A Practical Synthesis of Nicotinic Acid Derivatives by Palladium on Charcoal

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Nicotinic acid derivatives containing 2-acetylnicotinic acid **3** are very important intermediates for the preparation of commercial herbicides.[1] antiallergy agent,[2] and for the treatment of gastric and duodenal ulcer diseases.[3]

2-Acetylnicotinic acid **3** has been synthesized by a number of methods. Compound **3** has been synthesized by the reflux of nicotinic acid N-oxide with acetic anhydride, treatment of **1** with PCl_3[4] or PBr_3 or other reducing agent, and hydrolysis of **2**. Secondly 8-methylquinoline was ozonized to afford 2-acetylnicotinic acid.[5] Also, 6-oxyquinoline was also ozonized to afford 2-acetyl nicotinic acid **3**.[6] These processes were inadequate to synthesize the acid **3** industrially. Thus we focused on the development of the low-cost synthetic method of **3**, the very important intermediate for herbicides.

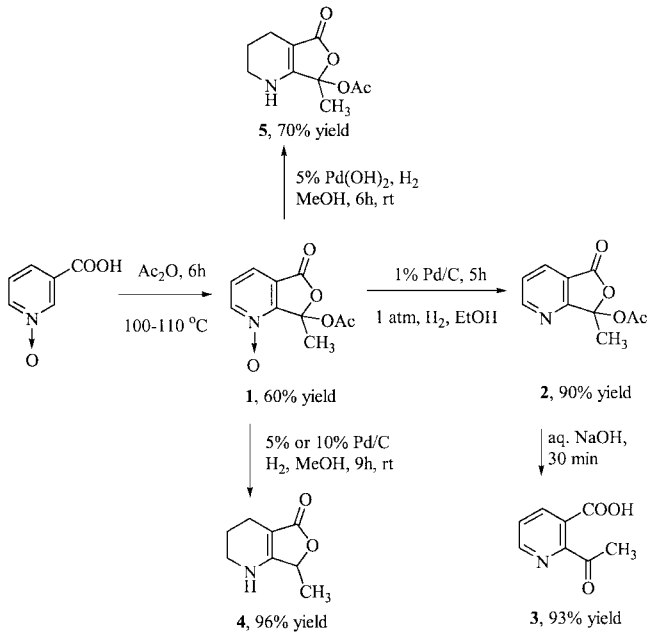
It was well known that nicotinic acid *N*-oxide reacted with acetic anhydride by an intramolecular electrophilic reaction mechanism proposed by Nagano[7] to give **1**.

It was published that compound **1** reduced under hydrogen atmosphere in the presence of Pd/C to give **2** without the explanation about the detailed reaction condition,[8] but we obtained the unique results in the reactions of **1** with 1% Pd/C, 5% or 10% Pd/C and 5% $Pd(OH)_2$, respectively.

A solution of compound **1** (0.1 g, 0.45 mmol) in methanol was stirred under hydrogen atmosphere in the presence of 5% Pd/C (1 mass equiv., 0.1 g) or 10% Pd/C (1 mass equiv., 0.1 g) for 9 h at room temperature. The catalyst was removed by filtration with Celite 545, and the filtrate was evaporated under reduced pressure to give **4** in 96% yield. Also, a solution of compound **1** (0.1 g, 0.45 mmol) in methanol was stirred in the presence of 5% $Pd(OH)_2$ (0.5 mass equiv., 50 mg) under hydrogen atmosphere for 6 h. The solid obtained by the same method as the above work-up was purified by column chromatography on silica gel (*n*-hexane : ethyl acetate = 4 : 1) to afford the white solid **5** in 70% yield.

Compound **1** reacted with 1% Pd/C (0.25 mass equiv., 25 mg) to give the deoxygenated compound **2**, in which its basicity was too weak to give the deacetylated compound. In 5% or 10% Pd/C reaction condition, **1** was reduced to the compound having piperidine moiety, which was deacetylated by its basicity and its complexing with Pd/C to give the compound having double bond, and finally to give **4** by further reduction. In the reaction of **1** with 5% $Pd(OH)_2$, the reaction condition was so weak to give the deacetylated intermediate that **1** was reduced to only piperidine moiety **5**.

In conclusion, we have developed the method that can be capable to apply for a large scale synthesis of **3** from the reaction of **1** with 1% Pd/C. Also, we have elucidated that compound **1** reacts with 5% or 10% Pd/C to give **4** and with 5% $Pd(OH)_2$ to give **5** in high yield, respectively.



Scheme 1. Syntheses of Nicotinic Acid Derivatives.

Experimental Section

General. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on Varian Gemini 300 MHz spectrometer with tetramethylsilane as internal standard. IR spectra were recorded on a MIDAC 101025 FT-IR spectrometer. Melting point was determined by Thomas Hoover capillary melting point apparatus. Column chromatography was performed on Merck silica gel 60 (230-400 mesh) using appropriate solvents. TLC was carried out using glass sheets precoated with silica gel 60 F_{254} prepared by E. Merck.

7-Methyl-2,3,4,7-tetrahydro-1*H*-furo[3,4-*b*]pyridin-5-on (4): R_f 0.43 (ethyl acetate); yield 96%; mp 83-85 °C; ^1H NMR ($CDCl_3$) 5.78 (s, 1H), 4.79 (dd, J = 13.3, 6.6 Hz, 1H), 3.34-3.31 (m, 2H), 2.24 (t, J = 6.1 Hz, 2H), 1.85-1.77 (m, 2H), 1.44 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.4, 168.1, 90.7, 73.7, 41.9, 21.2, 19.2, 17.8; IR (KBr) 3292, 1716, 1634, 1558, 1348, 1292, 1102, 1032 cm^{-1}; Anal.

calculated for $C_8H_{11}N_1O_2$: C, 62.73, H, 7.24, N, 9.14. Found: C, 62.70, H, 7.25, N, 9.01.

Acetic acid 7-methyl-5-oxo-1,2,3,4,5,7-hexahydro-furo [3,4-*b*]pyridin-7-yl ester (5): R_f 0.65 (ethyl acetate); yield 70%; mp 167-169 °C; ^{1}H NMR ($CDCl_3$) δ 5.99 (s, 1H), 3.31-3.29 (m, 2H), 2.23 (t, J = 6.0 Hz, 2H), 2.05 (s, 3H), 1.80 (s, 3H), 1.79-1.73 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.8, 170.0, 163.7, 103.0, 92.1, 41.9, 23.0, 22.1, 20.7, 17.7; IR (KBr) 3258, 1766, 1728, 1632, 1554, 1344, 1226, 1134, 928.0 cm^{-1}; Anal. calculated for $C_9H_{10}N_1O_4$: C, 56.96, H, 6.20, N, 6.63. Found : C, 56.60, H, 6.18, N, 6.47.

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