REACTION OF PENTAFLUOROPYRIDINE AND α-LITHIATED ARYLACETONITRILES WITH n-BUTYLLITHIUM AND METHYLLITHIUM IN ETHER

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Abstract - Treatment of one equivalent each of pentafluoropyridine (6) and n-butyllithium with two equivalents of lithioarylacetanitirles (3) gave α-aryl-4-n-butyl-3,5,6-trifluoro-2-pyridylacetonitrile (9) in good yields (83-85%). Similar treatment of equivalent amounts of 6, 3, and methyllithium gave α-aryl-2,3,5,6-tetrafluoro-4-pyridylacetonitriles (11) also in good yields (79-87%). The introduction of the n-butyl and α-arylacetanitirle groups most likely arose through nucleophilic aromatic substitution pathways.

We showed recently that 2,3,5,6-tetrachloro-4-pyridyllithium (2), prepared by treating pentachlormopyridine (1) with n-butyllithium, reacts with α-lithioarylacetonitriles (3) in THF providing mixtures containing mainly α-aryl-2,3,5,6-tetrachloro-4-pyridylacetonitriles (4) and α-aryl-3,5,6-trichloro-2-pyridylacetonitriles (5) plus minor quantities of α-aryl-3,4,5,6-tetrachloro-2- and α-aryl-2,4,5,6-tetrachloro-3-pyridylacetonitriles. The product ratios of 4 to 5 varied from those heavily in favor of 4 through those containing approximate equal amounts of 4 and 5 to those heavily in favor of 5. Subsequently, we found that ether slurries of one equiv. of α-lithioarylacetonitriles (3) when added to ether solutions of one equivalent of 2,3,5,6-tetrachloro-4-pyridyllithium (2) at -70 °C give clear, red solutions upon warming to -20 °C. Further warming of the reaction mixture to room temperature produces bright scarlet precipitates, which upon proton quench provide α-aryl-2,3,5,6-tetrachloro-4-pyridylacetonitriles (4) in excellent yields (98-80%). A mechanism was proposed in which the key step involves a lithium-chlorine exchange between 2 and α-lithio-α-chloroarylacetonitriles. We have extended these perhalopyridine studies to the reaction of pentafluoropyridine (6) with α-lithioarylacetonitriles (3) using n-butyllithium and methyllithium, respectively, and report the results herein.

Treatment of equimolar amounts of pentafluoropyridine (6) and n-butyllithium at -70 °C followed by an equimolar amount of a variety of α-lithioarylacetonitriles (3) in ether gave α-aryl-4-n-butyl-3,5,6-trifluoro-2-pyridylacetonitrile (9) in fair yields (40-50%). However by using two equimolar quantities of 3 per equimolar amounts of 6 and n-butyllithium the yields of 9 were dramatically increased to 83-85%. (eq. 1). The substitution of the 4- and 2-fluorine atoms by n-butyl and cyanomethyl...
groups, respectively, most likely occur stepwise with n-butylation occurring first at the 4-position, since 6 has been shown to undergo preferential 4-substitution by n-butyllithium. The mechanism for each step most likely proceeds through the usual nucleophilic aromatic substitution pathway since lithium-fluorine exchange between 6 and 3 is unlikely. This mechanism also is supported by the fact that two moles of 3 are required for high yields of 9; the extra mole of 3 being consumed in the α-deprotonation of 9.

On the other hand, similar treatment of equimolar quantities of 6 and methyllithium, with 3 gave only α-aryl-4-n-buty1-2,3,5,6-tetrafluoro-2-pyridylacetonitrile (11) in very good yields ranging from 79 to 87% (eq. 2). Under these conditions, substitution of the 4-fluorine atom in 6 by the α-lithioarylacetonitrile (3) occurs exclusively; the methyllithium simply serves to deprotonate 11 to 10.

Although 6 reacts with methyllithium under similar temperature conditions, we failed to detect methylated products. In fact, in our hands, the reaction of 6 with methyllithium using that reported method gave only small amounts of 4-methylperfluoropyridine (<5%) and recovered 6 (85%). Nonetheless, methyllithium serves as a more convenient and less expensive base for the deprotonation of 11 than a second equivalent of more expensive α-lithiated nitriles (3), since the former is converted to a significantly less volatile material (methane) enabling the ready isolation of desired nitrile products (11).

EXPERIMENTAL

General Data. All preparations were done under an atmosphere of dry O2-free N2 contained in a balloon possessing a needle protruding through a rubber septum attached to one of the reaction flask necks. All reagents were obtained from Aldrich and were distilled or recrystallized prior to use. The glassware was heated at 125 °C in an oven overnight prior to use. The elemental analyses were carried out by the Elemental Analysis Group at Southern Methodist University. 1H Nmr spectra were
obtained on a 200 MHz spectrometer using tetramethylsilane as reference and IR spectra were determined on a FT infrared spectrophotometer.

**General Procedure for the Preparation of α-Aryl-4-n-butyl-3,5,6-tetrafluoro-2-pyridylacetonitrile (9) and α-Aryl-2,3,5,6-tetrafluoro-4-pyridylacetonitrile (11).** To a cooled (-70°C) solution containing 10 mmol (2.21 g) of 2,3,4,5,6-pentafluoropyridine (6) in 50 ml of ether was added a cooled solution (-70°C) of n-BuLi (4 ml, 2.5 M in hexanes, 11 mmol) or methyllithium (7.1 ml of a 1.4 M solution in ether), and the resulting solution was stirred for 2 h at -70°C. In a separate flask, 11 mmol of the α-lithioacylonitrile (3) was prepared by the dropwise addition to a solution containing 11 mmol of the arylacetonitrile in 40 ml of ether at -70°C. The resulting slurry was cannulated into a solution containing 6, which was allowed to warm to room temperature. During that time the slurry dissolved to give a bright yellow-scarlet solution, which was stirred overnight. The mixture was quenched with saturated aqueous NH₄Cl (25 ml) and extracted thrice with 25 ml portions of CH₂Cl₂. The combined organic extracts were combined and dried (Na₂SO₄), the solvent removed (rotary evaporator), and the residue eluted on 600 mesh silica gel (19:1, hexane:acetone) to give 9 or 11 when n-butyl- or methyllithium was used. The mp, ¹H nmr, and elemental analyses of products are shown below.

**α-Phenyl-4-n-butyl-3,5,6-tetrafluoro-2-pyridylacetonitrile (9a):** Viscous oil; ¹H nmr (CDCl₃) δ 0.92 (t, J = 7.0 Hz, 3 H), 1.35 (m, 2 H), 1.59 (m, 2 H), 2.72 (t, J = 7.0 Hz, 2 H), 5.40 (s, 1 H), 7.33-7.44 (m, 5 H). Anal. Calcd for C₂₃H₁₅N₃F₆: C, 67.10; H, 4.97; N, 9.21. Found: C, 67.17; H, 5.03, N, 9.29.

**α-(3-Methoxyphenyl)-4-n-butyl-3,5,6-tetrafluoro-2-pyridylacetonitrile (9b):** Viscous oil; ¹H nmr (CDCl₃) 6 0.92 (t, J = 7.0 Hz, 3 H), 1.35 (m, 2 H), 1.59 (m, 2 H), 2.72 (t, J = 7.0 Hz, 2 H), 3.80 (s, 3 H), 5.36 (s, 1 H), 6.89-7.30 (m, 4 H). Anal. Calcd for C₂₃H₁₅N₃O₃F₆: C, 67.91; H, 5.38; N, 8.80. Found: C, 67.79; H, 5.45, N, 8.89.

**α-(4-Methoxyphenyl)-4-n-butyl-3,5,6-tetrafluoro-2-pyridylacetonitrile (9c):** Viscous oil; ¹H nmr (CDCl₃) 6 0.92 (t, J = 7.0 Hz, 3 H), 1.35 (m, 2 H), 1.59 (m, 2 H), 2.72 (t, J = 7.0 Hz, 2 H), 3.80 (s, 3 H), 5.34 (s, 1 H), 6.87 (d, J = 6.5 Hz, 2 H), 7.36 (J = 6.5 Hz, 2 H). Anal. Calcd for C₂₃H₁₅N₃O₃F₆: C, 67.91; H, 5.38; N, 8.80. Found: C, 67.86; H, 5.35, N, 8.76.

**α-(1-Naphthyl)-4-n-butyl-3,5,6-tetrafluoro-2-pyridylacetonitrile (9d):** Viscous oil; ¹H nmr (CDCl₃) 6 0.92 (t, J = 7.0 Hz, 3 H), 1.35 (m, 2 H), 1.59 (m, 2 H), 2.72 (t, J = 7.0 Hz, 2 H), 6.09 (s, 1 H), 7.49-8.16 (m, 7 H). Anal. Calcd for C₂₁H₁₅N₃F₆: C, 79.22; H, 5.42; N, 8.85. Found: C, 79.28; H, 5.42; N, 8.93.

**α-(2-Thienyl)-4-n-butyl-3,5,6-tetrafluoro-2-pyridylacetonitrile (9e):** Viscous oil; ¹H nmr (CDCl₃) 6 0.92 (t, J = 7.0 Hz, 3 H), 1.35 (m, 2 H), 1.59 (m, 2 H), 2.72 (t, J = 7.0 Hz, 2 H), 5.63 (s, 1 H), 6.96-7.30 (m, 3 H). Anal. Calcd for C₁₅H₁₅N₂F₈: C, 58.05; H, 4.22; N, 9.03. Found: C, 58.12; H, 4.18; N, 9.10.

**α-(3-Methylphenyl)-4-n-butyl-3,5,6-tetrafluoro-2-pyridylacetonitrile (9f):** Viscous oil; ¹H nmr (CDCl₃) 6
0.92 (t, J = 7.0 Hz, 3 H), 1.35 (m, 2 H), 1.59 (m, 2 H), 2.35 (t, J = 7.0 Hz, 2 H), 2.72 (t, J = 7.0 Hz, 2 H), 5.63 (s, 1 H), 7.12-7.42 (m, 4 H). Anal. Caled for C_{10}H_{12}F_{2}: C, 67.91; H, 5.38; N, 8.80. Found: C, 68.01; H, 5.44; N, 8.85.

α-Phenyl-2,3,5,6-tetrafluoro-4-pyridylacetonitrile (IIa): colorless solid, mp 90-91 °C (EtOH/H_{2}O). \(^1^H \text{nmr (CDCl}_3\) \(\delta 5.58(s, 1 H), 7.42(m, 5 H).\) Anal. Caled for C_{10}H_{12}F_{2}: C, 58.66; H, 2.27; N, 10.52. Found: C, 58.78; H, 2.34; N, 10.57.

α-(3-Methoxyphenyl)-2,3,5,6-tetrafluoro-4-pyridylacetonitrile (IIb): colorless solid, mp 71-72 °C (EtOH/H_{2}O); \(^1^H \text{nmr (CDCl}_3\) \(\delta 3.80(s, 3 H), 5.54(s, 1 H), 6.98-7.40(m, 4 H).\) Anal. Caled for C_{10}H_{12}F_{2}: C, 54.94; H, 2.84; N, 9.86. Found: C, 55.02; H, 2.87; N, 9.94.

α-(4-Methoxyphenyl)-2,3,5,6-tetrafluoro-4-pyridylacetonitrile (IIc): colorless solid, mp 65-66 °C (EtOH/H_{2}O); \(^1^H \text{nmr (CDCl}_3\) \(\delta 3.80(s, 3 H), 5.58(s, 1 H), 6.90(d, J = 6.8 Hz, 2 H), 7.35(d, J = 6.8 Hz, 2 H).\) Anal. Caled for C_{10}H_{12}F_{2}: C, 54.94; H, 2.84; N, 9.86. Found: C, 54.97; H, 2.79; N, 9.85.

α-(1-Naphthyl)-2,3,5,6-tetrafluoro-4-pyridylacetonitrile (IId): colorless solid, mp 120-121 °C (EtOH/H_{2}O); \(^1^H \text{nmr (CDCl}_3\) \(\delta 5.58(s, 1 H), 7.42(m, 5 H).\) Anal. Caled for C_{10}H_{12}F_{2}: C, 64.45; H, 2.80; N, 8.80.

α-(2-Thienyl)-2,3,5,6-tetrafluoro-4-pyridylacetonitrile (IIe): colorless solid, mp 81-82 °C (EtOH/H_{2}O); \(^1^H \text{nmr (CDCl}_3\) \(\delta 5.78(s, 1 H), 7.03-7.40(m, 3 H).\) Anal. Caled for C_{10}H_{12}F_{2}: C, 48.53; H, 1.48; N, 10.29. Found: C, 48.60; H, 1.45; N, 10.34.

α-(3-Methylphenyl)-2,3,5,6-tetrafluoro-4-pyridylacetonitrile (IIf): colorless solid, mp 95-97 °C (EtOH/H_{2}O); \(^1^H \text{nmr (CDCl}_3\) \(\delta 2.37(s, 3 H), 5.54(s, 1 H), 7.15-7.30(m, 3 H).\) Anal. Caled for C_{10}H_{12}F_{2}: C, 60.01; H, 2.88; N, 10.00. Found: C, 60.07; H, 2.90; N, 10.08.

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