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 

3D J 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 CH3Cl provided the 2-methoxy pyridine-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-methylbenzenesulfonate anion in DMF (quantitative yield). After methylation 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 D3; dopamine D3; antiemetic agent; regioselective synthesis

Potent and selective serotonin-3 (5-HT3) receptor antagonists, such as DAT-582 [(R)-N-[1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepin-6-yl]-1H-indazole-3-carboxamide dihydrochloride], discovered in our laboratories, granisetron and ondansetron are effective in the control of emesis induced by cancer chemotherapeutic agents. The traditional antiemetic agent domperidone, a peripheral dopamine 

3D receptor antagonist, has been shown to be effective in the prevention of nausea and vomiting resulting from a variety of causes. However, domperidone is only minimally effective against chemotherapy-induced nausea and vomiting. In the course of our studies on the structure–activity relationships (SARs) of DAT-582, benzamides with an alkyl group on the nitrogen atom in the hexahydro-1,4-di azepine ring, such as the 1-ethyl-4-methylhexahydro-1,4-di azepine ring were found to show dopamine D3 receptor antagonistic activity along with 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-amino hexahydro-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 D3 and 5-HT3 receptors antagonistic activity. AS-8112 was finally selected as a promising broad antiemetic agent. 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-methoxy- pyridine-3-carboxylic acid (3) 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-pivaloylamino)pyridine-3-carboxylate (6) according to the method of Coldwell et al. 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-pivaloylamino)pyridine (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) prepared from 4. Reaction of 7 with MeI in the presence of NaH pro-

![Fig. 1](image)

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vided the 6-(N-methyl-N-pivaloyl)aminopyridine-3-carboxylate 6 in only 17% yield. Displacement reaction of the fluo-
rine atom of 6 by methoxide anion produced from potassium tert-butoxide and MeOH was accompanied by ester ex-
change and de-acetylation to give 8 in 68% yield. Bromination of 8 with N-bromosuccinimide (NBS) followed by alkaline hy-
drolysis of the resulting 9 produced the desired pyridine-3-
carboxylic acid 1 in 96% yield. On the other hand, after alkaline hy-
drolysis of 8, bromination of 2-methoxy-6-methyl-
aminopyridine-3-carboxylic acid (10) gave the 5-bromopy-
ridine-3-carboxylic acid 1 in 88% yield along with 3,5-di-
bromo-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-Dihalogeno-
pyridine-3-carboxylic Esters 12 and 16. In order to im-
prove 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)\(^9\) with methylamine was carried out. Treatment of 12 with 20% methylamine in EtOH at \(-25^\circ C\) gave a mixture of methyl 2-fluoro-6-methylaminopyridine-3-carboxylate (13) and the re-
gioisomer 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 com-
 pound 13 (55%) as a solid by crystallization and flash chro-
matography on silica gel. The position of the methylaminogroup of 13 was determined by differential nuclear Over-
ehauer effect (NOE) experiment; irradiation at \(2.98 \text{ ppm (N-Me)}\) enhanced signal intensity of the adjacent pyridine 5-proton (\(\delta 6.23\)) (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 \(^\circ C\) 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 
\(-78^\circ C\) did not proceed (run 2). The reaction in N,N-
dimethylformamide (DMF) at 5 \(^\circ C\) and lower temperatures 
(\(-30^\circ C\), \(-60^\circ C\)) afforded the 6-methylaminopyridine-3-
carboxylic ester 13 as major product (runs 3—5). Using CH\(_3\)CN, tetrahydrofuran (THF) and CH\(_2\)Cl\(_2\) as solvents at 5 \(^\circ C\), 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 re-
action.

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-

![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](image-url)
sary. Ester 16 prepared by esterification 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-CH2Ph) 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 CH3CN, CH2Cl2 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 CH3Cl2 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

<table>
<thead>
<tr>
<th>Run</th>
<th>Conditions</th>
<th>13 (%)</th>
<th>14 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH, 5 °C, 10 min</td>
<td>46</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>MeOH, -78 °C, 3 h</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>DMF, 5 °C, 10 min</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>DMF, -30 °C, 1 h</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>DMF, -60 °C, 3 h8)</td>
<td>53</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>CH3CN, 5 °C, 10 min</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>THF, 5 °C, 10 min</td>
<td>39</td>
<td>61</td>
</tr>
<tr>
<td>8</td>
<td>CH2Cl2, 5 °C, 10 min</td>
<td>25</td>
<td>75</td>
</tr>
</tbody>
</table>

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%).

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

<table>
<thead>
<tr>
<th>Run</th>
<th>R</th>
<th>Conditions</th>
<th>17a, b (%)</th>
<th>18a, b (%)</th>
<th>19 (%)</th>
<th>16 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>THF, 5 °C</td>
<td>12</td>
<td>49</td>
<td>12</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>DMF, 5 °C</td>
<td>32</td>
<td>51</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>MeOH, 5 °C</td>
<td>4</td>
<td>9</td>
<td>37</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>CH2Ph</td>
<td>THF, -20 °C</td>
<td>14</td>
<td>86</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Run</th>
<th>Conditions</th>
<th>20 (%)</th>
<th>21 (%)</th>
<th>22 (%)</th>
<th>12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃CN, 5°C, 10 min</td>
<td>61</td>
<td>19</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN, 5°C, 10 min</td>
<td>74</td>
<td>14</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>THF, 5°C, 10 min</td>
<td>77</td>
<td>14</td>
<td>14</td>
<td>4.5</td>
</tr>
<tr>
<td>4</td>
<td>THF, -30°C, 1.5 h</td>
<td>67</td>
<td>18</td>
<td>N.D.</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>THF, -78°C, 3 h</td>
<td>15</td>
<td>4</td>
<td>N.D.</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>MeOH, 5°C, 10 min</td>
<td>18</td>
<td>80</td>
<td>2</td>
<td>N.D.</td>
</tr>
<tr>
<td>7</td>
<td>DMF, 5°C, 10 min</td>
<td>15</td>
<td>27</td>
<td>29</td>
<td>2</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Run</th>
<th>Conditions</th>
<th>23 (%)</th>
<th>24 (%)</th>
<th>22 (%)</th>
<th>16 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOMe in CH₃Cl₂</td>
<td>85</td>
<td>15</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>2</td>
<td>NaOMe in THF</td>
<td>79</td>
<td>14</td>
<td>7</td>
<td>N.D.</td>
</tr>
<tr>
<td>3</td>
<td>NaOMe in DMF</td>
<td>28</td>
<td>69</td>
<td>3</td>
<td>N.D.</td>
</tr>
<tr>
<td>4</td>
<td>NaOMe in MeOH</td>
<td>24</td>
<td>74</td>
<td>2</td>
<td>N.D.</td>
</tr>
<tr>
<td>5</td>
<td>tert-BuOK/MeOH</td>
<td>20</td>
<td>72</td>
<td>N.D.</td>
<td>8</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Run</th>
<th>R</th>
<th>Conditions</th>
<th>25a (%)</th>
<th>26a (%)</th>
<th>26a (%)</th>
<th>16 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>NaH, DMF, 5°C, 1 h</td>
<td>91</td>
<td>9</td>
<td>N.D.</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>tert-BuOK, DMF, -5°C, 2 h</td>
<td>88</td>
<td>12</td>
<td>N.D.</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>tert-BuOK, THF, -5°C, 1 h</td>
<td>50</td>
<td>50</td>
<td>N.D.</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>tert-BuOK, THF, -30°C, 1 h</td>
<td>50</td>
<td>50</td>
<td>N.D.</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>4-Me₃C₆H₄</td>
<td>NaH, DMF, room temp., 15 min</td>
<td>52</td>
<td>48</td>
<td>N.D.</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>4-Me₃C₆H₄</td>
<td>tert-BuOK, DMF, room temp., 45 min</td>
<td>93.7</td>
<td>6.3</td>
<td>N.D.</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>4-Me₃C₆H₄</td>
<td>tert-BuOK, DMF, 5°C, 30 min</td>
<td>94.1</td>
<td>5.9</td>
<td>N.D.</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>4-Me₃C₆H₄</td>
<td>tert-BuOK, DMF, -5°C, 1 h</td>
<td>95.2</td>
<td>4.8</td>
<td>N.D.</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>4-Me₃C₆H₄</td>
<td>tert-BuOK, DMF, -30°C, 1 h</td>
<td>97.0</td>
<td>3.0</td>
<td>N.D.</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>4-Me₃C₆H₄</td>
<td>tert-BuOK, THF, room temp., 1 h</td>
<td>65</td>
<td>22</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

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

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, CH₃Cl₂, 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, 32.6, 37.7 and 37.5, respectively, and CH₃Cl₂ 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...
more polar and better ionizing solvents having higher dielectric constants afforded predominantly the 6-isomers except for CH$_3$CN. In general, the more dispersed the charge distribution of anionic transition state in a nucleophile 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$_3$CN behaves as if it was a solvent with low dielectric constant. The detailed mechanism of reactions using CH$_3$CN 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 treatment 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 9:7:2:3 in a quantitative yield. The mixture was treated with sodium methoxide to afford the corresponding 2- and 6-methoxypropyridine-3-carboxylates, which were purified by recrystallization from AcOEt to give the pure 2-methoxypropyridine-3-carboxylate in 87% yield. Oxidation of 27 with m-chloroperbenzoic acid (MCPBA) produced the sulfone 28 along with the corresponding sulfone derivative in a ratio of 11:1 in an excellent yield. The ratio of the sulfone 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 methylene 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 nucleophile 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, CH$_3$Cl, and CH$_3$CN 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 instrument. $^1$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 $\delta$ (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 (Fujil silica FL60D).

2-Fluoro-6-(N-methyl-N-pivaloylamino)pyridine (5) A mixture of 2,6-difluoropyridine (2, 50.0 g, 0.43 mol) and methylene (240 ml of cu. 30% EOH) 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$_2$CO$_3$ was added, the residue was extracted with CHCl$_3$, and the extract was washed with CHCl$_3$. The extract was dried over anhydrous K$_2$CO$_3$, and concentrated to dryness to give 59 g of crude 2-fluoro-6-methylaminopyridine as an oil. Pivaloyl chloride (78.6 g, 0.61 mol) was added dropwise to a solution of crude 2-fluoro-6-methylaminopyridine and Et$_3$N (96.8 g, 0.96 mol) in CH$_2$Cl$_2$ (150 ml) at ca. 0 °C. The reaction mixture was stirred at room temperature overnight and then washed successively with water, 2% aqueous H$_2$SO$_4$, 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, $J_{3,4b}=3.0$ Hz, $J_{3,4a}=8.0$ Hz, 3-H), 7.18 (1H, dd, $J_{2,3}=2.0$ Hz, $J_{2,4}=8.0$ Hz, 5-H), 7.83 (1H, dd, $J_{7,8}=8.0$ Hz, $J_{7,6}=8.0$ Hz, 3-H), 4.4 (4H, m). MS: m/z 211 (M$^+$.)

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$_3$Me), 3.42 (3H, s, NMe), 4.41 (2H, q, $J=7.0$ Hz, CH$_2$Me), 7.37 (1H, dd, $J_{1,2}=15.8$ Hz, $J_{4,5}=8.2$ Hz, 5-H), 8.33 (1H, dd, $J_{3,4}=9.5$ Hz, $J_{3,2}=8.2$ Hz, 4-H). MS: m/z 283 (M$^+$).

Methyl 2,6-Difluoropyridine-3-carboxylate (12) Concentrated H$_2$SO$_4$ (5 ml) was added dropwise to a solution of 11 (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 (CHCl₃) to give 64.0 g (93%) of 12 as an oil. 1H-NMR δ: 3.96 (3H, s, CO₂Me), 6.93 (1H, d, J = 2.0 Hz, 5-H), 8.52 (1H, d, J = 2.0 Hz, 6-H), 8.18 (2H, d, J = 8.2 Hz, 4-H). MS m/z: 174 (M⁺).

Methyl 2-Fluoro-6-methylaminopyridine-3-carboxylate (13) (Methyl 2-Fluoro-6-methylaminopyridine-3-carboxylic acid (14)) Methylamine (72 g of 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 5.7 g (39%) of 13, mp 156–159 °C. 1H-NMR δ: 2.98 (3H, d, J = 3.0 Hz, NHMe), 3.87 (3H, s, CO₂Me), 4.10 (1H, d, J = 5.0 Hz, 4-H), 7.85 (2H, d, J = 8.2 Hz, 4-H). MS m/z: 185 (M⁺). IR ν cm⁻¹: 3271, 3134, 1701, 1630, 1319. Anal. Calcd for C₇H₇NO₂: 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 CHCl₃, and the extract was washed with brine. The solvent was evaporated, and the residue was purified by flash chromatography (CHCl₃) to give 16.1 g (42%) of a viscous oil and 6.5 g (16%) of 13 as a solid.

Methyl 2-Bromo-6-methylaminopyridine-3-carboxylate (9) 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 NaHCO₃, water and brine and concentrated to give 1.4 g (90%) of 9 as a solid, which was identified with the sample obtained above, on the basis of TLC, IR, and 1H-NMR comparisons.

Methyl 5-Bromo-2-methyl-6-methylaminopyridine-3-carboxylate (29) 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 precipitate was collected by filtration, washed with water and dried to give 9.8 g (96%) of 29, mp 136–138 °C (diethyl ether–hexane).

Methyl 2-Hydroxy-6-methylaminopyridine-3-carboxylate (30) A mixture of 7 (5.0 g, 0.052 mol) in MeOH (50 mL) was stirred at the same temperature for 5 min, and cold water (220 mL) was added. The resulting precipitate was collected by filtration, washed with water and dried to give 21.8 g (95%) of 30, mp 189–190 °C (EtOH).

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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 spectrums.

Methyl 2-Chloro-6-methylaminopyridine-3-carboxylate (17a): 1H-NMR δ: 2.98 (3H, d, J=4.8 Hz, NMe), 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, NMe), 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, NMe), 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-methoxyphenylpyridine-3-carboxylate (20): 1H-NMR δ: 3.90 (3H, s, OMe), 4.04 (3H, s, CO2Me), 6.53 (1H, dd, JF5,=3.0 Hz, J4=8.1 Hz, 5-H), 8.31 (1H, d, JF=8.1 Hz, J5=8.1 Hz, 4-H).

Methyl 2-Fluoro-6-methoxyphenylpyridine-3-carboxylate (21): 1H-NMR δ: 3.92 (3H, s, OMe), 3.98 (3H, s, CO2Me), 6.66 (1H, dd, JF=1.3 Hz, J4=8.4 Hz, 5-H), 8.24 (1H, dd, JF=9.3 Hz, J5=8.4 Hz, 4-H).

Methyl 2,6-Dimethoxyphenylpyridine-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-methoxyphenylpyridine-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-methoxyphenylpyridine-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), 7.17 (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).

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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References