimethoxymethylpyridines 15a and b is shown in Chart 4; initial deprotonation of the ionizable methylamino group with methoxide anion followed by elimination of the fluoro anion as shown by the arrows (see 17) produces the highly reactive key intermediate 18 (path A). Subsequent attack on the CF₂ residue of intermediate 18 with second equivalent of methoxide anion leads to the rearomatization of 18, and the formation of 19 which is capable of eliminating the second and ultimately the third fluoro anions to afford the 3-trimethoxymethylpyridine 15a. On the other hand, the formation of 15b might be explained as follows; initial methoxide anion attack at the 2 position of the pyridine ring of 13a gives the Meisenheimer-type adduct 20 (path B). In path B-1, normal elimination of the chlorine atom at 2 position occurs (giving 21), but the trifluoromethyl group in the product 21 is activated by methoxide anion to form the intermediate 18b. Conversion of the reactive intermediate 18b into 15b would be due to a mechanism similar to that for the formation of the 3-trimethoxymethylpyridine 15a from 18a. In path B-2, 20 eliminates a fluoride ion from the trifluoromethyl group rather than a chloride ion from the ring to produce the reactive intermediate 22, which can give the 3-trimethoxymethylpyridine 15b via attack on the methoxide anion at the side-chain carbon and analogous repeated sequences. Transformation of 15a into 15b did not occur, probably because of the steric hindrance of the bulky 3-trimethoxymethyl group. The high reactivity of the trifluoromethyl group conjugated with an ortho- or para-hydroxy or amino function has been accounted for by activation as in paths A and B-1.11–13) In addition, mechanisms analogous to path B-2 have been proposed to account for the abnormal reactivity of 3-trifluoromethyl-quinoline and -imidazole.14,15)

The development of a shorter route to 1 was desired. One strategy shown in Chart 5 was particularly attractive. Initially, bromination of 13a with NBS was carried out to give the 5-bromo-2-chloro-6-methylamino-3-trifluoropyridine (23) in a quantitative yield. Reaction of 23 with a large amount of sodium methoxide produced a mixture of 2-chloro-3-trimethoxymethylpyridine 24a and the corresponding 2-methoxypyridine 24b in ca. 0.7:1 ratio, which was used in the next acid-hydrolysis step without further purification.
The mixture of 24a and b was treated with 2 N HCl solution to provide a mixture of the pyridine-3-carboxylic esters 25a and 8 as a crude solid. Once again, the mixture (25a, 8) was treated with sodium methoxide to give 8 exclusively, which was hydrolyzed with an alkaline solution without isolation to produce the desired product 1 in 39% overall yield. The crude pyridine-3-carboxylic acid 1 obtained was unacceptably impure due to the presence of 5-bromo-2-chloro-6-methylaminopyridine-3-carboxylic acid (25b), a nonmethylation product of 25a (0.8—0.7% by HPLC). The structure of 25b was speculated by 1H-NMR and MS.

In order to improve the regioselectivity at position-6 of the pyridine ring, reaction of 12 with the more bulky N-benzylmethylamine was examined. Treatment of 12 with ca. 1.1 mol eq of N-benzylmethylamine in DMF at 60 °C afforded a mixture of the 6-benzylmethylamino derivative 26a and the regioisomer 26b as an oil in a ratio of >98: <2 in a quantitative yield. The structure of the major product 26a was confirmed by 1H-NMR and MS, and the position of the benzylmethylamino group of 26a was determined by differential NOE experiment; irradiation at δ 3.11 (N-Me) enhanced signal intensity of the adjacent pyridine 5-proton (δ 6.36). Without further purification of the oil, the mixture of 26a and b was treated with sodium methoxide in MeOH to give a mixture of 6-benzylmethylamino-2-methoxy-3-trifluoropyridine (27a) and the regioisomer 27b as an oil in a ratio of <98: <2 in 91% yield. In the mixture thus obtained, the 3-trimethoxymethylpyridines were not detected by 1H-NMR spectrum and the trifluoromethyl group of 27a and b was left intact. Due to the absence of an acidic proton at the amino group, the normal nucleophilic substitution reaction was proceeded at the 2 and 6 positions of the pyridine ring to produce the corresponding 2- and 6-methoxy derivatives. This experimental result reveal that path B→B-1 would be exclusive in our proposed two mechanisms for the formation of 15b as shown in Chart 4. After hydrogenolysis of the mixture of 27a and b, the resulting mixture of 14a and b was reacted with a large excess of sodium methoxide in MeOH at reflux temperature to afford only the 3-trimethoxymethylpyridine 15b as a solid in a good yield. From 1H-NMR spectrum and HPLC, the regioisomer of 15b was not detected in the solid. Acid hydrolysis of 15b and recrystallization from ethyl acetate gave the key intermediate 7 in 55% overall yield from the starting material 12 (Chart 6). Preparation of multikilogram amounts of 1 via 7 using this process was carried out without any significant problems or yield loss.

**Synthesis of Methyl 6-Amino-2-methoxypyridine-3-carboxylate (32) from 2,6-Dichloro-3-trifluoromethylpyridine (12)**

Coldwell et al. reported that methyl 6-amino-2-methoxypyridine-3-carboxylate (32) was prepared from 2,6-difluoropyridine via 2-fluoro-6-pivaloylamino-pyridine and ethyl 2-fluoro-6-pivaloylamino-3-pyridinecarboxylate in ca. 20% overall yield. The disadvantage of this method is the moderate yield (44%) of the ethoxycarboxylation at the 3 position of 2-fluoro-6-pivaloylamino-pyridine at −78 °C and the use of silica gel column chromatography for purification. In order to improve this method, we applied the novel synthetic route to 7 from 2,6-dichloro-3-trifluoromethylpyridine (12).

Treatment of 12 with more bulky and diprotected amine of ammonia, dibenzylamine instead of N-benzylmethylamine in 1-methyl-2-pyrrolidone as a solvent at 120 °C gave only 6-dibenzylamino-2-chloro-3-trifluoromethylpyridine (28) in 89% yield. The formation of the regioisomer was not detected by 1H-NMR spectrum. The position of the dibenzylamino group of 28 was determined by NOE experiment; irradiation at δ 4.80 (CH2Ph) enhanced signal intensity of the adjacent pyridine 5-proton (δ 6.32). When 28 was treated with sodium methoxide in MeOH, only the 2-methoxy-3-trifluoromethylpyridine 29 was obtained and the non-corresponding 3-trimethoxymethylpyridine was formed owing to the absence of acidic proton at the 6-amino group. Hydrogenolysis of 29 over palladium hydroxide afforded 6-amino-2-methoxy-3-trifluoromethylpyridine (30) in 98% yield. In a similar reaction to that described for the pathway.
to 7 from 15a, the trifluoromethyl group of 30 was converted into the corresponding methoxy carbonyl group (giving 32) via the 3-trimethoxymethylpyridine 31 in an excellent yield. The 1H-NMR spectrum of 32 thus obtained was identical to that of the sample reported by Coldwell et al. The total yield of 32 from 12 was 59% (Chart 7).

**Conclusion**

We have established an efficient route for the synthesis of 1, the carboxylic acid moiety of a novel promising broad antiiemic agent AS-8112, from 2,6-dichloro-3-trifluoropyridine (12). Synthesis of methyl 2-methoxy-6-methylaminopyridine-3-carboxylate (7), the key intermediate of 1, by a sequence containing regioselective nucleophilic substitution reaction of 12 with N-benzylmethylamine, methylation of 3-trifluoromethyl group conjugated with a para-methylen function, and acid hydrolysis of the orthoester group was accomplished. The novel route with seven steps, which was applied to a large-scale synthesis of 1 improved significantly the overall yield (>50%).

**Experimental**

All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Shimadzu FTIR-9200PC spectrometer with KBr disks. Atmospheric pressure chemical ionization (APCI) and fast atom bombardment (FAB) MS were obtained on an Ishihara Sangyo Kaisha, Ltd. (Japan); 97.76% purity. HPLC [column, C18; eluent, CH3CN (A)–0.05% aqueous CF3CO2H (B); flow rate, 0.8 ml/min; detection, 245 nm]; the retention times of 13a and b were 5.5 and 6.4 min, respectively.

1-Chloro-6-methylaminopyridine (5) and 1-Chloro-6-methylamino-3-trimethoxymethylpyridine (6). A mixture of 1-ethylamine (217 g, 3.0 mol) and tetrahydrofuran (210 ml) was heated to reflux for 13 h and cooled to room temperature. After evaporation of the solvent, the residue was poured into ice-water (300 ml). The resulting precipitates were collected by filtration and dried to give a mixture of 15a and b (87 g) as a white solid. 1H-NMR δ: 2.39 (3H, d, J = 8.6 Hz, Py-5), 2.73 (1H, d, J = 8.6 Hz, Py-4); the retention time of 15b was 3.55 (1H, br, NH of 15b), 3.92 (1H, br, NH of 15b), 5.92 (1H, d, J = 6.8 Hz, Py-5 of 15b), 6.28 (1H, d, J = 6.8 Hz, Py-5 of 15a), 7.72 (1H, d, J = 8.3 Hz, Py-4 of 15b), 7.87 (ca. 0.9H, d, J = 8.6 Hz, Py-4 of 15a). MS (APCI) m/z: 243 (MH+ of 15b), 247 (MH+ of 15a). IR cm⁻¹: 3373, 2945, 1609, 1508, 1375, 1275.

2-Chloro-6-methoxy-6-methylaminopyridine-3-carboxylate (16) and 2-Chloro-6-methoxy-6-methylaminopyridine-3-carboxylate (17). Five percent aqueous H₂SO₄ solution (20 ml) was added dropwise to a solution of 15a (6.5 g, 0.03 mol) and 28% sodium methoxide in MeOH (703 g, 16.5 mol) and tetrahydrofuran (THF) (210 ml) was heated to reflux for 13 h and cooled to room temperature. After evaporation of the solvent, the residue was poured into ice-water (300 ml). The resulting precipitates were collected by filtration and dried to give a mixture of 15a and b (87 g) as a white solid. 1H-NMR δ: 2.38 (3H, d, J = 8.6 Hz, Py-5), 3.04 (d, J = 5.1 Hz, NMe of 15a), 3.90 (3H, OMe, of 15a), 4.52 (1H, br, NH of 15b), 5.07 (ca. 0.9H, d, J = 6.8 Hz, Py-5 of 15b), 6.28 (1H, d, J = 6.8 Hz, Py-5 of 15a), 7.72 (1H, d, J = 8.3 Hz, Py-4 of 15b), 7.87 (ca. 0.9H, d, J = 8.6 Hz, Py-4 of 15a). MS (APCI) m/z: 197 (MH+ of 15a), 247 (MH+ of 15b).

5-Bromo-2-chloro-6-methoxy-6-methylaminopyridine (23a) and 5-Bromo-2-chloro-6-methoxy-6-methylaminopyridine (23b). A solution of NBS (59.5 g, 0.33 mol) and 28% sodium methoxide in MeOH (703 g, 16.5 mol) and tetrahydrofuran (THF) (210 ml) was heated to reflux for 13 h and cooled to room temperature. The mixture was stirred at the same temperature for 0.5 h and concentrated to dryness to give 63 g of a mixture of 16 and 17 as a white solid. 1H-NMR δ: 2.97 (ca. 2H, d, J = 5.1 Hz, NH of 17), 2.98 (3H, s, NMe of 17), 3.82 (1H, s, OMe of 17), 3.87 (3H, s, CO-OMe of 17), 3.97 (ca. 2H, CO-OMe of 17), 4.87 (ca. 0.7H, br, NH of 16), 5.35 (1H, br, NH of 16), 5.94 (ca. 0.7H, d, J = 8.4 Hz, Py-5 of 17), 6.29 (1H, d, J = 6.8 Hz, Py-5 of 16), 8.01 (ca. 0.7H, d, J = 8.4 Hz, Py-4 of 17), 8.04 (1H, d, J = 8.6 Hz, Py-4 of 16). IR cm⁻¹: 3356, 1693, 1610, 1269. MS (APCI) m/z: 197 (MH+ of 17), 210 (MH+ of 16).
Methyl 5-Bromo-2-chloro-6-methylaminopyridine-3-carboxylate (25a) and Methyl 5-Bromo-2-methoxy-6-methylaminopyridine-3-carboxylate (28) 2 N HCl solution (500 ml) was added dropwise to a suspension of a mixture of 24a and b (113 g) in MeOH (400 ml) at ca. 5 °C. The mixture was stirred at the same temperature for 20 min. After neutralization with NaHCO₃ powder, the insoluble materials were collected by filtration to give 130 g (71%) of crude 25a. 5-bromo-2-chloro-6-methylaminopyridine-3-carboxylate (25a) and methyl 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylate (28) as a white solid. 1H-NMR δ: 3.08 (3H, d, J = 5.7 Hz, NMe of 8), 3.10 (ca. 2H, d, J = 5.7 Hz, NMe of 25a), 3.88 (ca. 2H, s, CO₂Me of 25a), 4.02 (3H, s, OMe of 8), 5.38 (1H, br, NHMe of 25a), 5.52 (ca. 0.6H, br, NHMe of 25a), 8.15 (1H, s, Py-4 of 8), 8.20 (ca. 0.7H, s, Py-4 of 25a). MS (APCI) m/z: 276 (MH⁺ of 8), 280 (MH⁺ of 25a).

HPLC [(A : B = 65 : 35), detection, 245 nm]; the retention times of 25a and 28 were 10.8 and 27.5 min, respectively.

Methodylation of 25a and 8 and Acid Hydrolysis A mixture of 25a and 8 (130 g), 28% sodium methoxide in MeOH (289 g, 1.5 mol) and THF (1000 ml) was heated to reflux for 10 h and cooled to room temperature. After addition of water (1000 ml), the mixture containing only 8 was stirred at room temperature for 30 min and acidified with 30% HCl solution under ice-cooling. The resulting precipitates were collected by filtration to give 54 g of a mixture of methyl 2-methoxy-6-methylaminopyridine-3-carboxylate (26b) and 27b was detected in ca. 5% by HPLC. After concentration of the filtrate, the precipitates were collected by filtration to afford 18 g of 1. Ethanol (250 ml) was added to the solid (72 g) and the suspension was heated to reflux for 11 h and cooled to room temperature. The insoluble 1 was collected by filtration. Once again, a suspension of 1 in Ethanol (200 ml) was heated to reflux for 1 h and cooled to room temperature. The insoluble 1 was collected by filtration and dried to give 51 g (65% from 24) as a white solid. 1H-NMR δ: 7.45 (10H, m, arom. H 3), 7.55 (1H, d, J = 8.8 Hz, Py-5 of 8), 7.67 (1H, d, J = 8.8 Hz, Py-5 of 26a), 7.70 (1H, d, J = 8.8 Hz, Py-5 of 25b), 8.01 (1H, d, J = 8.5 Hz, Py-4), IR cm⁻¹: 3393, 2949, 1709, 1597, 1263, 1236. HPLC [(A : B = 55 : 45), detection, 319 nm]; the retention time of 1b was 51.5 min.

Methyl 2-Methoxy-6-methylaminopyridine-3-carboxylate (7) 1 A solution of a mixture of 14a and b (388 g, 1.9 mol) in MeOH (380 ml) was heated to reflux for 28% sodium methoxide in MeOH (500 ml). The resulting solid was collected by filtration and dissolved in a mixture of CHCl₃ (2000 ml) and water (500 ml). The organic layer was separated, dried over anhydrous MgSO₄ and evaporated to leave 347 g (76%) of 15b as a white solid, mp 148—150 °C. 1H-NMR δ: 2.92 (3H, d, J = 5.1 Hz, NMe), 3.11 (OH, s, (OMe)₃), 3.91 (3H, s, OMe), 4.46 (1H, br, NHMe of 15b). MS (APCI) m/z: 243 (MH⁺). IR cm⁻¹: 3381, 2947, 1609, 1573, 1381. HPLC [(A : B = 65 : 35), detection, 245 nm]; the retention times of 14a and b were 71 and 8.6 min, respectively.

2-Methyl-6-methylamino-3-trimethoxymethylpyridine (15b) A solution of a mixture of 14a and b (388 g, 1.9 mol) in MeOH (380 ml) was heated to reflux for 28% sodium methoxide in MeOH (500 ml). The resulting solid was collected by filtration and dissolved in a mixture of CHCl₃ (2000 ml) and water (500 ml). The organic layer was separated, dried over anhydrous MgSO₄ and evaporated to leave 347 g (76%) of 15b as a white solid, mp 148—150 °C. 1H-NMR δ: 2.92 (3H, d, J = 5.1 Hz, NMe), 3.11 (OH, s, (OMe)₃), 3.91 (3H, s, OMe), 4.46 (1H, br, NHMe of 15b). MS (APCI) m/z: 243 (MH⁺). IR cm⁻¹: 3381, 2947, 1609, 1573, 1381. HPLC [(A : B = 65 : 35), detection, 245 nm]; the retention times of 14a and b were 71 and 8.6 min, respectively.

3-carboxylate (7) 1 A solution of a mixture of 14b and ca. 35% 3-carboxylate of the theoretical hydrogen (ca. 5 h), the catalyst was filtered off. The filtrate was concentrated to leave a residue, which was dissolved in ethyl acetate (990 ml). The solution was washed with 5% aqueous Na₂CO₃ solution (300 and 150 ml) and concentrated to dryness to give ca. 220 g (quantitative yield) of a mixture of 14a and b as a yellow oil, which was used in the next step without further purification. 1H-NMR δ: 2.93 (3H, d, J = 4.9 Hz, NMe of 14b), 3.93 (3H, s, OMe of 14a), 4.73 (1H, br, NHMe of 14a), 5.89 (1H, d, J = 8.3 Hz, Py-5 of 14a), 5.99 (0.05H, s, 150 ml) and concentrated to dryness to give ca. 220 g (quantitative yield) of a mixture of 14a and b as a yellow oil, which was recrystallized from iso-PrOH to afford 250 g (67.5%) of 29 as colorless crystals. After concentration of the mother liquid, the residue was chromatographed on silica gel with hexane/ethyl acetate (9:1 to 4:1) to give a pale yellow oil. The oil was crystallized from iso-PrOH to afford 22.2 g (73%) of 29 as colorless crystals, mp 88—89 °C. 1H-NMR δ: 3.91 (3H, s, OMe), 4.81 (2H, s, CH₂Ph of 29), 6.05 (1H, d, J = 8.8 Hz, Py-5), 7.22—7.42 (10H, m, arom. H 2), 7.55 (1H, d, J = 8.4 Hz, Py-4). Anal. Calcd for C₂₉H₂₇F₃N₂O: C, 76.73; H, 5.14; N, 7.52; F, 15.31. Found: C,
6-Amino-2-methoxy-3-trifluoromethylpyridine (30) A solution of 29 (38.0 g, 0.10 mol) in a mixture of 10% aqueous MeOH (600 ml) and acetic acid (100 ml) was hydrogenated over 20% palladium hydroxide on carbon (wet, 3.8 g) at room temperature under a pressure of 3.2 kg/cm². After absorption of the theoretical hydrogen, the catalyst was filtered off. The filtrate was concentrated to leave an aqueous solution, which was neutralized with solid K₂CO₃ and extracted with CHCl₃. The extract was washed with brine and concentrated to give 19.3 g (98%) of 30 as a pale yellow oil, which solidified on standing at room temperature, mp 51—55 °C. 1H-NMR δ: 3.92 (3H, s, OMe), 4.61 (2H, br s, NH₂), 5.88 (1H, d, J= 58.2 Hz, Py-5), 7.56 (1H, d, J= 8.2 Hz, Py-4). HRFAB-MS m/z: 192.0517 (Calcd for C₇H₇F₃N₂O: 192.0510). MS (APCI) m/z: 193 (MH⁺). IR cm⁻¹ 3408, 3369, 1643, 1605, 1585, 1406, 1323.

Methyl 6-Amino-2-methoxypyridine-3-carboxylate (32) A solution of a mixture of 30 (86.5 g, 0.45 mol) in MeOH (450 ml) was added dropwise to 28% sodium methoxide in MeOH (608 g, 3.15 mol) at ca. 65 °C for 2.5 h. The mixture was heated to reflux for 0.5 h and cooled to room temperature. The solvent was evaporated and the residue was dissolved in H₂O and CHCl₃. The organic layer was separated and washed with brine and the aqueous layer was extracted with ethyl acetate. The extract was again washed with brine. The solvent of CHCl₃ and ethyl acetate extracts was evaporated to give an yellow solid containing 6-amino-2-methoxy-3-trimethoxymethylpyridine (31). The solid was dissolved in a mixture of MeOH (500 ml) and water (250 ml). After addition of 5% aqueous H₂SO₄ solution (25 ml), the mixture was stirred overnight at room temperature. The mixture was concentrated and then the resulting precipitates were collected by filtration, washed with EtOH and dried to give 73.6 g (90%) of 32 as colorless crystals, mp 162—164 °C. 1H-NMR δ: 3.83 (3H, s, OMe), 3.96 (3H, s, CO₂Me), 4.75 (2H, br s, NH₂), 6.05 (1H, d, J= 8.3 Hz, Py-5), 8.01 (1H, d, J= 8.3 Hz, Py-4). MS (APCI) m/z: 183 (MH⁺). Anal. Calcd for C₈H₁₀N₂O₃: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.64; H, 5.56: N, 15.21. IR cm⁻¹ 3508, 3346, 3248, 1695, 1682, 1651, 1593, 1564.

References and Note