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INVESTIGATION ON THE REACTION OF 2-CHLORO-10*H*-PHENOTHIAZINE UNDER ARYNE FORMING CONDITIONS

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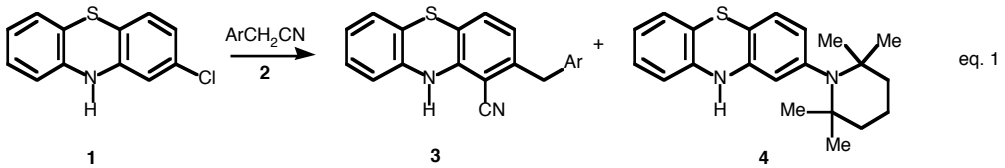
Abstract – The reaction of 2-chloro-10*H* -phenothiazine with a variety of aryl-acetonitriles and α-cyano-*o*-tolunitrile in the presence of LTMP gave 2-arylmethyl-10*H*-phenothiathiazine-1-carbonitriles and 13-amino-14*H*-naphtho[2,3-*b*]phenothiazine-8-carbonitrile, respectively. Interestingly, LTMP effectively trapped 10-lithio-1,2-didehydrophenothiazine to give 2-(2,2,6,6-tetramethylpiperidin-1-yl)-10*H*-phenothiazine.

We[1-9] have recently shown that arynes possessing charged substituents (*e.g.* benzyne-3-carboxylate,[1-6] 3,4-didehydro-5-nicotinamidate,[6,7] 2,3-didehydrobenzyl oxide,[6,7] 2,3-didehydophenoxide[6,8,9]) can be trapped by various lithiated arylacetonitriles or 1,4-dipolar nucleophiles (*e.g.* lithiated α-cyano-*o*-tolunitrile and 3-thienylacetonitrile). Depending upon the nature of the aryne, the initially formed adducts can proceed to products by the usual aryne pathway,[10] a tandem addition-rearrangement pathway,[11] a [4+2] cycloaddition pathway, or a combination of the latter two pathways. These one-step reactions, which use readily available starting materials, have given rise to a large number of multi-substituted and/or polycyclic arenes or heterocycles. For several of these compounds, this aryne synthesis is the method of choice since non-aryne synthetic methodologies would require several steps. This paper reports an extention of this aryne synthetic methodology to the reaction of 2-chloro-10*H*-phenothiazine with various arylacetonitriles, and α-cyano-*o*-tolunitrile.

The reaction of 2-chloro-10*H*-phenothiazine (**1**) with certain arylacetonitriles (**2a-e**) in the presence of LTMP (lithium 2,2,6,6-tetramethylpiperidide) was first carried out. As shown in eq 1, the corresponding 2-arylmethyl-10*H*-phenothiazine-1-carbonitriles (**3a-e**) were obtained in

42-61% yields in this way. In addition, minor amounts of 2-(2,2,6,6-tetramethylpiperidin-1-yl)-10*H*-phenothiazine (**4**) were obtained in yields of 5-15%, respectively.



1 **3** **4**

a Ar = C_6H_5 , 52%
b Ar = 4-$MeOC_6H_4$, 54%
c Ar = naphthlen-1-yl, 58%
d Ar = thiophen-2-yl, 34%
e Ar = 2,3-di(MeO)-C_6H_3 , 42%

5-15%

Experimentally, these reactions were carried using a reverse-addition method. This method involved first adding one equiv of aryne precursor (**1**) to 6 equiv of LTMP at –70 °C then adding 2 equiv of nitrile (**2a-e**). The resulting mixture was allowed to warm to room temperature, during which aliqoutes of the reaction mixture were taken at various times and analysed by GC/MS. The results indicated that the reaction started slowly around – 40 °C , but was essentially completed after stirring at abient temperature for 6 h for nitriles (**2a-c** and **2e**). The thiophene nitrile (**3d**) reaction was over in 1.5 h; further stirring resulted in decomposition and thus lower yields of product (**3d**).

The structures of **3a-e** were determined by IR, ^{1}H-NMR, ^{13}C NMR spectroscopy and elemental analysis. Additionally, the structure of **3a** was ascertained by X-Ray crystallographic analysis, an ORTEP[12] from which is shown in the Figure. This structure confirms that nucleophilic

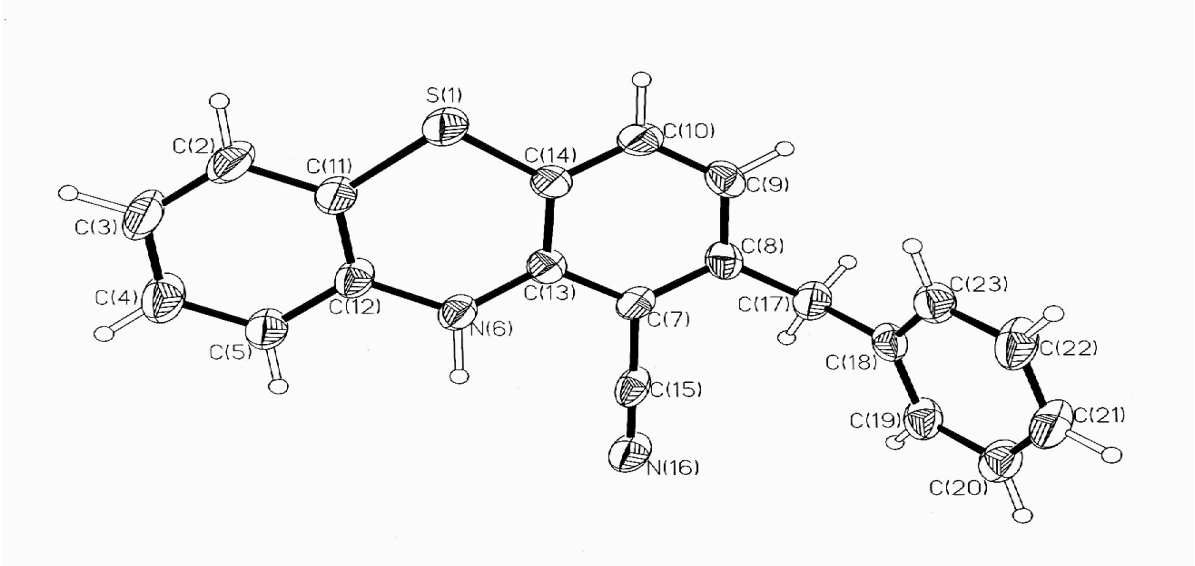
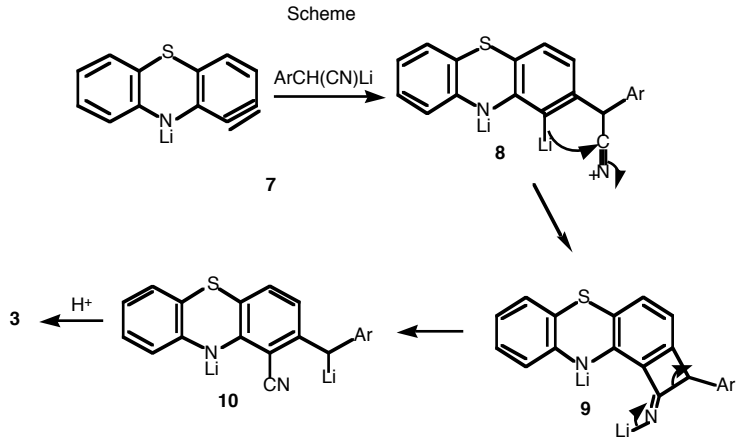


Figure ORTEP of compound (**3a**)

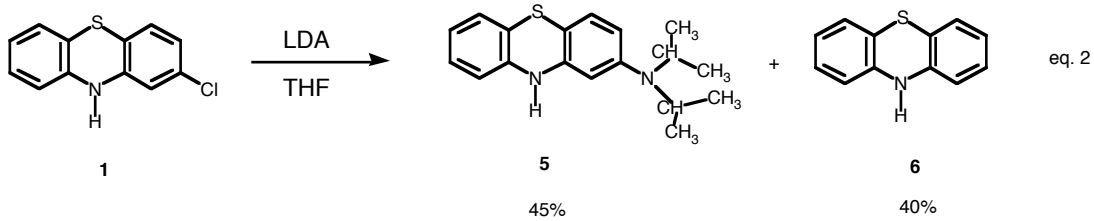
addition (as shown in the Scheme) occurred regioselectively to the 2-position of 10-lithio-1,2-didehydro-10*H*-phenothiazine (**7**) to give adduct (**8**). This orientation is consistent with previous calculation[13] that showed that the orienting effect of a lithiated atom (N-Li in this case) is determined primarily by the inductive effect of the lithiated atom. The X-Ray structure also

Scheme



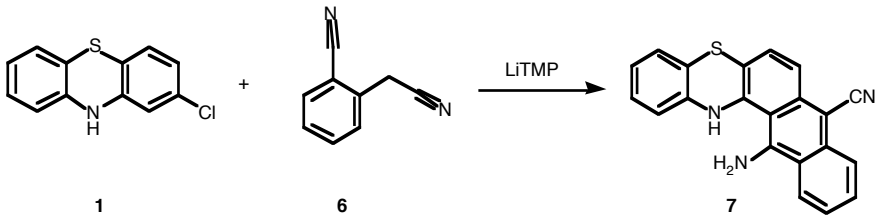
confirmed that the initially formed adduct (**8**) proceeded to products by the tandem addition-rearrangement pathway rather than the usual aryne mechanism. As also shown in the Scheme, the former pathway involves the cyclization of **8** (the key step)*via* addition of the C-Li of the arene onto the cyano carbon to the benzocyclobutanimium intermediate (**9**), which opens up to the rearranged cyano carbanion (**10**). Acidic workup then affords the observed products (**3**). That adduct (**8**) undergoes cyclization exclusively is consistent with previous studies,[14] which showed that electron-releasing groups by resonance (N-Li in this case) enhanced the cyclization process by increasing the nucleophilicity of the C-Li cyclization.

Surprisingly, LTMP added to 10-lithio-1,2-didehydrophenozine, since this sterically demanding base had been previously assumed to be a poor trap for benzyne.[15] To our knowledge this is the first example of LTMP functioning as a benzyne trap in the presence of other nucleophiles. Interestingly, treating **1** and LTMP in the absence of a nitrile was found to give **4** in only 15% yield and a substantial amount of tar. We subsequently treated **1** with LDA (lithium diisopropylamide) as shown in eq. 2 and found that 2-diisopropylamino-10*H*-phenothiazine (**5**) and 10*H*-phenothiazine (**6**), the reduced product,[15] were formed in yields of 45% and 40%,



respectively. The yield ratio of the aminated product to reduced product found here are substantially lower than that found previously from the reaction of 2-chloro-10-methyl-10*H*-phenothiazine.[16] This difference may reflect the greater reactivity (lower selectivity) of 10-lithio-1,2-didehydro-10*H*-phenothiazine as compared to the 10-methyl analog.[17]

Compound (**1**), as shown in eq. 3, also reacted with the 1,4-dipolar nucleophile, α-cyano-*o*-tolunitrile (**6**), to give 13-amino-14*H*- naphtho[2,3-*b*]-10*H*-phenothiazine-8-carbonitrile (**7**) in 52% yield.



1 **6** **7** eq. 3

In conclusion, we have shown that 10-lithio-1,2-didehydrophenothiazine containing a 10-lithio group is trapped regioselectively by cyano anions derived from arylacetonitriles and to give adducts that proceed to 2-arylmethyl-1-cyano-10*H*-phenothiazines. These products should provide ready access to highly functionalized phenothiazines, which are difficult to synthesis by non-aryne synthetic methodology.

EXPERIMENTAL

Melting points were taken on a Mel-Temp II capillary apparatus and are uncorrected with respect to stem correction. IR spectra were recorded on a Nicolet Magna-IR^{TM} 550 FTIR spectrophotometer, and the ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker AVANCE DRX-400 Multi-nuclear NMR spectrometer; chemical shifts were referenced to TMS as internal standard. Elemental analyses were obtained from the SMU Elemental Analysis Laboratory. 2-Chloro-10*H* -phenothiazine, arylacetonitriles (2), LDA, 2,2,6,6-tetraimethyl-piperidine, and *n*-BuLi were purchased from Aldrich Chemical Company. Diisopropylamine was refluxed over and distilled from calcium hydride. Tetrahydrofuran (THF) was distilled from Na/benzophenone immediately prior to use. The glassware was heated at 125 ^{o}C in an oven overnight prior to use. All benzyne reactions were done under an atmosphere of dry O_2-free N_2 *via* balloon.

General Procedure for Aryne Reactions. In a flame-dried flask flushed with nitrogen, fresh LTMP (862 mg, 6.0 mmol) was prepared by adding *n*-BuLi (6.0 mmol, 2.4 mL of 2.5 M solution in hexane) to a solution of 2, 2', 6, 6'-tetramethylpiperidine (846 mg, 6.0 mmol) in THF (50 mL) at -70 ^{o}C. After stirring for 10 min, 2-chloro-10*H*-phenothiazine (233 mg, 1.0 mmol) was added and the stirring contiuned for 20 min. Then the appropriate nitrile (2.0 mmol) was added and the resulting light green slurry was stirred to rt during which time a clear green solution formed. The green solution slowly changed to deep red while the stirring was continued for 6 h (1.5 h in the

case of the thienylacetonitrile (**2d**) reaction. The reaction solution was quenched with saturated NH_4Cl solution (30 mL) and then extracted with methylene chloride. The combined extracts were washed with 6% HCl then dried (Na_2SO_4) and concentrated (rotary evaporator) to give a crude material. Chromatography of this mixture on silica gel (hexane-acetone, 9:1) gave the pure product (**3a-e** or **6**). The mp, elemental analyses and NMR spectral data of these products are given below.

2-Benzyl-10*H*-phenothiazine-1-carbonitrile (3a): green crystals, yield 52 %., mp 166.0-166.5 ^{O}C (EtOAc). IR (KBr) ν_{max} 3333, 2222, 1461, 1435,1298, 732, 695 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 4.04 (s, 3 H), 6.78 (d, J = 8.0 Hz, 1 H), 6.91 (t, J = 8.0 Hz, 1 H), 6.98 (d, J = 7.6 Hz, 1 H), 7.11 (m, 3 H), 7.30 (m, 4 H), 7.67 (s, 1 H). ^{13}C NMR (acetone-d_6) δ 39.8, 97.5, 116.1, 117.2, 117.4, 117.5, 123.4, 124.1, 126.6, 127.0, 128.3, 129.1, 131.0, 139.5, 140.2, 144.1, 145.1. Anal. Calcd for $C_{20}H_{14}N_2S$: C, 76.40; H, 4.40; N, 8.01; S, 10.20. Found: C, 76.45; H, 4.47; N, 8.10; S, 10.26.

2-(4-Methoxybenzyl)-10*H*-phenothiazine-1-carbonitrile (3b): yellow crystals, mp 143-144 ºC (EtOAc), 54 % yield; IR (KBr) ν_{max} 3333, 2222, 1510, 1463, 1301, 1249, 814, 739. ^{1}H NMR (acetone-d_6) δ 3.76 (s, 3 H), 3.97 (s, 2 H), 6.78 (t, J = 8.0 Hz, 1 H), 6.87 (d, J = 8.8 Hz, 2 H), 6.92 (t, J = 8.0 Hz, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 7.08 (m, 3 H), 7.19 (d, J = 8.0 Hz, 2 H), 7.66 (s, 1 H). ^{13}C NMR (acetone-d_6) δ 38.9, 55.0, 97.5, 114.1, 115.7, 117.0, 117.5, 122.9, 123.7, 126.3, 127.9, 130.0, 131.2, 140.2, 140.5, 145.1, 158.5. Calcd for $C_{21}H_{16}N_2OS$: C, 73.23; H, 4.68; N, 8.13; S, 9.31. Found: C, 73.20; H, 4.78; N, 8.21; S, 9.45.

2-[(Naphthalen-1-yl)methyl]-10*H*-phenothizine-1-carbonitrile (3c): green crystals, mp 187.5-188.0 ºC (EtOAc), 58% yield. IR (KBr) ν_{max} 3333, 2219, 1597, 1558, 1463, 1438, 1298, 785, 746. ^{1}H NMR (acetone-d_6) δ 4.23 (s, 2H), 6.48 (d, J = 8.0 Hz, 1 H), 6.94 (t, J = 7.2 Hz, 1 H), 6.98 (d, J = 7.2 Hz, 1 H), 7.04 (d, J = 8.0 Hz, 1 H), 7.09 (t, J = 7.2 Hz, 1 H), 7.14 (d, J = 7.2 Hz, 1 H), 7.31 (d, J = 7.2 Hz, 1 H), 7.51 (m, 3 H), 7.75 (s, 1 H), 7.86 (d, J = 8.0 Hz, 1 H), 7.93 (m, 2 H). ^{13}C NMR (DMSO-d_6) δ 36.8, 97.7, 116.0, 117.3, 117.4, 117.5, 123.1, 124.1, 124.4, 126.1, 126.4, 126.6, 126.9, 127.3, 127.8, 128.2, 129.2, 130.9, 131.9, 134.0, 135.1, 140.3, 143.5, 145.1. Anal. Calcd for $C_{24}H_{16}N_2S$: C, 79.09; H, 4.42; N, 7.69; S, 8.80. Found: C, 79.15; H, 4.48; N, 7.70; S, 8.93.

2-[(Thiophen-2-yl)methyl]-10-*H*-phenothiazine-1-carbonitrile (3d): yellow crystals, mp , 168-170 ºC (EtOAc), yield 58%. IR (KBr) ν_{max} 3333, 2222, 1460, 1435, 738, 694.^{1}H NMR (acetone-d_6) δ 4.23 (s, 2 H), 6.87 (d, J = 8.0 Hz, 1 H), 6.97 (m, 4 H), 7.09 (m, 2 H), 7.70 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ 34.2, 97.2, 115.7, 117.3, 117.4, 117.9, 123.0, 124.1, 125.4, 126.4, 126.6, 127.5,

128.3, 131.1, 140.2, 141.9, 143.6, 145.1. Anal. Calcd for $C_{18}H_{12}N_2S_2$: C, 67.47; H, 3.77; N, 8.74; S, 20.01. Found: C, 67.52; H, 3.70; N, 8.80; S, 20.20.

2-([3,4-Dimethoxyphenyl]methyl)-10-*H*-phenothiazine-1-carbonitrile (3e): light brown crystals, mp 125-126 °C (EtOAc), yield 42 %. IR (KBr) ν_{max} 3323, 2223, 1514, 1460, 1435, 1256, 1239, 1036, 768.^{1}H NMR (acetone-d_6) δ 3.76 (s, 6H), 3.97 (s, 2 H), 6.75-6.79 (m, 2 H), 6.96-6.99 (m, 1 H), 7.06-7.12 (m, 3H). 6.86 (d, J = 8.0 Hz, 1 H), 6.89-6.90 (m, 2 H), ^{13}C NMR (DMSO-d_6) δ 38.9, 55.9, 56.0, 97.3, 112.5, 1133.3, 116.1, 117.2, 117.3, 131.1, 123.1, 124.0, 126.6, 128.2, 131.0, 140.3, 114.7, 145.0, 148.0, 149.2. Anal. Calcd for $C_{22}H_{18}N_2O_2S$: C, 70.57; H, 4.85; N, 7.48; S, 8.56. Found: C, 70.44; H, 4.97; N, 7.39; S, 8.60.

2-(2,2,6,6-Tetramethylpiperidin-1yl)-10*H*-phenothiazine (4): colorless oil, yield 15%. ^{1}H NMR (acetone-d_6) δ 1.02 (s, 12 H), 1.53 (t, J = 6.4 Hz, 4 H), 1.69 (m, 2 H), 6.68 (m, 3 H), 6.78 (t, J = 8.4 Hz, 4 H), 6.84 (d, J= 8.4 Hz, 1 H), 6.94 (m, 2 H), 7.73 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ 18.1, 29.0, 42.1, 53.8, 114.5, 114.5, 117.7, 120.2,121.9, 125.1, 126.3, 127.4, 127.9, 141.8, 142.6, 146.2. MS *m/z*/338 (M), 325 (base) 198. Anal. Calcd for $C_{21}H_{26}N_2S$: C, 76.58; H, 7.74; N, 8.28; S, 9.47. Found: C, 76.60; H, 7.84; N, 8.35; S, 9.56.

13-Amino-14*H*-naphtho[2,3-*a*]-10*H*-phenothiazine-8-carbonitrile (6): brown solid, mp 244-246 °C (EtOAc), yield 22 %. IR (KBr) ν_{max} 3453, 3356, 2193, 1621, 1573, 1504, 1409; ^{1}H NMR (acetone-d_6) δ 6.44 (s, 2 H), 7.37 (t, J = 8.0 Hz, 1 H), 7.64 (m, 4 H), 7.71 (d, J = 8.0 Hz, 1 H), 7.81 (t, J = 8.0 Hz, 1 H), 8.42 (d, J = 8.0 Hz, 1 H), 8.92 (d, J = 8.0 Hz, 1 H), 9.05 (d, J = 8.0 Hz, 1 H). Anal. Calcd for $C_{14}H_{14}N_2S$: C, 69.39; H, 5.82; N, 11.56; S, 13.24; Found: C, 69.45; H, 5.97: N, 11.67; S, 13.37.

X-Ray Single Crystal Analysis of 3a. All data were collected on a Nicolet R3m/V diffractometer using the q-2q scan technique, Mo-Kα radiation $(\lambda = 0.71073\text{Å})$, scan speed 3.0-15 deg min^{-1}, scan range 3.5-44.0^0 and a graphite monochromator. Data were corrected for Lorentz, absorption, and polarization effects. The structures were solved by direct methods using SHELXS-86,[17] and the model was refined by using full-matrix least-squares techniques. Pertinent data are given in the Table 1.

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Table 1 X-Ray data collection and processing parameters for **3a**

formula	$C_{20}H_{14}N_2O$	T (K)	228
crystal dmns, cm^{-3}	0.35 X 0.25 X 0.15	decay, %	2.86
Space group	$P2_1/n$	Data collected	1358
a (Å)	16.018(7)	Unique Reflections	1055
b (Å)	4.516(2)	R_{int}	0.047
c (Å)	20.994(8)	Parameters	289
β (°)	110.11(1)	R, R_W	0.071, 0.096
V ($Å^3$)	1495.1(11)	$(\Delta\sigma)_{max}$	<0.01
Z-value	4	abs coeff, mm^{-1}	0.40; -.0.61
D calc (g-cm^3)	1.437	GOF	1.93

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