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

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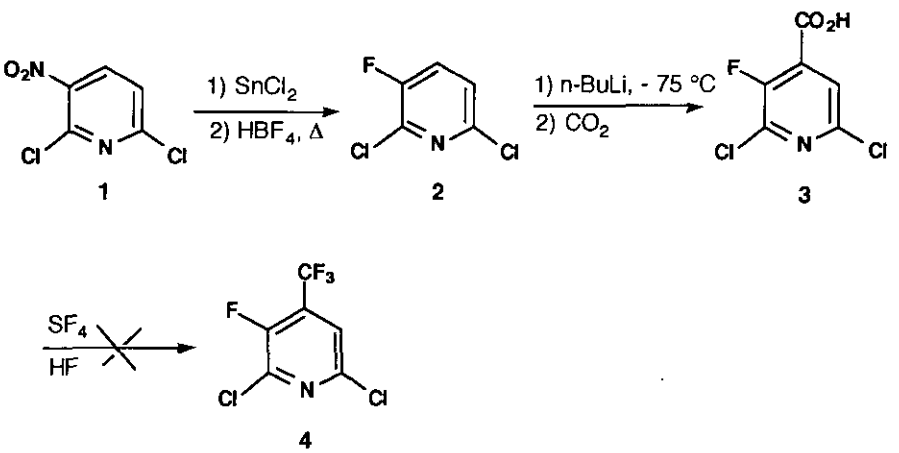
Abstract –The nicotinic acid (**15**), which could be a key intermediate for novel potential anti-bacterial 1,8-naphthyridine-3-carboxylic acid analogues, was prepared initiating with construction of the pyridine nucleus by ethyl 2-fluoroacetate and ethyl 2-trifluoroacetate.

As a continuation of our research to prepare 4-substituted nicotinic acids,[1] 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 [2] and by R. Balicki. [3]

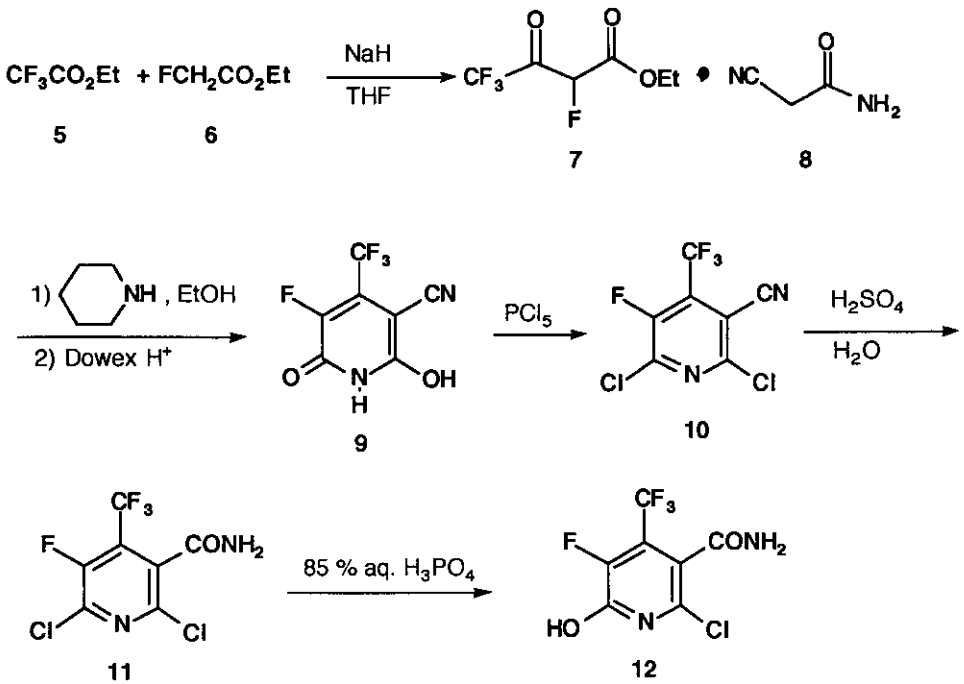
We first tried to introduce a carboxylic group on the 4-position of the 2,6-dichloro-3-fluoropyridine (**2**), obtained from the 2,6-dichloro-3-nitropyridine (**1**) *via* reduction with $SnCl_2$ in acidic medium, followed by

Scheme I



a Balz-Schiemann reaction (Scheme I).[4] The regioselective carboxylation of **2** was readily achieved at low temperature in 67 % yield with n-BuLi and CO_2 to afford **3**. Attempts to fluorinate this intermediate with SF_4 in HF at 60 °C or 120 °C were unsuccessful.[5]

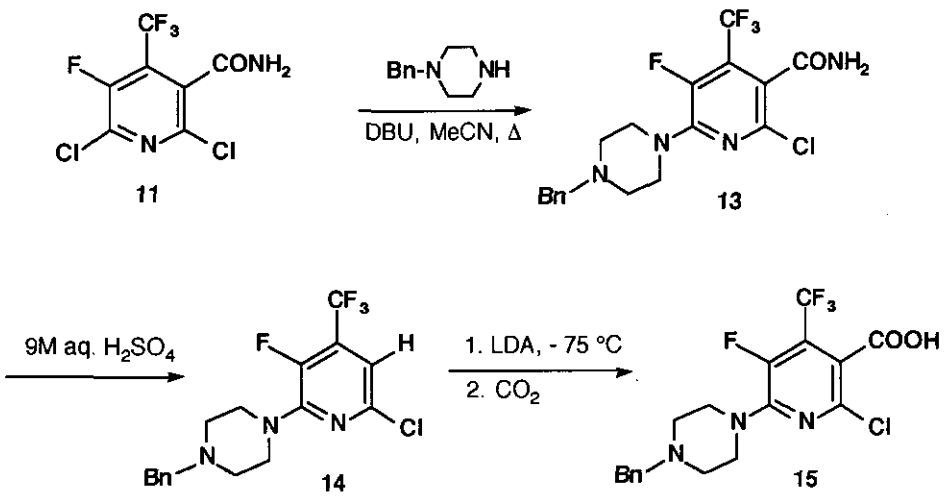
Scheme II



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.[6] 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^+ resin, furnished the pyridone (**9**) in 56 % yield.[7] Chlorination of **9** with two equivalents of PCl_5 at 125 °C for 19 h gave in quantitative yield the crude nicotinonitrile (**10**).[8] Next, the intermediate (**10**) was transformed in 87 % yield into the nicotinamide (**11**) by heating with conc. H_2SO_4 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-trifluoromethylnicotinic acid. Nevertheless the nicotinamide (**11**) after 12 h in refluxing H_3PO_4 afforded the nicotinamide (**12**) in 69

% yield (Scheme II).[9] 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_2, 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



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1. P. Di Cesare, A. Aulombard, D. Bouzard, J.P. Jacquet,and P. Remuzon, *J. Org Chem.*, submitted.
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 BF_3-etherate in ethanol [8] did not give the corresponding expected nicotinic acid ethyl ester.

10. The yields reported were not optimized. **3**: mp 143 °C (petr. ether); ^{1}H nmr (DMSO-d6) 7.85cd, J = 4 Hz, H-5); ^{19}F nmr (DMSO-d6) δ: -114.2 (d, J = 4 Hz, F-3). *Anal.* Calcd for $C_6H_2NO_2Cl_2F$: C, 34.32; H, 0.96; N, 6.67. Found: C, 34.27; H, 1.03; N, 6.48. **9**: mp 229 °C ($CHCl_3$); ^{19}F nmr (DMSO-d6) δ: -51.2 (d, J = 24.8 Hz, 3F, CF_3-4); -150.9 (m, 1F, F-5); ir (KBr): ν 3071, 2927, 2254, 2225, 1658, 1297, 1168 cm^{-1}. *Anal.* Calcd for $C_7H_2N_2O_2F_4$: C, 37.86; H, 0.91; N, 12.61. Found: C, 37.67; H, 1.04; N, 12.58. **10**: oil; ^{19}F nmr (DMSO-d6) δ: -51.2 (d, J = 21 Hz, 3F, CF_3-4); -112 (q, J = 21 Hz, 1F, F-5); ir (KBr):ν 2241, 1550, 1254, 1178 cm^{-1}. **11**: mp 181-182 °C (petr. ether); ^{1}H nmr (DMSO-d6) δ: 8.20 (s, 2H, $CONH_2$); ^{19}F nmr (DMSO-d6) δ: -50.8 (d, J = 18.4 Hz, 3F, CF_3-4); -114.5 (q, J = 18.4 Hz, 1F, F-5); ir (KBr): ν 3390, 3192, 1686, 1277, 1160 cm^{-1}. *Anal.* Calcd for $C_7H_2N_2OCl_2F_4$: 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}H nmr (DMSO-d6) δ: 7.93 (d, J = 36 Hz, $CONH_2$); ^{19}F nmr (DMSO-d6) δ: -50.6 (d, J = 18.3 Hz, 3F, CF_3-4); -114.5 (m, 1F, F-5); ir (KBr): ν 3396, 3322, 3194, 1690, 1272, 1048 cm^{-1}. *Anal.* Calcd for $C_7H_3N_2O_2ClF_4$ 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 CH_2Cl_2/acetone 92:8); ^{1}H nmr (DMSO-d6) δ: 2.49 (m, 4H, CH_2 piperazine); 3.53 (m, 6H, CH_2 benzyl and CH_2 piperazine); 7.31 (m, 5H, Ar); 7.90 (d, J = 37 Hz, $CONH_2$); ^{19}F nmr (DMSO-d6) δ: -50.25 (d, J = 18.8 Hz, 3F, CF_3-4); -126.33 (q, J =18.8 Hz, 1F, F-5); ir (KBr): ν 3313, 3162, 1698, 1272, 1142 cm^{-1}. *Anal.* Calcd for $C_{18}H_{17}N_4OClF_4$: 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 CH_2Cl_2/acetone 96:4); ^{1}H nmr (DMSO-d6) δ: 2.52 (m, 4H, CH_2 piperazine); 3.53 (s, 2H, CH_2 benzyl); 3.57 (m, 4H, CH_2 piperazine); 7.09 (d, J = 3.2 Hz, 1H, H-5); 7.28 (m, 5H, Ar); ^{19}F nmr (DMSO-d6) δ: -53.76 (d, J = 13.7 Hz, 3F, CF_3-4); -128.8 (q, J =13.7 Hz, 1F, F-5); ir (KBr): ν 3100, 3028, 2814, 1614, 1475, 1354, 1262, 1144 cm^{-1}. *Anal.* Calcd for $C_{17}H_{16}N_3ClF_4$: C, 54.63; H, 4.31; N, 11.24. Found: C, 54.44; H, 4.42; N, 11.28. **15**: mp 226-228 °C (CH_2Cl_2/MeOH, 75:25); ^{1}H nmr (DMSO-d6) δ: 2.65 (m, 4H, CH_2 pip.); 3.62 (m, 4H, CH_2 pip.); 3.68 (s, 2H, CH_2 benzyl); 7.34 (m, 5H, Ar); ^{19}F nmr (DMSO-d6) δ: -50.6 (d, J = 19 Hz, 3F, CF_3-4); -125.8 (q, J = 19 Hz, 1F, F-5); ir (KBr): ν 3431, 2937, 2870, 1649, 1603, 1421, 1327, 1271, 1146 cm^{-1}. *Anal.* Calcd for $C_{18}H_{16}N_3O_2ClF_4$: C, 51.75; H, 3.86; N, 10.06. Found: C, 51.55; H, 3.84; N, 10.08.

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