REACTION OF PENTACHLOROPYRIDINE 2,3,4,5-TETRACHLORO-4-PYRIDYLLITHIUM WITH α-LITHIATED ARYLACETONITRILES AND N-BUTYLLITHIUM

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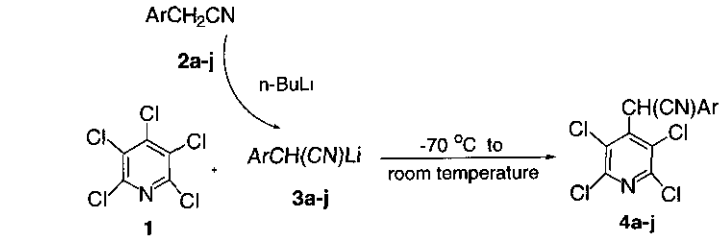
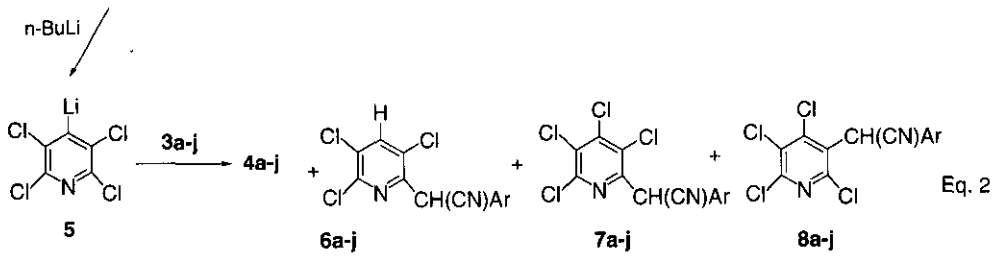
Abstract - Perchloropyridine (**1**) reacts smoothly at -70 °C with α-lithioarylacetonitriles(**3**) affording α–(aryl)-2,3,5,6-tetrachloro-4-pyridylacetonitriles (**4**). The 2,5,6-trichloro-3,4-dehydropyridine precursor, 2,3,5,6-tetrachloro-pyridyllithium (**5**), reacts similarly at -70 °C with **3**, but instead of providing 3,4-dehydropyridine products, α-(aryl)-2,3,4,5-tetrachlorophenylacetonitrile supplies mainly **4** and α-(aryl)-3,5,6-tri-chloro-2-pyridylacetonitriles (**6**) plus minor quantities of α–(aryl)-3,4,5,6-tetrachloro-2- (**7**) and α–(aryl)-2,4,5,6-tetrachloro-3-pyridylacetonitriles (**8**). The product ratios of **4** to **6** from these reactions as well as the relative yields of **4** from the reaction of **1** and **5** with **3** are highly dependent upon **3** To account for these results, an explanation in terms of competing lithium-chlorine exchanges between **1** or **5** with **3** or α–chloroarylacetonitriles (**9**) is proposed

During our recent studies[1,2] on polychloroarenes we obtained two results. First, treatment of perchlorobenzene with α–lithiated aryl-acetonitriles supplies α-aryl-2,3,4,5,6-perchlorophenylacetonitriles at remarkably low temperatures (-70 °C).[1] Secondly, new α-aryl-2,3,5,6-tetrachlorophenylacetonitriles are obtained, rather than perchlorobenzyne products, i e. α-aryl-2,3,4,5-tetrachlorophenylaceto-nitriles, when one mixes the tetrachlorobenzyne precursor, perchlorophenyllithium, with an α–lithioarylacetonitrile -70 °C, which is considerably less than that (0-20 °C)[2] required for perchloroaryne generation These nitrile products presumably arise by an initial lithium-chlorine exchange between perchlorobenzene (or perchlorophenyllithium) and α-lithioarylacetonitrile affording perchloro-phenyllithium (or 1,4-dilithioperchlorobenzene) and an α–chloroarylacetonitriles. Nucleophilic attack of the lithium (or dilithium) species onto the α–chloro nitrile affords the respective α–aryl nitrile To obtain more information on the scope and mechanism of these synthetically useful reactions, we have extended our studies to the pentachloropyridine system, and report the results herein.

RESULTS AND DISCUSSION

As shown in Eq. 1, the reactions of pentachloropyridine (**1**) with α–lithioarylacetonitriles (**3a-j**), which were prepared by treating the appropriate arylacetonitriles (**2a-j**) with n-butyllithium, were carried out at -70 °C- over a period of 2 h and for an additional 14 h at room temperature to afford α–aryl-2,3,5,6-tetrachloro-4-pyridylacetonitriles (**4a-j**) in moderate (87-65%, Entries 2, 5, 8, 9) to fair (42-39%, Entries 3, 4, 7)) to poor (< 24%, Entries 1, 6, 10) isolated yields. Attempts to increase the yields of **4** by extended heating resulted in the formation of higher molecular weight materials.





Treating 2,3,5,6-tetrachloro-4-pyridyllithium (**5**) (prepared by treating **1** with n-butyllithium)[2] and **3a-j** similarly gave mainly **4a-j** and α–aryl-3,5,6-trichloro-2-pyridylacetonitriles (**6a-j**) plus minor amounts (<10%) of α-aryl-3,4,5,6-tetrachloro-2-(**7a-j**)and α-aryl-2,4,5,6-tetrachloro-3-pyridylacetonitriles (**8a-j**). Moreover the product distributions of **4** and **6** are highly dependent upon the nature of **3**. Thus, **6c, e-g** are the principle products (46%, 53%, 83%, 63%, respectively) from the reactions involving **3c, e-g** (Entries 13, 15-17), whereas **4d, i, j** are the major products (64%, 39%, 80%, respectively) from **3d, i, j** (Entries 14, 19, 20). Roughly equal amounts of **4a, b, h** (24-33%) and **6a, b, h** (25-32%) are obtained from the other reactions (Entries 11, 12, 18) Moreover, the relative yields of **4** produced from the reaction of **1** with **3** and **5** with **3** also depends upon the α–lithiated nitrile (**3**). For example **4j** is obtained in a significantly higher yield (76%, Entry 20) from the reaction of **5** with 4-methylphenylacetonitrile (**3j**) than from the reaction of **1** with **3j** (<10%, Entry 10), whereas **4e** is supplied in 83% yield (Entry 5) from the reaction **1** with 3,4-methylenedioxyphenylacetonitrile (**3e**) and in 10% yield (Entry 15) from the reaction of **5** and **3.**

The ^{1}H nmr spectra and elemental analysis, which are listed in Table 2, and ir spectra of **4** and **6** are consistent with the proposed structures. For example, the ir spectra of all products reveals a characteristic CN peak at ν = 2240-2250 cm^{-1}. Furthermore, the

^{1}H nmr spectrum of each 2-pyridyl nitrile (**6**) exhibits an α–C<u>H</u>(Ar)CN) resonance approximately 0 50 ppm down field from that of

Table 1 % Yields of Compounds (**4**, **6-8**) from Reaction of **1** and **5** with **3**

Entry	Chloro-pyridine	**3** Aryl	Letter Design.	Yields, % **4**[b]	**7**[c]	**8**[c]	**6**[b]
1	**1**	C_6H_5	**a**	15	a	a	a
2	**1**	3-CH_3O-C_6H_4	**b**	46	a	a	a
3	**1**	4-CH_3O-C_6H_4	**c**	42[e]	a	a	a
4	**1**	3,4-di-(OCH_3)-C_6H_3	**d**	42[e]	a	a	a
5	**1**	3,4-(OCH_2O)-C_6H_3	**e**	83	a	a	a
6	**1**	1-Naphthyl	**f**	23[d]	a	a	a
7	**1**	2-Thiophene	**g**	39[e]	a	a	a
8	**1**	3-Thiophene	**h**	74	a	a	a
9	**1**	3-CH_3-C_6H_4	**i**	87	a	a	a
10	**1**	4-CH_3-C_6H_4	**j**	>10[d]	a	a	a
11	**5**	C_6H_5	**a**	24[c]		4	33
12	**5**	3-CH_3O-C_6H_4	**b**	33[c]	4	9	25
13	**5**	4-CH_3O-C_6H_4	**c**	31[c]	5	<3	46
14	**5**	3,4-di-(OCH_3)-C_6H_3	**d**	64	6	<3	12[c]
15	**5**	3,4-(OCH_2O)-C_6H_3	**e**	10[c]	5	<3	53
16	**5**	1-Naphthyl	**f**	<3[c]	5	<3	83
17	**5**	2-Thiophene	**g**	20[c]	6	5	63
18	**5**	3-Thiophene	**h**	27[c]	5	<3	32
19	**5**	3-CH_3-C_6H_4	**i**	39	<3	<3	19[c]
20	**5**	4-CH_3-C_6H_4	**j**	76	a	a	a

a. None detected. b. except where noted. c Estimated yields from ^{1}H nmr spectrum of reaction mixture.

d. Mainly starting materials (> 60%) recovered e. Approximately 15-30% starting materials recovered

its 4-pyridyl counterpart (**4**). Moreover, the ^{1}H nmr spectrum of each 2-pyridyl nitrile (**6**) shows a singlet at δ 7.74 corresponding to the chemical shift of the hydrogen at the 4 position of the pyridine ring.[3] Single crystal X-ray diffractometry of- α-(3-thiophene)-3,5,6-trichloro-2-pyridylacetonitrile further confirmed the orientation of the 4-H atom and 2-CH(Ar)CN substituent of the pyridine ring.[4] From the nature of the products and the low temperatures of the reactions, the aryne and <u>ipso</u> nucleophilic aromatic substitution mechanisms for these reactions are not likely. Scheme 1 outlines a possible mechanism for the formation of **4** from the reaction of **1** and **3** similar to that proposed for the reaction of hexachlorobenzene. and arylacetonitrile anions.[1] The first step involves a lithium-chlorine exchange between **1** and **3** yielding **5** and α–chloro-arylacetonitrile (**9**) This is followed by nucleophilic attack by **5** onto the reaction mixture yielding **4**, which under the basic conditions of the reactions is most likely deprotonated to its conjugate base (**10**). Proton quench of **10** yields **4**. A similar metal-halogen exchange/nucleophilic substitution mechanism was proposed by Gilman[4] to explain the ease with with 2,3,4,5,6-pentachloro-1-trimethylsilylbenzene is obtained at -70 °C from the reaction of hexachlorobenzene with trimethylsilyllithium.

Scheme 1

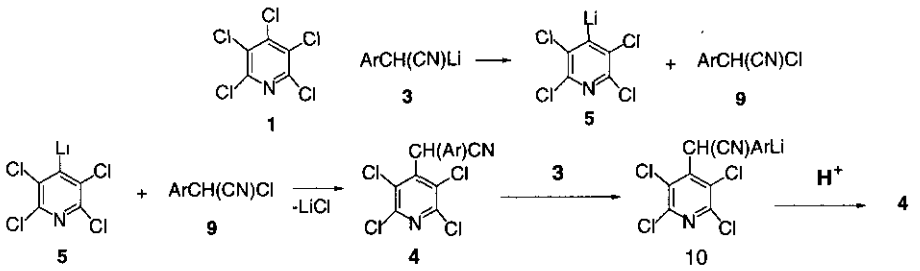
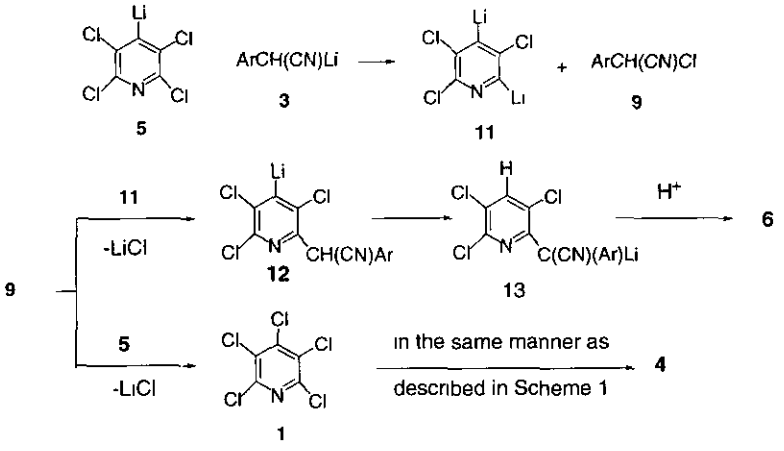


Table 2 Physical Properties of Compounds (**4**) and (**6**)

Comp No	Ar	mp (°C)	Anal Calcd (found)	1H NMR, δ ppm
4a	C_6H_5	89-90	C, 52 65 (52 78); H, 2.04 (2.10); N, 9.45 (9.34)	6.21 (s, 1 H, CHCN), 7.21-7.29 (m, 5 H)
4b	3-CH_3O-C_6H_4	115-116	C, 46.45 (46.54); H, 2.23 (2.30); N, 7.74 (7.82)	3.78 (s, 3 H, OCH_3), 6.20 (s, 1 H, CHCN), 6.84 (s, 1 H) 7.22-7.28 (m, 3 H)
4c	4-CH_3O-C_6H_4	111-112	C, 46.45 (46.41); H, 2.23 (2.21); N, 7 74 (7.87)	3.79 (s, 3 H, OCH_3), 6.18 (s, 1 H, CHCN), 6 86 (d, J = 5.8 Hz, 2 H), 7.25 (d, J = 5.8 Hz, 2 H)
4d	3,4-di-(CH_3O)-C_6H_3	180-181	C, 45.95 (46.10); H, 2.57 (2.71); N, 7 14 (7.23)	3.84 (s, 6 H, OCH_3), 6 18 (s, 1 H, CHCN), 6.86 (d, J = 5.8 Hz, 1 H), 7.25 (d, J = 5.8 Hz, 1 H)
4e	3,4-(OCH_2O)-C_6H_3	148	C, 44.72 (44 91); H, 1.61 (1.49); N, 7.45 (7.52)	5.97 (s, 2 H, OCH_2O), 6.14 (s, 1 H, CHCN), 6.74 (s, 1 H), 6.79 (s, 1 H),
4f	1-Naphthyl	210-211	C, 53.44 (53.51); H, 2.11 (2.21); N, 7 33 (7.41)	6.62 (s, 1 H, CHCN), 7.45 (d, J= 5.1 Hz, 2 H), 7.50-7.62 (m, 2 H), 7.82-7.9 (m, 3 H), 7.74 (s, 1 H)
4g	2-Thiophene	86-87	C, 39.08 (39 13); H, 1.19 (1.27); N, 8.29 (8.40)	6.15 (s, 1 H), CHCN), 6 92 (m, 1 H), 6.95 (m, 1 H), 7.3 (m, 1 H)
4h	3-Thiophene	120-121	C, 39.08 (39.20); H, 1.19 (1.21); N, 8.29 (8.33)	6.30 (s, 1 H), CHCN), 7 10 (m, 1 H), 7.20 (m, 1 H), 7 30 (m, 1 H)
4i	3-CH_3-C_6H_4	138	C, 46.74 (46 78); H, 2.42 (2.25); N, 8.39 (8.33)	2.35 (s, 3 H, CH_3), 6.20 (s, 1 H, CHCN), 7 11 (s, 1 H), 7.24 (m, 3 H)
4j	4-CH_3-C_6H_4	126	C, 46.74 (46.88); H, 2 42 (2.17), N, 8.39 (8.30)	2 34 (s, 3 H, CH_3), 6.20 (s, 1 H, CHCN), 7 19 (s, 4 H),
6a	C_6H_5	c	C, 52.47 (52.28); H, 2.37 (2.29); N, 9.41 (9.33)	6.21 (s, 1 H, CHCN), 7.24 (m, 4 H), 7 70 (s, 1 H, 4-H-C_5NCl_3)
6b	3-CH_3O-C_6H_4	c	C, 51 33 (51.47); H, 2.77 (2.71); N, 3.55 (3.61)	3.78 (s, 3 H, OCH_3), 5.45 (s, 1 H, CHCN), 6.84 (s, 1 H) 7.22-7.28 (m, 3 H), 7.75 (s, 1 H, 4-HC_5NCl_3)
6c	4-CH_3O-C_6H_4	c	C, 51.33 (51.29); H, 2.77 (2.81); N, 3 55 (3.53)	3.79 (s, 3 H, OCH_3), 5.57 (s, 1 H, CHCN), 6.86 (d, J = 5.8 Hz, 2 H), 7 25 (d, J = 5 8 Hz, 2 H), 7.74 (s, 1 H, 4-HC_5NCl_3)
6e	3,4-(OCH_2O)-C_6H_3	c	C, 49 23 (49.41); H, 2.07 (2.01); N, 8.20 (8.34)	5.55 (s, 2H, OCH_2O), 5.97 (s, 1 H, CHCN), 6.74 (s, 1 H), 6.92 (s, 2 H). 7.74 (s, 1 H, 4-HC_5NCl_3)
6f	1-naphthyl	c	C, 58.74 (58.79); H, 2.61 (2 70); N, 8.06 (8.20)	6.26 (s, 1 H, CHCN), 7.45 (d, J= 5 1 Hz, 2 H), 7.50-7.62 (m, 2 H), 7 82-7.9 (m, 3 H), 7.74 (s, 1 H, 4-HC_5NCl_3)
6g	2-thiophene	c	C, 43.52 (43.71); H, 1.66 (1.78); N, 9.23 (9.33)	5.86 (s, 1 H), CHCN), 7.10 (m, 1 H), 7.20 (m, 1 H), 7.30 (m, 1 H), 7.74 (s, 1 H, 4-HC_5NCl_3)
6h	3-thiophene	c	C, 43.52 (43.75); H, 1.66 (1.72); N, 9.23 (9.34)	5.70 (s, 1 H), CHCN), 7.10 (m, 1 H), 7.30 (m, 1 H), 7.38 (m, 1 H), 7.74 (s, 1 H, 4-HC_5NCl_3)
6i	3-CH_3-C_6H_4	138	C, 46.74 (46.78); H, 2.42 (2.25); N, 8.39 (8 33)	2 35 (s, 3 H, CH_3), 5.6 (s, 1 H,CHCN), 7.10 (m. 1 H), 7.19 (s, 1 H, 4-HC_5NCl_3), 7 24-7.31 (m, 3 H)

Scheme 2 outlines a possible pathway for the formation of **6** and **4** from **5**. As shown, an initial α–lithium-2- chlorine exchange between **5** and **3** gives the dilithio species (**11**) and α–chloro nitrile (**9**). These intermediates then combine in similar

Scheme 2



manner to that described in Scheme 1, yielding 4-lithio-2-pyridylacetonitrile (**12**). Internal neutralization of **12** followed by proton quench of the resulting α–lithio nitrile (**13**) yields **6**. The obtention of **4** from the reaction of **5** and **3** indicates that **9** most likely reacts with **5** to yields **1**, which then is converted to **4** via pathway described in Scheme 1. The formation of minor perchloro-2-pyridyl- (**7**) and perchloro-3-pyridylacetonitriles (**8**) may be similarly formed since their respective precursors perchloro-2-pyridyllithium and perchloro-3-pyridyllithium are known to be side products in the n-butyllithium mediated synthesis of **5** from 1 in THF/ hexanes solvent [6] It is possible that **4** could be formed by nucleophilic attack by the 4-lithio carbon of the dilithiopyridine (**11**) followed by exchange of the resulting 2-lithiated 4-substituted pyridine with **9** However, this is not as likely due to the greater nucleophilicity of the 2-lithio site as compared to the 4-lithio site in **11**. Scheme 2 suggests that influence of α-arylacetonitrile anions (**3**) on the product distribution of **4** and **6** is an outcome of the competition of **11** and **5** for the α-chloro-arylacetonitrile (**9**) Furthermore, it predicts that an additional source of chlorine other than the 2-chlorine atom in **5** is required for the synthesis of **9**, which may be n-butyllithium produced in the n-BuLi mediated preparation of **5** from 1.

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. Tetrahydrofuran (THF) was passed through a column containing neutral alumina then refluxed in the presence of sodium benzophenone ketyl until a permanent blue color was achieved. The arylnitriles, perchloropyridines, and n-BuLi were obtained from Aldrich and were distilled or recrystallized prior to

use. Melting points were taken on an electrochemical apparatus and are uncorrected. Ir spectra were determined on a Nicolet Magna ^{TM} 550 spectrometer, the nmr spectra were recorded on a Brucker 200 MHz WPSY spectrometer and chemical shifts are related to TMS as internal standard, and the elemental analysis were performed at the SMU Chemistry Analytical Laboratory using an ERBA elemental analyzer

General Procedure for the Preparation of α-Aryl-2,3,5,6-tetrachloro-4-pyridylacetonitrile (4). A solution of n-BuLi (4 ml, 2.5 M in hexanes, 11 mmol) was added dropwise to a solution containing 11 mmol of the arylacetonitriles (**3**) in 40 ml of THF at -70 °C. After the resulting solution of α- arylacetonitriles (**3**) was stirred for 2 h at -70 °C, it was cannulated into a solution containing containing 2.5 g (10 mmol) of pentachloropyridine (**1**) in 40 ml of THF for 2 h at -70 °C, and the resulting solution was stirred an additional 2 h. the acetone-dry ice bath was removed, and the reaction mixture was allowed to warm to room temperature where it was stirred overnight. The reaction mixture was then quenched with saturated aqueous NH_4Cl (25 ml) and extracted thrice with 25 ml portions of CH_2CH_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 **4**.

General Procedure for the Preparation of α-aryl-3,5,6-trichloropyridylacetonitrile (6). A solution containing 10 mmol of 2,3,5,6-tetrachloro-4-pyridyllithium (**5**) was prepared by adding dropwise 4.0 ml of a 2.5 M solution of n-BuLi in hexanes to a solution containing 2.49 g (10 mmol) of 2,3,4,5,6-pentachloropyridine (**1**) in 40 ml of THF at -70 °C. The solution was then stirred for 2 h at -70 °C, then cannulated into a solution containing 11 mmol of **4**, prepared by treating 11 mmol of **3** with n-BuLi (4 ml, 2.5 M in hexanes). The mixture was treated in identical manner as that described above for the preparation of **4**

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 Channel Systems Fellowship

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Received, 1st August 1994