REACTION OF PENTACHLOROPYRIDINE WITH α-LITHIATED ARYLACETONITRILES AND METHYLLITHIUM IN ETHER

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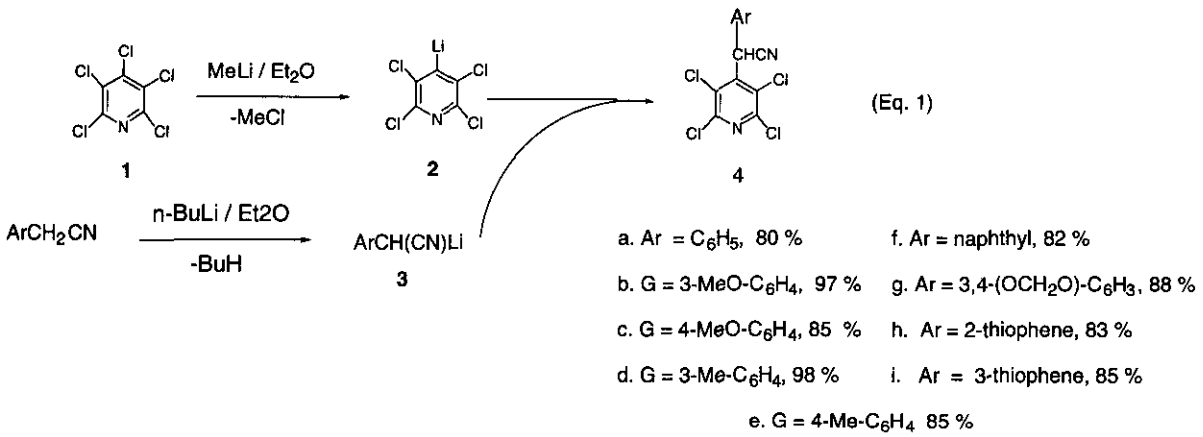
Abstract - Ether slurries of α-lithioarylacetonitriles (**3**) when added to ether solutions of 2,3,5,6-tetrachloro-4-pyridyllithium (**2**) at -70 °C give clear, red solutions upon warming to -20 °C. Further warming to room temperature, produces bright scarlet precipitates which upon proton quench provide α–aryl-2,3,5,6-tetrachloro-4-pyridylacetonitriles (**4**) in excellent yields (98-80%). A mechanism is proposed in which the key step involves a lithium-chlorine exchange between **2** and α–lithio-α–chloroarylacetonitriles (**7**). Experimental evidence for the intermediacy of **7** in these reactions is presented.

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.** Although these mixed results allow interesting mechanistic speculations, their application to organic synthesis is hindered by the vagaries of the α–lithioarylacetonitriles (**3**) on product distributions. Furthermore, although treatment of **1** with n-butyllithium in THF-hexanes yields mainly **2** (78%), it also supplies minor amounts 3,4,5,6-tetrachloro-2-pyridyllithium and 2,4,5,6-tetrachloro-3-pyridyllithium,[2] which are converted to α–aryl-3,4,,5,6-tetrachloro-2- and α–aryl-2,4,5,6-tetrachloro-3-pyridylacetonitriles.

We subsequently prepared 2,3,5,6-tetrachloro-4-pyridyllithium (**2**) uncontaminated with the perchloro-2- and 3-pyridyllithium by treating pentachloropyridine (**1**) with methyllithium in ethyl ether.[2] As shown in Eq. 1, when this solution was mixed with a slurry of α–lithioarylacetonitriles (**3**) in ether initially at -70 °C and resulting mixture was allowed to warm -20 °C the slurry dissolved to give a red solution. Upon warming the solution to room temperature, a bright, scarlet precipitate formed, which after proton quench and chromatographic separation, supplied α–aryl-2,3,5,6-tetrachloro-4-pyridylacetonitriles (**4**) in excellent isolated yields (98-82%).

α–perchloro-2- or 3-pyridylarylacetonitriles.

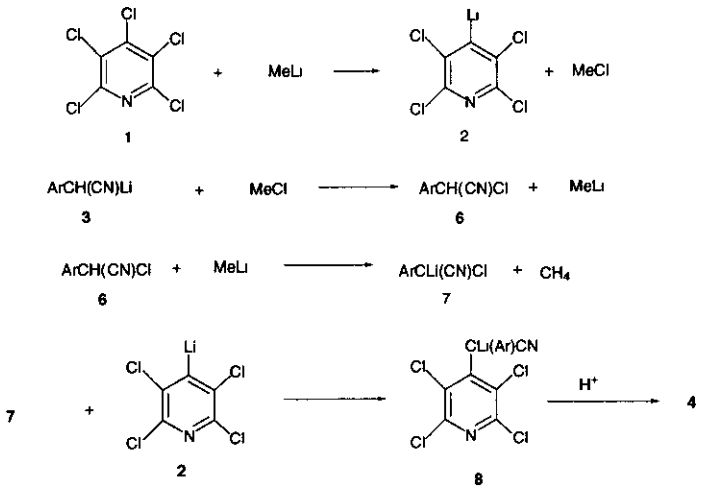


A possible pathway to account for the formation of **4** is shown in Scheme 1 in which α–lithiated nitriles (**3**) undergo lithium-chlorine exchange with the methyl chloride, formed in the methyllithium-mediated lithiation of **1**, providing α–chloroaryl-acetonitriles (**6**) and methyllithium which react further to give α–chloro-α–lithioarylacetonitriles (**7**). Subsequent lithium-chlorine exchanges between intermediates (**7**) and 2,3,5,6-tetrachloro-4-pyridyllithium (**2**) yield the highly colored α–lithio derivatives (**8**) which are converted to **4**, after proton quench. The exclusive obtainment of **4** from these reactions indicates that **3** undergoes lithium-halogen exchange with methyl chloride (**3**) rather than with the 2-chlorine atom in **2**, which apparently occurs in THF-mediated reactions of **2** and **3**. The greater selectivity of the lithium-chlorine exchange in the ether-mediated reactions in comparison to the THF-mediated reactions may reflect the significantly lower concentration of **3** due to its sparingly solubility in ether as compared to those of **3** in THF, in which **3** is completely soluble. To determine if ether-insoluble α-lithio-arylacetonitriles (**3**) react with methyl chloride, we mixed an ether slurry of α–lithio- 3,4-methylenedioxyphenylacetonitrile (**3g**) and methyl chloride at -70 °C, and found that indeed the slurry dissolved around -20 °C to give a yellow solution, which upon further warming to room temperature yielded a light yellow precipitate, presumably **7g**. Addition of water to a portion of the resulting slurry gave piperonal (**10**), most likely <u>via</u> cyanohydrin (**9**). The presence of chloride ion was confirmed by the precipitation of silver chloride by the addition of a 0.1N silver nitrate solution. The remaining portion was treated with tetrachloro-4-pyridyllithium (**2**) to give nitrile(**4g**), after proton quench. These results, summarized in Scheme 2, provide experimental evidence for the intermediacy of α–lithio-α–chloro-3,4-methylenedioxyphenylacetonitrile (**7g**).

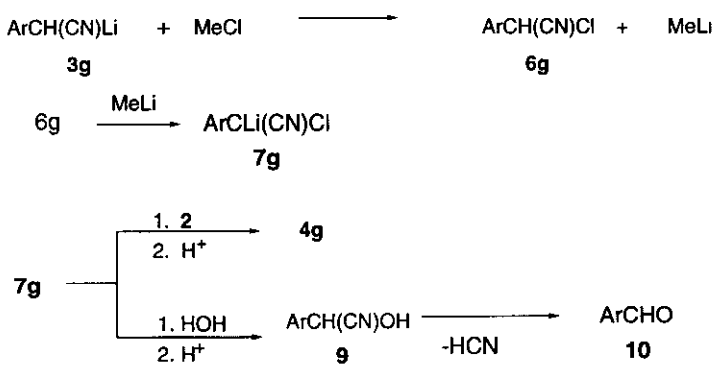
EXPERIMENTAL

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.

Scheme 1



Scheme 2



General Procedure for the Preparation of α-Aryl)-2,3,5,6-tetrachloro-4-pyridylacetonitrile (4). A solution containing 10 mmol (2.21 g) of 2,3,5,6-tetrachloro-4-pyridyllithium (**2**) in ether (50 ml) was prepared by adding dropwise 7.1 ml of a 1.4 M solution of MeLi in ether to a solution containing 2.49 g (10 mmol) of 2,3,4,5,6-pentachloropyridine (**1**) in 40 ml of ether at -70 °C, and the resulting solution was then stirred for 2 h at -70 °C. In a separate flask, 11 mmol of the α–lithioarylacetonitriles (**3**) was prepared by the dropwise addition of n-BuLi (4 ml, 2.5 M in hexanes, 11 mmol) to a solution containing 11 mmol of the arylacetonitriles in 40 ml of ether at -70 °C. The resulting slurry was cannulated into a solution containing **2** and slowly 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 then quenched with saturated aqueous NH_4Cl (25 ml) and extracted thrice with 25 ml portions of methylene chloride. 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 **4**. In all cases, the ^1H nmr spectra, mp and mixed mp were identical to those reported previously.[1]

Reaction of α–Lithio-3,4-methylenedioxyphenylacetonitrile (3g) and Methyl Chloride with 2 or Water. A 10 mmol slurry of α–lithio-3,4-methylenedioxyphenylacetonitrile (**3g**) and ether (50 ml) was prepared in similar fashion to that described in the general procedure for the preparation of α-aryl)-2,3,5,6-tetrachloro-4-pyridylacetonitrile (**4**). A 10 mmol (0.5 g) solution of methyl chloride in ether (50 ml) was then added, and the resulting mixture was warmed to -20 °C to give a clear, yellow solution. Further warming of that solution to room temperature yielded a yellow precipitate. Approximately one-half of that slurry was added to an ether solution (50 ml) of **2** (1.1 g, 5 mmol) to give an intense scarlet solution, which was stirred overnight and then treated in the same manner as described above for the preparation of **4** above to give **4g** (1.4 g, ca. 75% yield). The remaining portion of the colorless slurry was quenched with saturated ammonium chloride aqueous solution and worked up in the usual way to yield piperonal (**9**) whose identity was confirmed by comparison of it's ir and ^{1}H nmr spectra with those of an authentic sample.

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