INVESTIGATION OF THE REACTION OF 5-BROMONICOTINIC ACID WITH CERTAIN ARYLACETONITRILES AND LDA IN THF

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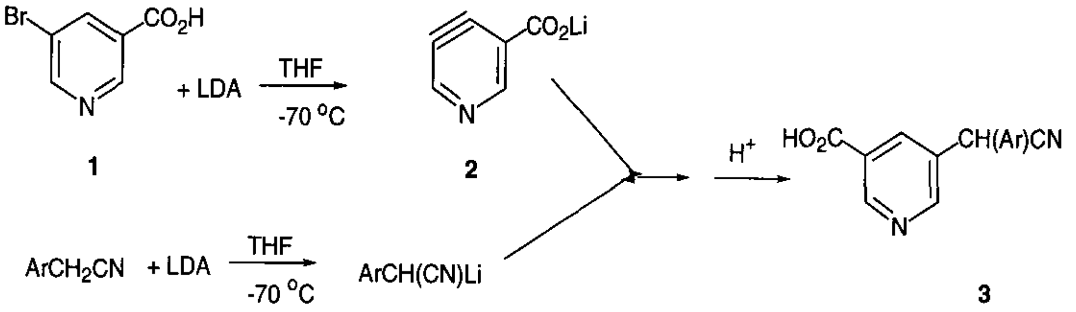
Abstract- The reaction of 5-bromonicotinic acid with various arylacetonitriles and LDA yields the corresponding 5-(α-arylcyanomethyl)nictonic acids in good yields. These cyano acids can be oxidatively decyanated to the respective 5-aroylnicotinic acids in excellent yields.

The influence of charged substituents on the orientation and reactivity of the aryne intermediates has been little studied. In a brief article, we[1] demonstrated that 2-chlorobenzoic acid reacted with various alkanenitriles in the presence of sodium amide in liquid ammonia to give 3-(α-cyanoalkyl)benzoic acids in good yields. Although the weakly inductive carboxylate group would have been expected to yield a mixture of 2- and 3-positional isomers,[2] the exclusive addition of the nitrile anions to the 1-position of benzyne 3-carboxylate indicated clearly that nitrile addition to the 2-position was discouraged by unfavorable electronic interactions between the carboxylate group and the nitrile anion.

Recently, we showed that 4-substituted 2-halobenzoic acids (R = H, Me, MeO) react with arylacetonitriles (**2**) at -70 °C in the presence of LDA in THF to yield predominantly rearranged 4-substituted 2-cyanobenzoic acids (40-61%) plus minor amounts (<2-7%) of 4-substituted 3-arylcyanomethylbenzoic acids. These reactions also most likely proceed *via* benzyne-3-carboxylate intermediates, which are rapidly formed at -70 °C upon the addition of the nitrile to a solution of the appropriate lithium halobenzoate. The base-initiated generation of an aryne from an haloarene at this low temperature is unprecedented.

We have extended the scope of the investigation of the orientations to arynes possessing charged substitutents to include 3,4-dehydropyridine-5-carboxylate (**2**). This hetaryne was conveniently generated at -70 °C by the reaction of the commercially available 5-bromonicotinic acid (**1**) with LDA in the presence of pre-formed α-lithiated arylacetonitriles, and, as shown in eq. 1, gave 3–(α–arylcyanomethyl)nicotinic acids

(**3a-f**) in moderate yields (60-75%).

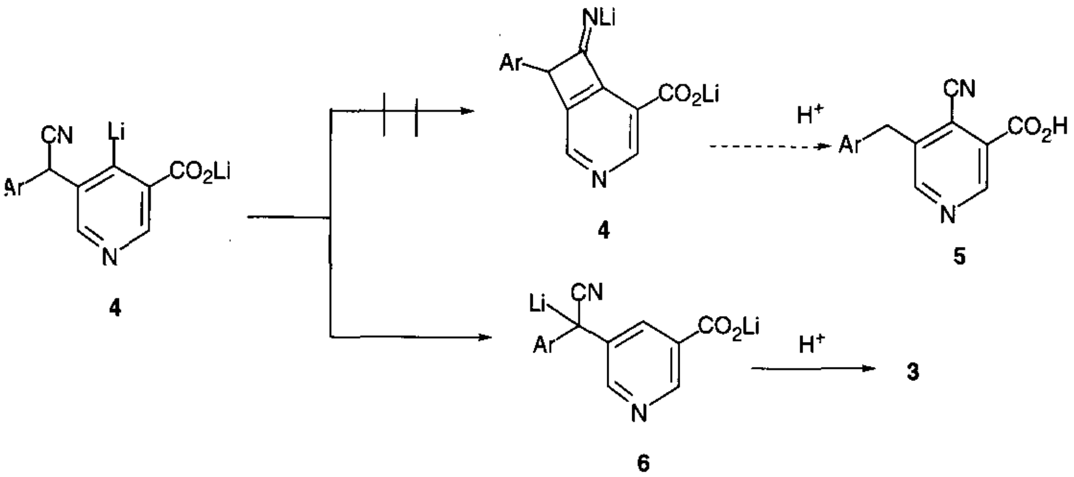


(eq. 1)

a. Ar = C_6H_5, 75%
b. Ar = 2-MeO-C_6H_4, 73%
c. Ar = 4-MeO-C_6H_4, 60%
d. Ar = 3,4-diMeO-C_6H_3, 61%
e. Ar = 1-naphthyl, 62%
f. Ar = 3-thienyl, 68%

The absence of rearranged nitrile products (**5**) similar to those obtained in the reaction of halobenzoic acids, probably reflects the decreased nucleophilicity of the lithiated site in the hetaryne-nitrile anion adduct (**4**) of the π-deficient pyridine ring,[3] which allows the competing aryne alkylation pathway[4] (*via* intermediate (**6**) to predominate over the tandem addition-rearrangement pathway[5] (see Scheme 1).

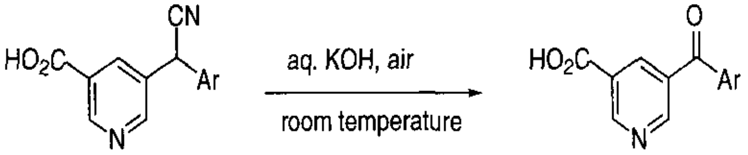
Scheme 1



The structures of **3a-f** were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy and HRMS spectral analysis. The ^{1}H NMR spectra were particularly useful in the determination of structure of compounds **3a-f**. For example, the hydrogens on the pyridine ring were completely separated from those on the benzene ring, which allowed the ready assignments of the respective ring hydrogen atoms. Furthermore, the signals of the three hydrogens in the pyridine ring were also well separated: 2-H (δ 9.09-9.34), 4-H (δ ~8.34-8.54

ppm) and 6-H (δ ~8.86-9.12 ppm). The most deshielded hydrogen atom 2-H was assigned on the basis of its presence adjacent to the more electronegative carboxylate group as compared to the location of 6-H adjacent to the less electronegative cyanomethyl group. Since the coupling constants $J_{(2\text{-H})(4\text{-H})}$ and $J_{(4\text{-H})(6\text{-H})}$ were similar the signal of 4-H was observed as an apparent triplet, whereas those of 2-H and 6-H appeared as doublets. The splitting patterns of the benzenoid hydrogen atoms were consistent with those observed in previous studies.[6]

To illustrate further the synthetic utility of this arynic reaction, the cyano acids (**3a-e**) were readily dehydrocyanated to the corresponding keto acids[7] (**7a-e**) in excellent yields (83-92%) by the treatment with a 10% potassium hydroxide solution in the presence of air at room temperature (eq. 2).



(eq. 2)

3a-e

7a-e

a. Ar = C_6H_5, 91%

b. Ar = 2-MeO-C_6H_4, 85%

c. Ar = 4-MeO-C_6H_4, 90%

d. Ar = 3,4-diMeO-C_6H_3, 92%

e. Ar = 1-naphthyl, 83%

The ^{1}H NMR, ^{13}C NMR, and HRMS spectra were consistent with proposed structures. These aryl nicotinyl ketones may serve as valuable intermediates in the synthesis of biologically active naturally and unnaturally occurring materials.

EXPERIMENTAL

Melting points were taken on an electrochemical apparatus and are uncorrected. IR spectra were obtained from a FTIR spectrometer and the ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer; chemical shifts were related to TMS as internal standard. HRMS spectral analyses were performed by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954). Tetrahydrofuran (THF) was distilled from Na/benzophenone prior to use. n-Butyllithium (n-BuLi) was purchased from Aldrich Chemical Company as a solution in hexane. The glassware was heated at 125 °C in an oven overnight prior to use. All the benzyne reactions were done under an atmosphere of dry O_2-free N_2 contained in a balloon possessing a needle protruding through a rubber septum attached to one of the necks of the reaction flask.

General Procedure for Arynic Reactions. In a flame-dried flask flushed with nitrogen, fresh LDA (15 mmol) was prepared by adding n-butyllithium (6 mL of a 2.5 M solution in hexane) to a solution of diisopropylamine (1.5 g, 15 mmol) in THF (30 mL) at -70 °C. After stirring for 10 min, 5-bromonicotinc acid (1.0 g, 5 mmol) in THF (30 mL) was added dropwise over 20 min and the stirring was continued for an additional 10 min at -70 °C. The appropriate arylacetonitrile (5 mmol) was then added during which time the solution developed a deep red color. The resulting solution was stirred an additional 30 min, then was allowed to warm to rt, stirred overnight, then quenched with 30 mL sat. NH_4Cl. The THF was evaporated under reduced pressure, and the remaining residue was extracted with methylene chloride (3 X 20 mL). The combined exacts were washed with brine (2 X 20 mL), dried (Na_2SO_4), and concentrated (rotary evaporator) to provide crude solid material. The mixture was subjected to flash column chromatography (silica gel) using a mixture of hexane/acetone (6:4) as the eluent to give a solid which was recrystallized from EtOAc. The mp, IR, HRMS and NMR spectral data, and elemental analyses of isolated compounds are given below.

5-(α-Phenylcyanomethyl)nicotinic Acid (3a): colorless solid, mp 207-209 °C; IR (Kbr) cm^{-1} 2266 (CN); ^1H NMR (acetone-d_6) δ: 5.87 (s, 1 H), 7.40-7.56 (m, 5 H), 8.37 (t, J = 2.2 Hz, 1 H), 8.92 (d, J = 2.2 Hz, 1 H), 9.12 (d, J = 2.2 Hz, 1 H). ^{13}C NMR (acetone-d_6) δ: 40.0, 119.74, 127.67, 128.65, 129.48, 130.42, 134.00, 136.49, 136.73, 151.03, 153.24, 165.93. HRMS: Calcd for $C_{14}H_{10}N_2O_2$: 238.0742. Found: 238.0743. Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23: N, 11.76. Found: C, 70.62; H, 4.30; N, 11.89.

5-(α–[2'-Methoxyphenyl]cyanomethyl)nicotinic Acid (3b): colorless solid, mp 172-174 °C; IR (KBr) cm^{-1} 2259 (CN); ^1H NMR (acetone-d_6) δ: 3.89 (s, 3 H), 5.90 (s, 1 H), 7.07-7.11 (m, 2 H), 7.41-7.44 (m, 1 H), 7.54-7.56 (m, 1 H), 8.34 (t, J = 2.0 Hz, 1 H), 8.86 (d, J = 2.0 Hz, 1 H), 9.09 (d, J = 2.0 Hz, 1 H). ^{13}C NMR (acetone-d_6) δ: 38.1, 54.74, 111.99, 118.06, 120.65, 122.88, 125.35, 125.83, .17, 129.94, 132.01, 135.29, 145.21, 149.27, 151.99, 155.90, 164.55, 174.99. HRMS: Calcd for

$C_{15}H_{12}N_2O_3$ 268.0848. Found: 268.0849. Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.13; H, 4.59; N, 10.52.

5-(α–[4'-Methoxyphenyl]cyanomethyl)nicotinic Acid (3c): colorless solid, mp 177-179 °C; ^{1}H NMR (acetone-d_6) δ: 3.81 (s, 3 H), 5.79 (s, 1 H), 7.00 (d, J = 8.8 Hz, 2 H), 7.44 (d, J = 8.8 Hz, 2H), 8.34 (t, J = 2.0 Hz, 1 H), 8.89 (d, J = 2.0 Hz, 1 H), 9.11 (d, J = 2.0 Hz, 1 H). ^{13}C NMR (acetone-d_6) δ: 39.27, 55.71, 115.72, 119.92, 127.47, 128.33, 129.91, 134.36, 136.59, 146.63, 150.94, 153.26, 160.84, 165.89. HRMS: Calcd for $C_{15}H_{12}N_2O_3$: 268.0848. Found: 268.0847. Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.10; H, 4.42; N, 10.60.

5-(α–[3',4'-Dimethoxyphenyl]cyanomethyl)nicotinic Acid (3d): colorless solid, mp 191-193 °C; ^{1}H NMR (acetone-d_6) δ: 3.81 (s, 3 H), 3.82 (s, 3 H), 5.75 (s, 1 H), 7.03-7.08 (m, 2 H), 7.10 (d, J = 1.8 Hz, 1 H), 8.35 (t, J = 2.1 Hz, 1 H), 8.90 (d, J = 2.1 Hz, 1 H), 9.10 (d, J = 2.1 Hz, 1 H). ^{13}C NMR (acetone-d_6) δ: 39.6, 56.16, 56.28, 112.43, 113.25, 119.88, 120.97, 134.26, 136.58, 150.67, 150.92, 151.05, 153.24, 165.94. HRMS: Calcd for $C_{16}H_{14}N_2O_4$: 298.0954. Found: 298.0954. Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H,4.73; N, 9.39. Found: C, 64.40; H, 4.76; N, 9.52.

5-(α-[1-Naphthyl)cyanomethyl])nicotinic Acid (3e): colorless solid, 260-270 °C; ^{1}H NMR (acetone-d_6) δ: 6.69 (s, 1 H), 7.55-7.63 (m, 4 H), 7.64-7.71 (m, 1 H), 7.85-8.00 (m, 2 H), 8.38 (t, J = 2.0 Hz, 1 H), 8.92 (d, J = 2.0 Hz, 1 H), 9.13 (d, J = 2.0 Hz, 1 H). HRMS: Calcd for $C_{18}H_{12}N_2O_2$: 288.0899. Found: 288.0892. Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 11.10. Found: C, 75.24; H, 4.29; N, 11.27.

5-(α-[3-Thienyl](cyanomethyl)nicotinic Acid (3f): colorless solid, mp 220-222°C; ^{1}H NMR (acetone-d_6) δ: 5.39 (s, 1 H), 7.18-7.20 (m, 1 H), 7.59-7.63 (m, 2 H) 8.38 (t, J = 2.0 Hz, 1 H), 8.92 (d, J = 2.0 Hz, 1 H), 9.13 (d, J = 2.0 Hz, 1 H). ^{13}C NMR (acetone-d_6) δ: 38.1, 119.74, 127.67, 128.65, 129.48, 130.42, 134.00, 136.49, 136.73, 151.03, 165.93, 176.43. HRMS: Calcd for $C_{12}H_8N_2O_2S$: 244.0306. Found: 244.0305. Anal. Calcd for $C_{12}H_8N_2O_2S$: C, 59.01; H, 3.30: N, 11.47. Found: C, 59.06; H, 3.35; N, 11.61.

Preparation of 5-Aroylnicotinic Acids:

A 0.5 mmol sample of nitrile (**3**) was dissolved in 2 mL of a 10% aq. KOH solution and stirred for 6 h. The solution was then neutralized with 1 N HCl and extracted with two portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried and evaporated to yield the keto acid (**7**). The keto acids were purified by recrystallization from aqueous acetone.

5-Benzoylnicotinic Acid (7a): colorless solid, mp 208-210 °C; IR (KBr) cm^{-1} 1663 (C=O); ^{1}H NMR (acetone-*d*$_6$) δ: 7.60-7.64 (m, 2 H), 7.74-7.77 (m, 1 H), 7.87-7.89 (m, 2 H), 8.60 (t, *J* = 2.2 Hz, 1 H), 9.12 (d, *J* = 2.2 Hz, 1 H), 9.34 (d, *J* = 2.2 Hz, 1 H). HRMS: Calcd for $C_{13}H_9NO_3$: 227.0582. Found: 227.0583. Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72, H, 3.99, N, 6.16. Found: C, 68.56, H, 4.04, N, 6.22.

5- (2'-Methoxybenzoyl)nicotinic Acid (7b): colorless solid, mp 254-255 °C; IR (KBr) cm^{-1} 1667 (C=O); ^{1}H NMR (acetone-*d*$_6$) δ: 3.65 (s, 3 H) 7.12-7.16 (m, 1 H), 7.16-7.24 (m, 1 H), 7.60-7.48 (m, 1 H), 7.61-7.65 (m, 1 H), 8.34 (t, *J* = 2.0 Hz, 1 H), 8.98 (d, *J* = 2.0 Hz, 1 H), 9.23 (d, *J* = 2.0 Hz, 1 H). HRMS: Calcd for $C_{14}H_{11}NO_4$: 257.0688. Found: 257.0689. Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.37, H, 4.31, N, 5.44. Found: C, 65.44, H, 4.34, N, 5.51.

5-(4'-Methoxybenzoyl)nicotinic Acid (7c): colorless solid, mp 183-184 °C; ^{1}H NMR (acetone-*d*$_6$) δ: 3.95 (s, 3 H) 7.12 (d, *J* =6.8 Hz, 2 H), 7.88 (d, *J* = 6.8 Hz, 2 H), 8.57 (t, *J* =2.0 Hz, 1 H), 9.07 (d, *J* = 2.0 Hz, 1 H), 9.32 (d, *J* = 2.0 Hz, 1 H). HRMS: Calcd for $C_{14}H_{11}NO_4$: 257.0688. Found: 257.0689. Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.37, H, 4.31, N, 5.44. Found: C, 65.48, H, 4.41, N, 5.53.

5-(3',4'-Dimethoxybenzoyl)nicotinic Acid (7d): colorless solid, mp 211-212 °C; IR (KBr) cm^{-1} 1666 (C=O); ^{1}H NMR acetone-*d*$_6$) δ: 3.87 (3, 3 H), 3.91 (s, 3 H), 7.09 (d, *J* = 4.4 Hz, 1 H), 7.40 (dd, *J* = 4.4 Hz, 1.9 Hz, 1 H), 7.47 (t, *J* = 2.0 Hz, 1 H), 8.54 (d, *J* = 2.1 Hz, 1 H), 9.05 (d, *J* = 2.1 Hz, 1 H). HRMS: Calcd for $C_{15}H_{13}NO_5$: 287.2714 Found: 287.2714. Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.72, H, 4.56, N, 4.88. Found: C, 62.76, H, 4.62, N, 4.93.

5-(1'-Naphthoyl)nicotinic Acid (7e): colorless solid, mp 155-157 °C; IR (KBr) cm^{-1} 1669 cm^{-1} (C=O); ^{1}H NMR (acetone-*d*$_6$) δ: 6.69 (s, 1 H), 7.55-7.63 (m, 4 H), 7.64-7.71 (m, 1 H) 8.38 (t, *J* = 2.0 Hz, 1 H), 8.92 (d, *J* = 2.0 Hz, 1 H), 9.13 (d, *J* = 2.0 Hz, 1 H). HRMS: Calcd for $C_{17}H_{11}NO_3$ 277.2788. Found: 277.2788. Anal. Calcd for $C_{17}H_{11}NO_3$: C, 73.64, H, 4.00, N, 5.05. Found: C, 73.69, H, 4.03, N, 5.10.

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