

**PREPARATION OF NEW 2-CHLORO-5-FLUORO-6-(4-PHENYL-METHYLPIPERAZINYL)-4-TRIFLUOROMETHYL-3-NICOTINIC ACID**

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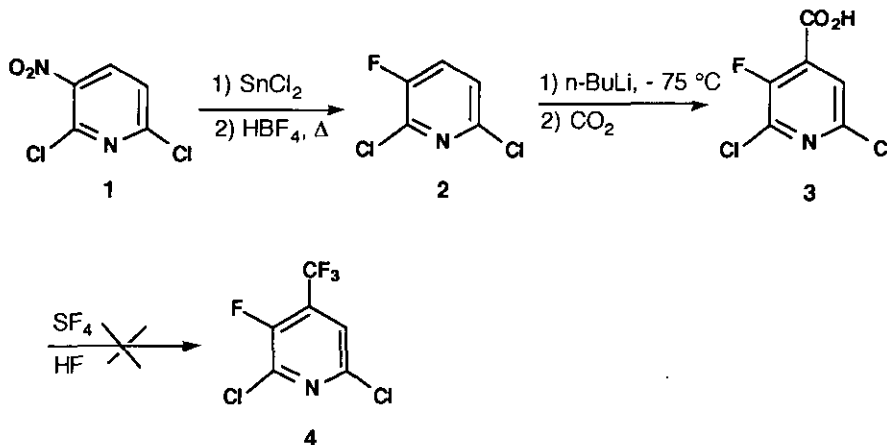
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**Abstract** –The nicotinic acid (15), which could be a key intermediate for novel potential anti-bacterial 1,8-naphthyridine-3-carboxylic acid analogues, was prepared initiating with construction of the pyridine nucleus by ethyl 2-fluoroacetate and ethyl 2-trifluoroacetate.

As a continuation of our research to prepare 4-substituted nicotinic acids,<sup>1</sup> we were interested in the synthesis of 4-trifluoromethyl-5-fluoronicotinic acids. To the best of our knowledge, the only example of 4-trifluoromethyl nicotinic acids has been described in a Swiss patent<sup>2</sup> and by R. Balicki.<sup>3</sup>

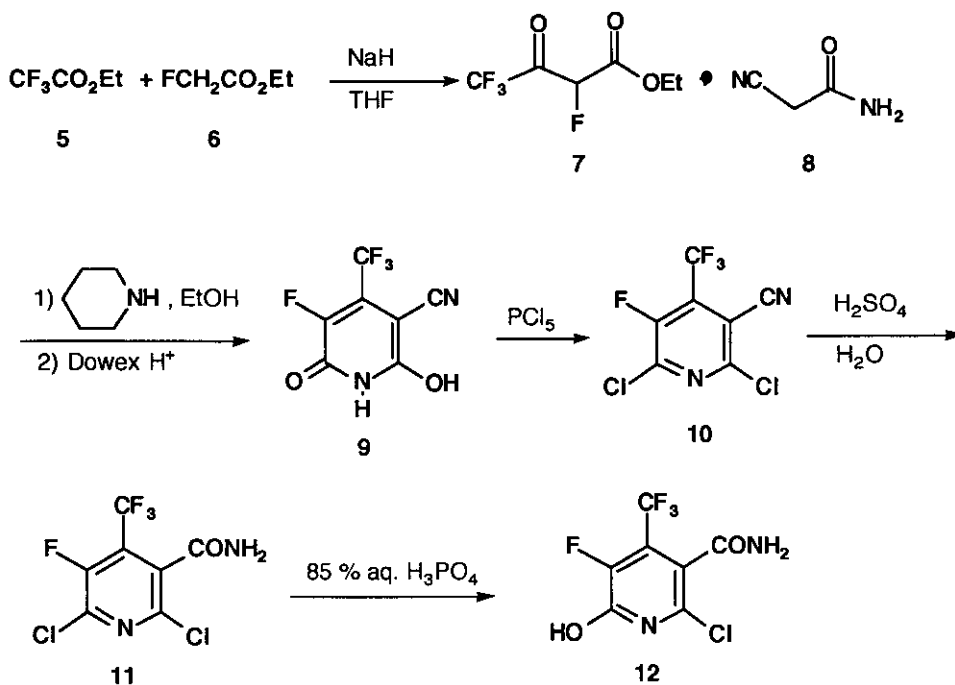
We first tried to introduce a carboxylic group on the 4-position of the 2,6-dichloro-3-fluoropyridine (2), obtained from the 2,6-dichloro-3-nitropyridine (1) *via* reduction with SnCl<sub>2</sub> in acidic medium, followed by

**Scheme I**



a Balz-Schiemann reaction (Scheme I).<sup>4</sup> The regioselective carboxylation of **2** was readily achieved at low temperature in 67 % yield with *n*-BuLi and CO<sub>2</sub> to afford **3**. Attempts to fluorinate this intermediate with SF<sub>4</sub> in HF at 60 °C or 120 °C were unsuccessful.<sup>5</sup>

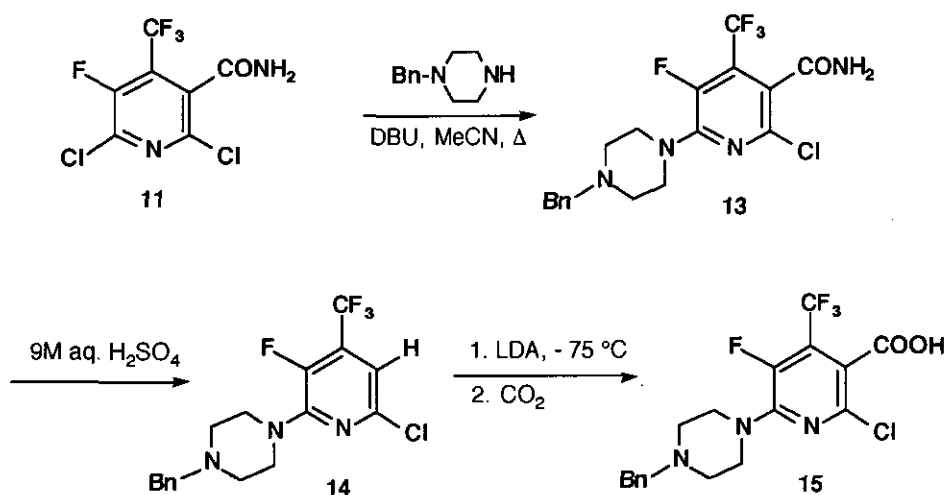
### Scheme II



Subsequently another strategy was chosen which implied construction of the pyridine nucleus by ethyl fluoroacetate and ethyl trifluoroacetate as starting materials (Scheme II). The tetrafluoroacetoacetate (**7**) was prepared by condensation of **6** with **5** according to a described procedure for a nicotinonitrile analogue.<sup>6</sup> Reaction of **7** with 2-cyanoacetamide (**8**) in EtOH with one equivalent of piperidine at 50 °C, followed by ion-exchange on a Dowex-H<sup>+</sup> resin, furnished the pyridone (**9**) in 56% yield.<sup>7</sup> Chlorination of **9** with two equivalents of PCl<sub>5</sub> at 125 °C for 19 h gave in quantitative yield the crude nicotinonitrile (**10**).<sup>8</sup> Next, the intermediate (**10**) was transformed in 87% yield into the nicotinamide (**11**) by heating with conc. H<sub>2</sub>SO<sub>4</sub> at 75 °C followed by addition of water and heating the suspension under reflux for 2 h. All attempts at either acidic or alkaline hydrolysis of **11** failed to give the desired 2,6-dichloro-5-fluoro-4-(trifluoromethyl)nicotinic acid. Nevertheless the nicotinamide (**11**) after 12 h in refluxing H<sub>3</sub>PO<sub>4</sub> afforded the nicotinamide (**12**) in 69

% yield (Scheme II).<sup>9</sup> To avoid the hydrolysis of the chlorine at position 6, the *N*-benzylpiperazine was condensed regioselectively on **11** at the 6-position to produce the nicotinamide (**13**) in 45 % yield (Scheme III). Strong acidic hydrolysis of the latter provided in 53 % yield the decarboxylated pyridine (**14**). Metalation of **14** with LDA, followed by carbonation with CO<sub>2</sub>, provided the nicotinic acid (**15**) in moderate yield (~10 %) with 80 % of recovery of starting material. The nicotinic acid (**15**) could be useful for the synthesis of potential antibacterial 5-trifluoromethyl-1,8-naphthyridine-3-carboxylic acids .

### Scheme III



### REFERENCES AND NOTES

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2. P. Baumann and M. Zimmermann, Swiss Patent CH 473 836 (1969) (Chem. Abstr., 1970, **72**, 21680 y).
3. R. Balicki and P. Nantka-Naminski, *Pol. J. Chem.*, 1979, **53**, 1515.
4. T. Miyamoto, J-i. Matsumoto, A. Minamida, Y. Nishimura, H. Egawa, and H. Nishimura, *J. Heterocycl. Chem.*, 1984, **21**, 673.
5. Only polymerization occurred.
6. M. S. Raasch, *J. Org. Chem.*, 1962, **27**, 1406.
7. S. Portnoy, *J. Org. Chem.*, 1965, **30**, 3377.
8. T. Miyamoto, H. Egawa, and J. Matsumoto, *Chem. Pharm. Bull.*, 1987, **35**, 2280.
9. Alkaline hydrolysis of **11** (refluxing 2N NaOH) gave a mixture of unidentified products. Reaction of **11**

with  $\text{BF}_3$ -etherate in ethanol <sup>8</sup> did not give the corresponding expected nicotinic acid ethyl ester.

10. The yields reported were not optimized. **3**: mp 143 °C (petr. ether);  $^1\text{H}$  nmr (DMSO- $d_6$ ) 7.85cd,  $J = 4$  Hz, H-5);  $^{19}\text{F}$  nmr (DMSO- $d_6$ )  $\delta$ : -114.2 (d,  $J = 4$  Hz, F-3). *Anal.* Calcd for  $\text{C}_6\text{H}_2\text{NO}_2\text{Cl}_2\text{F}$ : C, 34.32; H, 0.96; N, 6.67. Found: C, 34.27; H, 1.03; N, 6.48. **9**: mp 229 °C ( $\text{CHCl}_3$ );  $^{19}\text{F}$  nmr (DMSO- $d_6$ )  $\delta$ : -51.2 (d,  $J = 24.8$  Hz, 3F,  $\text{CF}_3$ -4); -150.9 (m, 1F, F-5); ir (KBr):  $\nu$  3071, 2927, 2254, 2225, 1658, 1297, 1168  $\text{cm}^{-1}$ . *Anal.* Calcd for  $\text{C}_7\text{H}_2\text{N}_2\text{O}_2\text{F}_4$ : C, 37.86; H, 0.91; N, 12.61. Found: C, 37.67; H, 1.04; N, 12.58. **10**: oil;  $^{19}\text{F}$  nmr (DMSO- $d_6$ )  $\delta$ : -51.2 (d,  $J = 21$  Hz, 3F,  $\text{CF}_3$ -4); -112 (q,  $J = 21$  Hz, 1F, F-5); ir (KBr):  $\nu$  2241, 1550, 1254, 1178  $\text{cm}^{-1}$ . **11**: mp 181-182 °C (petr. ether);  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$ : 8.20 (s, 2H,  $\text{CONH}_2$ );  $^{19}\text{F}$  nmr (DMSO- $d_6$ )  $\delta$ : -50.8 (d,  $J = 18.4$  Hz, 3F,  $\text{CF}_3$ -4); -114.5 (q,  $J = 18.4$  Hz, 1F, F-5); ir (KBr):  $\nu$  3390, 3192, 1686, 1277, 1160  $\text{cm}^{-1}$ . *Anal.* Calcd for  $\text{C}_7\text{H}_2\text{N}_2\text{OCl}_2\text{F}_4$ : C, 30.35; H, 0.73; N, 10.11; Cl, 25.6. Found: C, 30.11; H, 0.83; N, 9.97; Cl, 25.3. **12**: mp 214 °C (ether/petr. ether);  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$ : 7.93 (d,  $J = 36$  Hz,  $\text{CONH}_2$ );  $^{19}\text{F}$  nmr (DMSO- $d_6$ )  $\delta$ : -50.6 (d,  $J = 18.3$  Hz, 3F,  $\text{CF}_3$ -4); -114.5 (m, 1F, F-5); ir (KBr):  $\nu$  3396, 3322, 3194, 1690, 1272, 1048  $\text{cm}^{-1}$ . *Anal.* Calcd for  $\text{C}_7\text{H}_3\text{N}_2\text{O}_2\text{ClF}_4$ : C, 32.52; H, 1.17; N, 10.83; Cl, 13.71. Found: C, 32.15; H, 1.35; N, 10.44; Cl, 14.05. **13**: mp 170-172 °C (silica gel chromatography  $\text{CH}_2\text{Cl}_2$ /acetone 92:8);  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$ : 2.49 (m, 4H,  $\text{CH}_2$  piperazine); 3.53 (m, 6H,  $\text{CH}_2$  benzyl and  $\text{CH}_2$  piperazine); 7.31 (m, 5H, Ar); 7.90 (d,  $J = 37$  Hz,  $\text{CONH}_2$ );  $^{19}\text{F}$  nmr (DMSO- $d_6$ )  $\delta$ : -50.25 (d,  $J = 18.8$  Hz, 3F,  $\text{CF}_3$ -4); -126.33 (q,  $J = 18.8$  Hz, 1F, F-5); ir (KBr):  $\nu$  3313, 3162, 1698, 1272, 1142  $\text{cm}^{-1}$ . *Anal.* Calcd for  $\text{C}_{18}\text{H}_{17}\text{N}_4\text{OCIF}_4$ : C, 51.87; H, 4.11; N, 13.44. Found: C, 51.66; H, 4.35; N, 13.24. **14**: mp 60-62 °C (silica gel chromatography  $\text{CH}_2\text{Cl}_2$ /acetone 96:4);  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$ : 2.52 (m, 4H,  $\text{CH}_2$  piperazine); 3.53 (s, 2H,  $\text{CH}_2$  benzyl); 3.57 (m, 4H,  $\text{CH}_2$  piperazine); 7.09 (d,  $J = 3.2$  Hz, 1H, H-5); 7.28 (m, 5H, Ar);  $^{19}\text{F}$  nmr (DMSO- $d_6$ )  $\delta$ : -53.76 (d,  $J = 13.7$  Hz, 3F,  $\text{CF}_3$ -4); -128.8 (q,  $J = 13.7$  Hz, 1F, F-5); ir (KBr):  $\nu$  3100, 3028, 2814, 1614, 1475, 1354, 1262, 1144  $\text{cm}^{-1}$ . *Anal.* Calcd for  $\text{C}_{17}\text{H}_{16}\text{N}_3\text{ClF}_4$ : C, 54.63; H, 4.31; N, 11.24. Found: C, 54.44; H, 4.42; N, 11.28. **15**: mp 226-228 °C ( $\text{CH}_2\text{Cl}_2$ /MeOH, 75:25);  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$ : 2.65 (m, 4H,  $\text{CH}_2$  pip.); 3.62 (m, 4H,  $\text{CH}_2$  pip.); 3.68 (s, 2H,  $\text{CH}_2$  benzyl); 7.34 (m, 5H, Ar);  $^{19}\text{F}$  nmr (DMSO- $d_6$ )  $\delta$ : -50.6 (d,  $J = 19$  Hz, 3F,  $\text{CF}_3$ -4); -125.8 (q,  $J = 19$  Hz, 1F, F-5); ir (KBr):  $\nu$  3431, 2937, 2870, 1649, 1603, 1421, 1327, 1271, 1146  $\text{cm}^{-1}$ . *Anal.* Calcd for  $\text{C}_{18}\text{H}_{16}\text{N}_3\text{O}_2\text{ClF}_4$ : C, 51.75; H, 3.86; N, 10.06. Found: C, 51.55; H, 3.84; N, 10.08.