

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

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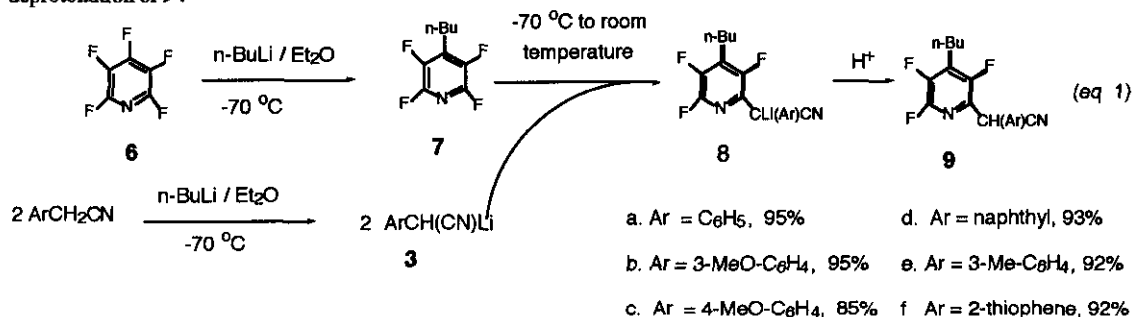
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Abstract - Treatment of one equivalent each of pentafluoropyridine (**6**) and n-butyllithium with two equivalents of lithioarylacetonitriles (**3**) gave α -aryl-4-n-butyl-3,5,6-trifluoro-2-pyridylacetonitrile (**9**) in good yields (83-85%). Similar 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 -arylacetonitrile groups most likely arise through nucleophilic aromatic substitution pathways.

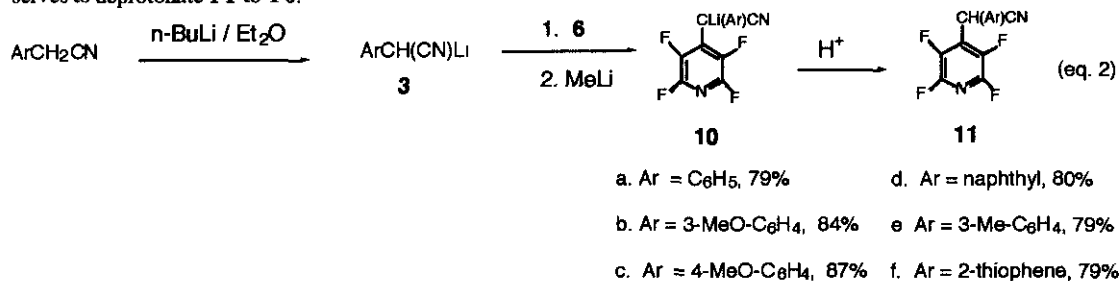
We¹ showed recently that 2,3,5,6-tetrachloro-4-pyridyllithium (**2**), prepared by treating pentachloropyridine (**1**) with n-butyllithium, reacts with α -lithioarylacetonitriles (**3**) in THF providing mixtures containing mainly α -aryl-2,3,5,6-tetrachloro-4-pyridylacetonitriles (**4**) and α -aryl-3,5,6-trichloro-2-pyridylacetonitriles (**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, we² 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.³ 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*-butyl-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 -lithioarylnitrile (**3**) occurs exclusively; the methyllithium simply serves to deprotonate **11** to **10**.



Although **6** reacts with methyllithium under similar temperature conditions,^{4,5} 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 methylolithium (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 -lithioarylacetonitrile (3) was prepared by the dropwise addition of 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 reaction mixture was quenched with saturated aqueous NH_4Cl (25 ml) and extracted thrice with 25 ml portions of CH_2Cl_2 . The combined organic extracts were combined and dried (Na_2SO_4), the solvent removed (rotatory evaporator), and the residue eluted on 600 mesh silica gel (19:1, hexane:acetone) to give 9 or 11 when n-butyl- or methylolithium 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 (CDCl_3) 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 $\text{C}_{17}\text{H}_{15}\text{N}_2\text{F}_3$: 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 (CDCl_3) 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), 3.80 (s, 3 H), 5.36 (s, 1 H), 6.89-7.30 (m, 4 H). Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{OF}_3$: 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 (CDCl_3) 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), 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 $\text{C}_{18}\text{H}_{17}\text{N}_2\text{OF}_3$: 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 (CDCl_3) 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), 6.09 (s, 1 H), 7.49-8.16 (m, 7 H). Anal. Calcd for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{F}_3$: 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 (CDCl_3) 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), 5.63 (s, 1 H), 6.96-7.30 (m, 3 H). Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{F}_3\text{S}$: 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 (CDCl_3) δ

0.92 (t, $J = 7.0$ Hz, 3 H), 1.35 (m, 2 H), 1.59 (m, 2 H), 2.35 (s, 3 H), 2.72 (t, $J = 7.0$ Hz, 2 H), 5.63 (s, 1 H), 7.12-7.42 (m, 4 H). Anal. Calcd for $C_{18}H_{17}N_2F_3$: 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 (11a): colorless solid, mp 90-91 °C (EtOH/H₂O), ¹H nmr (CDCl₃) δ 5.58 (s, 1 H), 7.42 (m, 5 H). Anal. Calcd for $C_{13}H_6N_2F_4$: 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 (11b): colorless solid, mp 71-72 °C (EtOH/H₂O); ¹H nmr (CDCl₃) δ 3.80 (s, 3 H), 5.54 (s, 1 H), 6.98-7.40 (m, 4 H). Anal. Calcd for $C_{14}H_8N_2OF_4$: 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 (11c): colorless solid, mp 65-66 °C (EtOH/H₂O); ¹H nmr (CDCl₃) δ 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. Calcd for $C_{14}H_8N_2OF_4$: 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 (11d): colorless solid, mp 120-121 °C (EtOH/H₂O); ¹H nmr (CDCl₃) δ 5.58 (s, 1 H), 7.42 (m, 5 H). Anal. Calcd for $C_{17}H_9N_2F_4$: C, 64.36; H, 2.86; N, 8.83. Found: C, 64.45; H, 2.80; N, 8.80.

α -(2-Thienyl)-2,3,5,6-tetrafluoro-4-pyridylacetonitrile (11e): colorless solid, mp 81-82 °C (EtOH/H₂O); ¹H nmr (CDCl₃) δ 5.78 (s, 1 H), 7.03-7.40 (m, 3 H). Anal. Calcd for $C_{11}H_4N_2F_4S$: 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 (11f): colorless solid, mp 95-97 °C (EtOH/H₂O); ¹H nmr (CDCl₃) δ 2.37 (s, 3 H), 5.54 (s, 1 H), 7.15-7.30 (m, 3 H). Anal. Calcd for $C_{14}H_8N_2F_4$: C, 60.01; H, 2.88; N, 10.00. Found: C, 60.07; H, 2.90; N, 10.08.

ACKNOWLEDGMENTS

This work was supported in part by grants from the Welch Foundation, Houston, TX, the Petroleum Research Corporation, administered by the American Chemical Society, and the Camille and Henry Dreyfus Foundation. One of us (HMR) thanks the Egyptian Ministry of Education for a Canal Systems Fellowship.

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