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

Edward R. Biehl,[*a] **Hala Mohammed Refat,**[b] **and Amamed A. Fadda**[b]

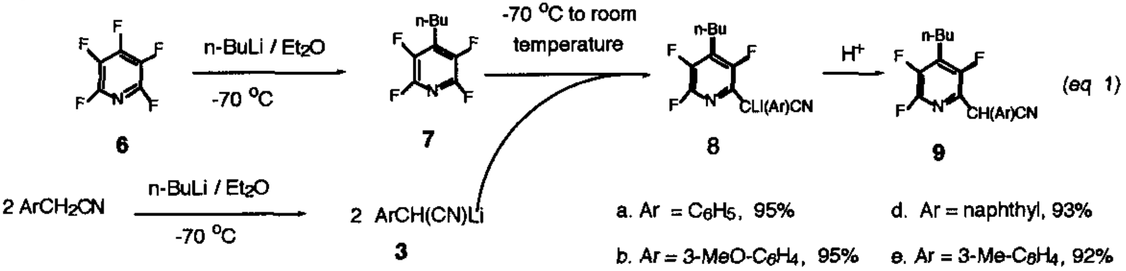
a. Department of Chemistry, Southern Methodist University, Dallas, TX 75275, U S A

b. Faculty of Science, Mansoura University, Mansoura, Egypt

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.

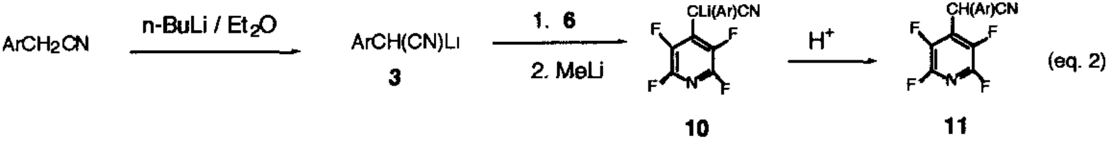
We[1] showed recently that 2,3,5,6-tetrachloro-4-pyridyllithium (**2**), prepared by treating pentachloropyridine (**1**) with n-butyllithium, reacts with α-lithioarylacetonitriles (**3**) in THF providing mixtures containing mainly α-aryl-2,3,5,6-tetrachloro-4-pyridylacetonitriles (**4**) and α-aryl-3,5,6-trichloro-2-pyridylacetonitriles (**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, we[2] 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-postion, since **6** has been shown to undergo preferential 4-substiution 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**.



a. Ar = C_6H_5, 95%
b. Ar = 3-MeO-C_6H_4, 95%
c. Ar = 4-MeO-C_6H_4, 85%
d. Ar = naphthyl, 93%
e. Ar = 3-Me-C_6H_4, 92%
f Ar = 2-thiophene, 92%

On the other hand, similar treatment of equimolar quantitites 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-lithioarylacetonitrile (**3**) occurs exclusively; the methyllithium simply serves to deprotonate **11** to **10**.



a. Ar = C_6H_5, 79%
b. Ar = 3-MeO-C_6H_4, 84%
c. Ar = 4-MeO-C_6H_4, 87%
d. Ar = naphthyl, 80%
e Ar = 3-Me-C_6H_4, 79%
f. Ar = 2-thiophene, 79%

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 O_2-free N_2 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 tetrametylsilane 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-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 methyllithium was used. The mp, ^{1}H nmr, and elemental analyses of products are shown below.

α-Phenyl-4-n-butyl-3,5,6-tetrafluoro-2-pyridylacetonitrile (9a): Viscous oil; ^{1}H 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 $C_{17}H_{15}N_2F_3$: 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; ^{1}H 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 $C_{18}H_{17}N_2OF_3$: 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; ^{1}H 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 $C_{18}H_{17}N_2OF_3$: 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; ^{1}H 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 $C_{21}H_{17}N_2F_3$: 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; ^{1}H 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 $C_{15}H_{13}N_2F_3S$: 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; ^{1}H 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/H_2O), ^{1}H nmr ($CDCl_3$) 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/H_2O); ^{1}H nmr ($CDCl_3$) 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 °C (EtOH/H_2O); ^{1}H nmr ($CDCl_3$) 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 °C (EtOH/H_2O); ^{1}H nmr ($CDCl_3$) 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 °C (EtOH/H_2O); ^{1}H nmr ($CDCl_3$) 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/H_2O); ^{1}H nmr ($CDCl_3$)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.

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