A Practical Synthesis of 4-Amino-2-(Trifluoromethyl)nicotinic Acid

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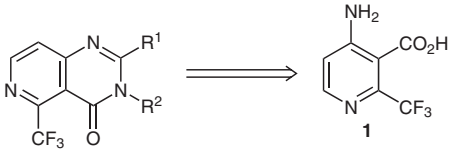
Abstract: A practical synthesis of 4-amino-2-(trifluoromethyl)-nicotinic acid is described. 2-(Trifluoromethyl)pyridine was lithiated using lithium 2,2,6,6-tetramethylpiperidide (LTMP) in the presence of 1,3-dimethyl-2-imidazolidinone (DMI) and followed by CO_2 quench to give the C-3 carboxylation product. Subsequent directed C-4 lithiation of carboxylation product afforded 4-iodo-2-(trifluoromethyl)nicotinic acid, which was coupled with *tert*-butyl carbamate under Pd-catalyzed conditions and followed by Boc deprotection to yield the title product in four steps and 50% overall yield.

Key words: pyridine, directed lithiation, trifluoromethyl, iodination, Boc-amide, amination

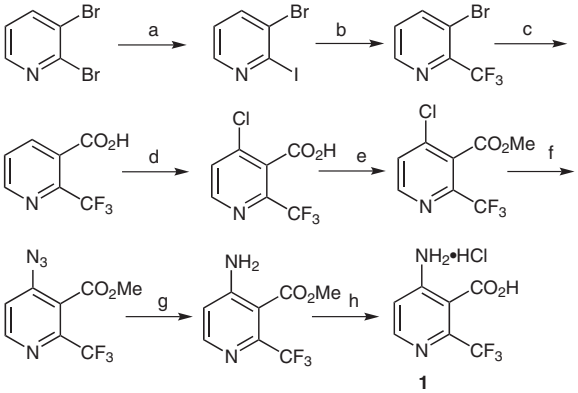
4-Amino nicotinic acids are useful building blocks for syntheses of heterocyclic molecules of medicinal relevance, such as naphthyridines, azaquinazolines, azaquinazolinones, and pyridyldiazepinones.[2] Recently, to support the preparation of 5-(trifluoromethyl)pyrido[4,3-*d*]pyrimidine-4(3*H*)-one derivatives as calcium-sensing receptor antagonists for treatment of osteoporosis,[3] we were tasked to devise a practical process-scale synthesis of the critical intermediate 4-amino-2-(trifluoromethyl)nicotinic acid (**1**, Scheme 1).



Scheme 1 Retrosynthetic analysis of azaquiazolinones

Although the original eight-step linear sequence starting from 2,3-dibromopyridine (Scheme 2) served well for discovery analogue syntheses, it suffered several drawbacks limiting its potential as a feasible scale-up option. Specifically, in this synthesis, the installation of the CF_3 group at C-2 position with Ruppert's reagent was demanding, which required flame-heating a mixture of spray-dried potassium iodide and copper(I) iodide at a reduced pressure of $1.33 \cdot 10^{-3}$ bar. The synthesis was also complicated with thermal hazards associated with the involvement of sodium azide, diazomethane, and an azide intermediate. Furthermore, hexachloroethane in the chlorination step was not considered an environmentally benign reagent. On the other hand, a known literature synthesis of the ethyl ester of **1**[4] involved the highly toxic gaseous and low boiling (bp –64 °C[5]) trifluoroacetonitrile as the starting material.

Attracted by the metalation reaction of 2-(trifluoromethyl)pyridine (**2**) at the C-3 described by Schlosser et al.[6] and the availability of **2** in bulk from a number of suppliers,[7] we decided to enable a scalable synthesis starting from **2**. Following the reported procedures (LTMP, –78 °C, 6 h; CO_2), the C-3 carboxylated product **3** was obtained in 60–72% yields. In this reaction, the lithium anion solution was required to equilibrate for six hours at –78 °C before it was quenched with CO_2. The long equilibration time was necessary to allow the C-4 lithiopyridine anions formed initially under kinetic control to equilibrate to the thermodynamically more favorable C-3 lithiopyridine. Since it is costly to run cryogenic reactions on large scales for long hours, we sought to shorten the lithium anion equilibration time, and found the introduction of 1.0 equivalent of 1,3-dimethyl-2-imidazolidinone (DMI)[8] dramatically accelerated the anion equilibrium process. Thus, quenching the anion solution with CO_2 within one hour gave **3** in 63–77% yields, and the carboxylation product resulted from C-4 lithiation was not detected under the reaction conditions. With **3** in hand, the C-4 lithiation[9] and halogenation were carried out uneventfully under similar conditions shown in Scheme 1. We opted to



Scheme 2 Original synthesis of 4-amino-2-trifluoromethyl nicotinic acid. *Reagents and conditions*: (a) TMSCl, NaI, EtCN, reflux, 85%; (b) $TMSCF_3$, KF (spray-dried), CuI, NMP, r.t. to 35 °C, 62%; (c) Mg turnings, THF, reflux; CO_2 (g), 74%; (d) LTMP, THF, –70 °C, –85 °C to –75 °C, then C_2Cl_6, –75 °C. (e) CH_2N_2, EtOAc, 99%; (f) NaN_3, DMF, 45–50 °C, 98%; (g) concd HI, 0 °C, 96%; (h) LiOH, THF–dioxane–H_2O (3:2:1), 85 °C, 95%.

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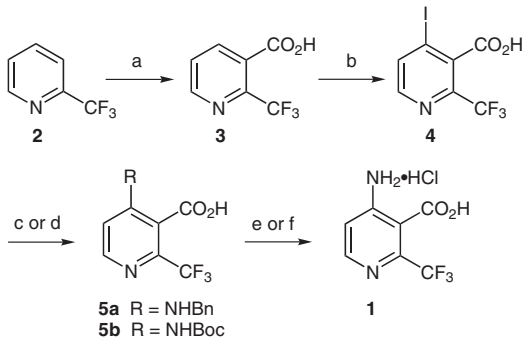
use iodine instead of hexachloroethane as halogenation reagent, and obtained **4**[7e] in 65–77% yields. Both lithiation steps were scaled up successfully to multikilogram batches.

To streamline the synthesis, we planned to avoid the ester intermediate and the subsequent step of ester hydrolysis. Although amination of halogen-substituted nicotinic acids using ammonia is not reported,[10] 2-halo benzoic acids were known to undergo direct substitution using ammonia (ethanolic or aqueous) to give the corresponding 2-aminobenzoic acids.[11] The electron-withdrawing trifluoromethyl group at the C-2 was expected to facilitate the S_NAr reaction. Thus, we attempted the use of ammonia (7 M in MeOH or concd NH_4OH; with or without the presence of copper salts as catalysts) under sealed-tube conditions (170 °C bath temperature, 4 h). To our surprise, we did not observe any desired product from the S_NAr reaction, rather, 4-iodo-2-(trifluoromethyl)pyridine, resulted from the decarboxylation, was detected at ca. 25% (by HPLC) under these conditions. Nevertheless, the employment of large excess of benzylamine (5.8 equiv) at 120 °C gave the desired product **5a** as the major peak by HPLC analysis. Again 5–8% of 4-iodo-2-(trifluoromethyl)pyridine was observed in the reaction. Removal of the excess benzylamine was found tedious. Further decarboxylation occurred when the reaction mixture was subjected to high vacuum distillation. It was subsequently found convenient to derivatize the excess benzylamine to the corresponding acetamide (Ac_2O–Et_3N) that was readily removed by acid–base extractive workup. Compound **5a** was isolated in 73% yield after crystallization using this method.



Scheme 3 Synthesis of 4-amino-2-(trifluoromethyl)nicotinic acid. *Reagents and conditions*: (a) LTMP, –70 °C, then CO_2 (g) or dry ice, 77%; (b) LTMP, –70 °C; then I_2; (c) $BnNH_2$, 120 °C, then Ac_2O, Et_3N; (d) $BocNH_2$, $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, *tert*-amyl alcohol, 84%; (e) H_2 (100 psi), $Pd(OH)_2/C$, MeOH, AcOH, 50 °C, 73%; (f) HCl (g), MeOH, 100%.

The debenzylation also turned out to be troublesome due to the complication of the pyridine reduction giving rise to the corresponding piperidine impurities. After screening the hydrogenolysis conditions, the reaction was optimized to run in methanol (10 mL/g) and acetic acid (2 mL/g) under 6.89 bar H_2 in the presence of $Pd(OH)_2/C$ (10% wt/wt) at 50 °C. Under these conditions, the pyridine reduction was minimized to ca. 10%. The piperidine impurities were removed by recrystallization after converting the crude product to the hydrochloride salt, and the desired product was isolated in 74% yield without chromatography.

With the robustness issues encountered in the benzylamine displacement and the subsequent debenzylation steps in mind, we turned our attention to Pd-catalyzed aryl amination. As the free-base form of **1** is zwitterionic, and its isolation from aqueous phase is cumbersome, we quickly settled on the use of *tert*-butyl carbamate as the choice of the nitrogen nucleophile for the convenience of Boc removal and formation of the hydrochloride salt in one operation. Uneventfully, reaction of **4** with *tert*-butyl carbamate in the presence of $Pd_2(dba)_3$ and Xantphos proceeded to give **5b** in 84% yield (Scheme 3).[12] The removal of the Boc group was readily effected with HCl (g) to give **1**[13] as a hydrochloride salt in quantitative yield. This method was proved superior to the benzylamine substitution approach and allowed us to provide substantial quantities of **1** to support preclinical needs.

In summary, we have developed a practical synthesis of 4-amino-2-(trifluoromethyl)nicotinic acid from commercially available 2-(trifluoromethyl)pyridine in four steps and 50% overall yield. The C-3 carboxylation step was made more feasible on production scale with the addition of DMI as a co-solvent that significantly shortened the anion equilibration time in a cryogenic reactor. The Pd-catalyzed amination of **4** in its free carboxylic acid form further streamlined the synthesis. It is noteworthy that analogous amination reactions precedented in the literature[14] had been limited to esters of nicotinic acids.

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(12) 4-Iodo-2-(trifluoromethyl)nicotinic acid (50 g, 158 mmol), Boc-amide (22.2 g, 189 mmol), and Cs_2CO_3 (103 g, 315 mmol) were combined in 2-methyl-2-butanol (500 mL) that was previously bubbled with dry nitrogen. The reaction flask was purged four times with nitrogen by applying vacuum to the flask then flushed with dry nitrogen. Xantphos (2.74 g, 4.73 mmol) and $Pd_2(dba)_3$ (2.89 g, 3.15 mmol) were added. The nitrogen purging sequence was repeated four times. The reaction was then heated to reflux (104–107 °C internal temperature) for 2 h. Upon confirmation of reaction completion by HPLC analysis, the reaction was cooled to r.t., and the solids (mostly Cs_2CO_3) were removed by filtration. The filter cake was rinsed with EtOAc. The filtrate was concentrated under reduced pressured to give a dark orange oil. To this was added CH_2Cl_2 (250 mL), the resulting mixture was stirred for 10 min, and a slurry was obtained. The solids were collected by filtration, rinsed with CH_2Cl_2 (25 mL), and dried to give **5b** (40.6 g, 84%) as a white solid: mp 180–182 °C (EtOAc). ^{1}H NMR (400 MHz, MeOH-d_4): δ = 8.36 (d, 1 H, *J* = 4.0 Hz), 8.31 (d, 1 H, *J* = 4.0 Hz), 1.51 (s, 9 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ = 173.1, 170.4, 153.4, 149.0, 145.8, 144.6 (q, *J* = 33 Hz), 115.96, 82.7, 28.8. MS (ESI$^+$): *m/z* = 307.0 [M + 1]$^+$, 251 [M + 1 – *t*-Bu]$^+$, 206.9 [M + 1 – Boc]$^+$. Anal. Calcd for $C_{12}H_{13}F_3N_2O_4 \cdot H_2O$: C, 44.45; H, 4.66; F, 17.58; N, 8.64. Found: C, 44.16; H, 4.77; F, 17.28; N, 8.56.
(13) Compound **5b** was dissolved in MeOH (150 mL), and HCl (gaseous, 5.75 g, 158 mmol) was bubbled into the solution. A white solid began to precipitate in 5 min. MeOH was removed under reduced pressure to give **1** as a white solid: mp 214–215 °C (MeOH, dec. observed). ^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.85 (d, 1 H, *J* = 7.0 Hz), 6.90 (d, 1 H, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, MeOH-d_4): δ = 166.1, 157.8, 139.3, 136.2 (q, *J* = 37.5 Hz), 119.2 (q, *J* = 275.8 Hz), 116.8 (q, *J* = 2.0 Hz), 112.2. MS (ESI$^+$): *m/z* = 207.2 [M + 1]$^+$, 189.0 [M + 1 – H_2O]$^+$. Anal. Calcd for $C_7H_6ClF_3N_2O_2$: C, 34.66; H, 2.49; Cl, 14.61; F, 23.50; N, 11.55. Found: C, 34.52; H, 2.55; Cl, 14.48; F, 23.36; N, 11.37.
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