REACTION OF CHLORO DERIVATIVES OF 10-BENZYL- AND 10-(4'-FLUOROBENZYL)PHENOTHIAZINES WITH NITRILES AND AMINES UNDER ARYNE-FORMING CONDITIONS

Jennifer L. Self, Subhash P. Khanapure, and Edward R. Biehl*

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

Abstract 2-Chloro-10-benzylphenothiazine (**1**) and 2-chloro-10-(4'-fluorobenzyl)phenothiazine (**2**) react with aliphatic nitriles (**3** and **4**) and LDA to yield typical 2-substituted aryne products (**9a,b** and **9g,h**, respectively). However, treatment of **1** with aromatic nitriles (**5-8**) and LDA supplies 2-(arylmethyl)-1-cyano rearranged nitriles (**10c-f**), whereas **2**, when treated similarly, affords both rearranged nitriles (**10i-l**) and typical 2-arylated nitrile products (**9i-j**). An explanation in terms of the effect of substitutents on the competing aryne and tandem addition-rearrangement pathways is presented. The crystal structure of one of the rearranged 1-cyanophenothiazines (**10c**) was obtained and reveals that the molecule adopts the "extra" conformation in which the 10-benzyl group is in the *psuedo axial* position. The reaction of **1** and **2** with various lithium amides in the corresponding free amine solvents gives the corresponding 2-aminated products (**11**) and (**12**) in excellent yields. Both 1-chloro-10-benzylphenothiazine (**18**) and **1** supply the same product, 10-benzyl-2-N,N-diisopropylaminophenothiazine (**11a**), when made to react with LDA in diisopropylamine solvent, indicating that each of these reactions proceeds *via* the same aryne intermediate, and not through the $S_{RN}1$ mechanism.

INTRODUCTION

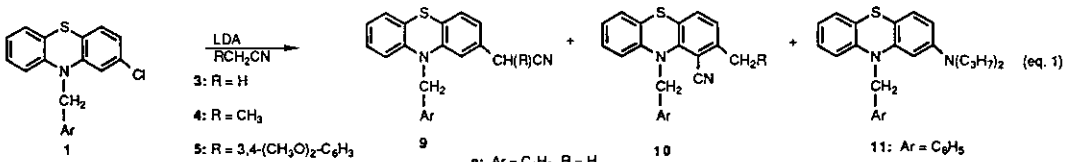
We[1,2] showed previously that certain 2-halophenothiazines react with α–lithiated nitriles under LDA-mediated aryne-forming conditions to yield α–arylated nitriles and / or rearranged ortho-(arylmethyl)cyanophenothiazines. These nitrile products are presumed to arise by the usual aryne[3] and / or [2+2] non-concerted tandem addition-rearrangement[4] mechanisms, respectively. The extent to which these mechanisms compete with each other is very dependent upon the nature of the nitrile and haloarene.[5] For example, both 2-chloro-10-methylphenothiazine[1] and 7-bromo-2-(trifluoromethyl)-10-methyphenothiazine[2] react with aliphatic nitriles and LDA to yield typical α–arylated nitrile products. In contrast, the former phenothiazine reacts with arylacetonitriles and LDA to supply only rearranged nitrile products, whereas the latter, when treated similarly, affords both α–arylated nitrile and rearranged nitrile products in a ratio of 4:1, respectively. N, N-Diisopro-

pylaminophenothiazines are also obtained, occasionally as major products, in LDA-mediated halophenothiazine aryne reactions, in spite of the steric bulk of the LDA. By treating certain halophenothiazines with lithium amides in the corresponding amine solvent in the absence of nitriles, aminated phenothiazines can be obtained in excellent yields even using sterically-hindered amide / amine systems such as LDA / diisopropylamine and di-*sec*-butylamide / di-*sec*-butylamine.[2]

To gain more insight into the influence of substitutents on the competition between the aryne and tandem addition-rearrangement aryne (TARA) pathways, the reaction of 10-benzyl-2-chloro- (**1**) and 2-chloro-10-(4'-fluorobenzyl)phenothiazines (**2**) with various alkyl- (**3**,**4**) and arylacetonitriles (**5-8**) and LDA was investigated. Additionally, the use of alkyl amide / alkylamine systems for the synthesis of amino derivatives of **1** and **2** was explored.

Results and Discussion

The products formed from the reaction of the chlorophenothiazines (**1** and **2**) with nitriles (**3-8**) and LDA are depicted in eq. 1. Thus, the reaction of **1** and **2** with the aliphatic nitriles (**3** and **4**) gave typical α-arylated



a: Ar = C_6H_5, R = H
b: Ar = C_6H_5, R = CH_3
c: Ar = C_6H_5, R = 3,4-$(CH_3O)_2$-C_6H_3
d: Ar = C_6H_5, R = 3-CH_3O-C_6H_4
e: Ar = C_6H_5, R = 3,4,5-$(CH_3O)_3$-C_6H_2
f: Ar = C_6H_5, R = 3-CF_3-C_6H_4
g: Ar = 4-F-C_6H_4, R = H
h: Ar = 4-F-C_6H_4, R = CH_3
i: Ar = 4-F-C_6H_4, R = 3,4-$(CH_3O)_2$-C_6H_3
j: Ar = 4-F-C_6H_4, R = 3-CH_3O-C_6H_4
k: Ar = 4-F-C_6H_4, R = 3,4,5-$(CH_3O)_3$-C_6H_2
l: Ar = 4-F-C_6H_4, R = 3-CF_3-C_6H_4

nitrile products. For example, treatment of acetonitrile (**3**) and propionitrile (**4**) with **1** and LDA afforded 10-benzyl-2-(cyanomethyl)phenothiazine (**9a**) (49%) and 10-benzyl-2-(α-cyanoethyl)phenothiazine (**9b**) (63%), respectively. Similarly, the reaction of these nitriles with **2** supplied 2-(cyanomethyl)-10-(4'-fluorobenzyl)-phenothiazine (**9g**) (39%) and 2-(α-cyanoethyl)10-(4'-fluorobenzyl)phenothiazine (**9h**) (48%). Smaller amounts of 10-benzyl-2-(N,N-diisopropylamino)phenothiazine (**11a**) (10-20%) and 10-(fluorobenzyl)-2-(N,N-diisopropylamino)phenothiazine (**12a**) (12-25%) were obtained from the reaction of **1** and **2**, respectively. The reaction of **1** and **2** with arylacetonitriles (**5-8**) and LDA gave mixed results. For example, the 10-benzyl derivative (**1**) underwent reaction with **5-8** and LDA to yield rearranged 2-aryl-10-benzyl-1-cyanophenothiazines (**10c** [18%],**10d** [20%], **10e** [13%] and **10f** [22%]), whereas the 4'-fluorobenzyl

derivative (2) afforded both rearranged (**10i** [12%], **10j** [15%], **10k** [8%], and **10l** [14%]) and typical aryne substitution nitrile products (**9i** [>10%], **9j** [>10%], **9k** [<5%], and **9l** [23%]). The major product in each of these arylacetonitrile reactions with **1** and **2** was N,N-diisopropylamino derivative of **11** (*ca.* 30-35%) and **12** (*ca.* 35-40%), respectively.

The structures of the rearranged nitriles (**10c-f, i-l**) and unrearranged α-arylated nitriles (**9i-l**) were ascertained by nmr, ir and ms analyses. In addition, the structure of **10c** was confirmed by single crystal x-ray crystallographic analysis.[6] The ORTEP[7] drawing of **10c**, shown in the Figure, reveals that the methylene

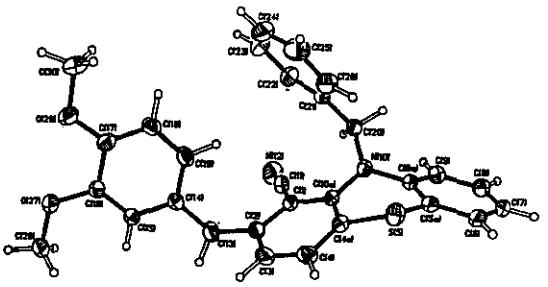
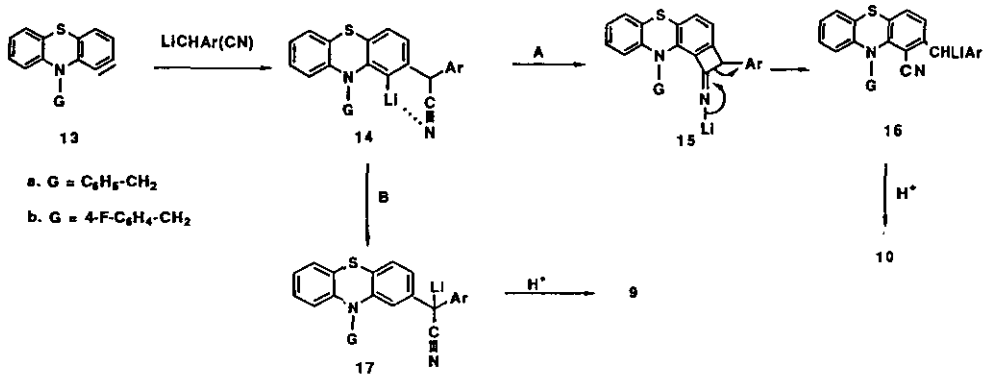


Figure. ORTEP of Molecule **10c**

carbon of the 10-benzyl group lies in the plane encompassing the N_{10}, C_{9a}, and C_{10a} atoms. The sum of the bond angles about N_{10} is approximately 360° indicating that the hybridization of that nitrogen atom is sp^2. That **10c** adopts the "extra" *(quasi-axial)* conformation rather than the more commonly observed "intra" *(quasi-equatorial)* conformation in 10-substituted phenothiazines could reflect a peri effect by the 1-cyano group similar to that exhibited by the 1-chloro group in 1-chloropromazine.[8] However, since 10-benzyl-phenothiazine also exists in the less common "extra" conformation,[9] it is problematical whether the 1-cyano group by itself could alter the conformation of the middle phenothiazine ring of **10c**.

An explanation for the change in the nitrile product distribution from exclusive rearranged products to mixtures of rearranged and unrearranged nitrile products caused by the incorporation of a 4'-fluoro group into the 10-benzyl ring is given in the Scheme. As shown, the first step in each mechanism involves the initial addition of

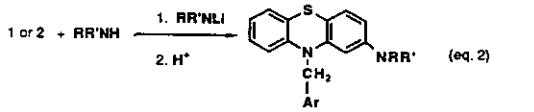


Scheme

the α–lithiated nitrile and aryne (**13**) to form adduct (**14**) which is partitioned between the rearrangement pathway (**A**) and the usual aryne pathway (**B**). The extent to which each of these pathways participates in the reaction depends on the relative rates of the cyclization step of **14** to the benzocyclobutanimine (**15**) in **A** and on the lithium-proton exchange of **14** to α–lithio species (**17**) in **B**. Apparently the electron-density (and hence nucleophilicity) at the 1-lithio site in those adducts containing the 10-benzyl group (**14a**) is sufficiently high to allow the cyclization step to **15a** in pathway **A** to win out completely over lithium proton exchange to **17** in pathway **B**. However, the incorporation of the electronegative 4'-fluorine atom in **14b** apparently reduces the electron-density at the 1-lithio site to such an extent that the usual aryne pathway (**B**) predominates over the rearrangement pathway. That the 4'-flourine atom is able to alter the outcome of the TARA-aryne pathway competition even though it is somewhat remote from the cyclization site is but another example of the subtlety of substituent effects in LDA-mediated aryne reactions.[5]

Previously, we have suggested that aliphatic nitriles are dilithiated under the reaction conditions used in the LDA-mediated aryne reactions, and, as such, form adducts with arynes in which the crucial cyclization step in rearrangement pathway is precluded by the electronic and steric constraints present in the adduct.[2]

Recently, Martin et al.[8] suggested that the apparent regioselective aminations of 3-chloro-10-methylphenothiazine and 2-chlorophenothiazines under the usual aryne-forming conditions do not involve the aryne intermediates but rather proceed via an $S_{RN}1$ mechanism.[10] To determine if the above amines (**14**) were in fact produced by an $S_{RN}1$ mechanism, 10-benzyl-2-chlorophenothiazine (**1**) and 1-chloro-10-benzylphenothiazine (**18**) were treated with LDA in diisopropylamine. Each of these reactions gave the same amine, 10-benzyl-2-(N,N-diisopropylamino)phenothiazine (**11a**) in excellent yields (92%), indicating that both proceed through the same aryne intermediate (**13a**), and not through an $S_{RN}1$ pathway. Additionally, **1** and **2** were treated with various alkali amides in the corresponding free amine solvent and were found to give the corresponding 2-amino derivatives (**11b** [95%], **11c** [96%], and **11d** [90%]) and (**12a** [94%] and **12b** [93%]), respectively (eq. 2). Nmr analysis of the crude reaction mixture revealed the absence of any 1-amino isomer, indicating that these aminations were completely regioselective.



11: Ar = C_6H_5 a, R = R' = iso-C_3H_7 **12**: Ar = 4-F-C_6H_4
b, R = R' = C_2H_5
c, R = R' = sec-C_4H_9
d, R = t-C_4H_9, R' = H

EXPERIMENTAL

All reagents were purchased from Aldrich Chemical Company. The amines were dried over calcium hydride and distilled prior to use; *n*-butyllithium was used as received. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. Ir spectra were recorded on a Perkin-Elmer 283 grating spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded on an IBM-Bruker WP 200-SY spectrometer and

chemical shifts were related to tetramethylsilane as an internal standard. High resolution mass spectral analyses were performed by the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility (Grant No. CHE 8211164).

Preparation of 10-Benzyl-2-chlorophenothiazine (1): In a 500 ml flask 5.28 g (0.11 mol) sample of sodium hydride (50% dispersion in mineral oil) was first washed with dry hexane. Then 100 ml of THF was added, the resulting suspension was cooled to 0-5 °C, and a solution of 2-chlorophenothiazine (22.7 g, 0.1 mol) in THF (100 ml) was added dropwise, while stirring. The reaction mixture was stirred for 1 h and then benzyl bromide (14.27 ml, 0.12 mol) was added dropwise between 5-10 °C and the stirring was continued for an additional 1 h, during which the solution changed in color from red to gray. Methanol (20 ml) was then added to quench any unreacted sodium hydride and excess benzyl bromide, the solvent was removed in vacuo (rotatory evaporator), and the residue was dissolved in methylene chloride (125 ml). The resulting solution was washed with water (3 X 50 ml), dried (Na_2SO_4) and evaporated to yield a brown residue. Distillation of the brown residue in a Kugelrohr apparatus (200-205 °C, 0.250 Torr) afforded a thick yellowish liquid (26.3 g, 83%) which was crystallized to give colorless crystals; mp 90-92 °C (hexane). ^{1}H nmr ($CDCl_3$) δ 5.07 (s, 2H), 6.68 (m, 2H), 6.87-7.08 (m, 5H), 7.37 (m, 5H); ir ($CHCl_3$) ν_{max} 1593, 1522, 1464 cm^{-1}; ms m/z 323 (M^+), 325 (M^++2). *Anal.* Calcd for $C_{19}H_{14}NClS$: C, 70.47; H, 4.36; N, 4.33. Found: C, 70.55; H, 4.45; N, 4.35.

Preparation of 2-Chloro-10-(4'-fluorobenzyl)phenothiazine (2): Using similar procedure as described above for the preparation of **1**, **2** was obtained as a colorless powder in 87 % yield; mp 83-85 °C (hexane); ^{1}H nmr ($CDCl_3$) δ 5.03 (s, 2 H), 6.87-7.28 (m, 11 H); ir ($CHCl_3$) ν_{max} 1594, 1567, 1508, 1464, 1409, 1215 cm^{-1}. *Anal.* Calcd for $C_{19}H_{13}NClFS$: C, 66.76; H 3.83; N 4.10. Found: C, 66.86; H, 3.92; N, 4.08.

Preparation of 10-Benzyl-1-chlorophenothiazine (18): 1-Chlorophenothiazine was first prepared by literature procedure,[11] then converted to **18** in a similar manner as that described above for **1**: mp 85-87°C (hexane). Anal. Calcd for $C_{19}H_{14}NClS$: C, 70.47; H, 4.36; N, 4.33. Found: C, 70.55; H, 4.45; N, 4.35.

General Procedure for the Reaction of 1 and 2 with Various Nitriles Under Aryne-Forming Conditions. In a flame-dried flask flushed with nitrogen, LDA (45 mmol) was prepared by adding diisopropylamine (45 mmol) into a cold solution (-70 °C) of *n*-butyllithium (30 mmol, 2.5 M in hexane) in THF (75 ml). Then the appropriate nitrile (15 mmol) in THF (50 ml) was added dropwise over 20 min and the reaction mixture was allowed to warm to -40 °C at which point a solution of **1** or **2**. (15 mmol) in THF (50 ml) was added dropwise. The solution was allowed to warm to room temperature slowly over a period of 2 h, then the resulting dark reddish solution was quenched with absolute ethanol, the solvent was evaporated under reduced pressure, and the residue was extracted with methylene chloride (2 X 50 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated (rotary evaporator) to provide an oil which was purified by flash column chromatography (silica gel) using hexane:acetone (19:1) as the eluent. The characterization of those products which could be obtained in pure state are given below.

10-Benzyl-2-(cyanomethyl)phenothiazine (9a): Colorless thick oil; ^{1}H nmr ($CDCl_3$) δ 3.71 (s, 2H), 5.11 (s, 2 H), 6.59 (d, J = 1.7 Hz, 1 H) ; 6.77 (d, J = 7.0 Hz, 1 H), 6.93-7.40 (m, 10H); ir ($CHCl_3$) ν_{max}

2245 (CN), 1521, 1470 cm^{-1}; ms, m/z 328 (M^+), 237 (M^+-$CH_2C_6H_5$) *Anal.* Calcd for $C_{21}H_{16}N_2S$: C, 76.80 H, 4.91 N, 8.53. Found: C, 76.98; H, 4.76; N, 8.42.

10-Benzyl-2-(α-cyanoethyl)phenothiazine (9b): Colorless thick oil; ^1H nmr ($CDCl_3$) δ 1.43 (d, *J* = 7.2 Hz, 3 H), 3.67 (q, *J* = 7.2 Hz, 1 H), 5.11 (s, 2 H), 6.59 (d, *J* = 1.7 Hz, 1 H) ; 6.77 (d, *J* = 7.0 Hz, 1 H), 6.93-7.40 (m, 10H); ir ($CHCl_3$) ν_{max} 2245 (CN), 1521, 1470 cm^{-1}; ms, m/z 363 (M^+), 251 (M^+-$CH_2C_6H_5$) *Anal.* Calcd for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30 N, 8.18. Found: C, 76.98; H, 5.30; N, 8.22.

10-Benzyl-1-cyano-2-(3',4'-dimethoxybenzyl)phenothiazine (10c): Colorless crystals (EtOAc); mp 137-139 °C ; ^1H nmr ($CDCl_3$) δ 3.84 (s, 3 H), 3.87 (s, 3 H), 4.05 (s, 2 H), 5.4 (s, 2 H), 6.55-7.52 (m, 14 H); ir ($CHCl_3$) ν_{max} 2219 (CN), 1590, 1516 cm^{-1}; ^{13}C nmr ($CDCl_3$) δ 39.54, 55.80, 57.00, 104.30, 111.46, 112.35, 117.26, 120.87, 124.07, 126.87, 127.35, 127.91, 128.23, 129.80, 130.69, 131.22, 136.43, 144.83, 145.13, 147.81, 148.61, 149.03. *Anal.* Calcd for $C_{29}H_{24}N_2O_2S$: C, 77.39; H, 5.10; N, 6.44. Found: C, 77.45; H, 5.15; N, 6.41.

10-Benzyl-1-cyano-2-(3'-methoxybenzyl)phenothiazine (10d): Thick oil; ^1H nmr ($CDCl_3$) δ 3.79 (s, 3 H), 4.09 (s, 2 H), 5.42 (s, 2 H), 6.70-7.35 (m, 15H); ir ($CHCl_3$) ν_{max} 2220 (CN), 1598, 1520, 1451. *Anal.* Calcd for $C_{28}H_{22}N_2OS$: C, 74.64; H 4.92; N 6.21. Found: C, 74.77; H, 4.99; N, 6.24.

10-Benzyl-1-cyano-2-(3',4',5'-trimethoxybenzyl)phenothiazine (10e): Colorless crystals (EtOAc); mp 160-162 °C; ^1H nmr ($CDCl_3$) δ 3.81 (s, 6 H), 3.83 (s, 3 H), 4.15 (s, 2 H), 5.44 (s, 2 H), 6.40 (s, 2 H) 6.80-7.45 (m, 11 H); ir ($CHCl_3$) ν_{max} 2220 (CN), 1592, 1519 cm^{-1}. *Anal.* Calcd for $C_{30}H_{26}N_2O_3S$: C, 72.85 ; H, 5.30; N, 5.66. Found: C, 72.80; H, 5.33; N, 5.67.

10-Benzyl-1-cyano-2-(3'-trifluorobenzyl)phenothiazine (10f): Colorless needles (hexane); mp 115-117 °C; ^1H nmr ($CDCl_3$) δ 4.15 (s, 2 H), 5.41 (s, 2 H), 6.77-7.53 (m, 14 H); ir ($CHCl_3$) ν_{max} 2220, (CN), 1521, 1470 cm^{-1}. Anal. Calcd for $C_{29}H_{19}N_2F_3S$: C, 76.75; H, 4.53; N, 6.63. Found: C, 76.83; H, 4.60; N, 6.69.

2-(Cyanomethyl)-10-(4'-fluorobenzyl)phenothiazine (9g): Colorless thick oil; ^1H nmr ($CDCl_3$) δ 3.73 (s, 2H), 5.07 (s, 2 H), 6.66 -7.40 (m, 11 H); ir ($CHCl_3$) ν_{max} 2240 (CN), 1523, 1470 cm^{-1}. *Anal.* Calcd for $C_{21}H_{16}N_2FS$: C, 76.80 H, 4.91; N, 8.53. Found: C, 76.79; H, 5.10; N, 8.77.

2-(α-Cyanoethyl)-10-(4'-fluorobenzyl)phenothiazine (9h): Colorless thick oil; ^1H nmr ($CDCl_3$) δ 1.46 (d, *J* = 7.2 Hz, 3 H), 3.68 (q, *J* = 7.2 Hz, 1 H), 5.07 (s, 2 H), 6.66 -7.40 (m, 11 H); ir ($CHCl_3$) ν_{max} 2240 (CN), 1523, 1470 cm^{-1}. *Anal.* Calcd for $C_{22}H_{18}N_2FS$: C, 73.10; H, 5.02; N, 7.75. Found: C, 73.19; H, 5.10; N, 7.87.

Compounds 9i, 9j, 9k: These compounds could not be obtained in pure state; their presence was inferred by the characteristic methylene CH δ 4.80–4.90.

2-α-Cyano-α-3'-([trifluoromethyl]phenyl)methyl-10-(4'-fluorobenzyl)phenothiazine (9l): Thick oil; ^1H nmr ($CDCl_3$) δ 4.87 (s, 1 H), 5.01 (s, 2 H), 6.65-7.25 (m, 14 H); ir ($CHCl_3$) ν_{max} 2240, (CN), 1591, 1523 cm^{-1}. *Anal.* Calcd for $C_{28}H_{18}N_2F_4S$: C, 68.56; H, 3.70; N, 5.71. Found: C, 68.71; H, 3.77; N, 5.70.

1-Cyano-10-(4'-fluorobenzyl)-2-(3',4'-dimethoxybenzyl)phenothiazine (10i): Colorless crystals (EtOAc): mp 137-139 °C; ^1H nmr ($CDCl_3$) δ 3.85 (s, 3 H), 3.87 (s, 3 H), 4.03 (s, 2 H), 5.36 (s, 2

H), 6.62 (d, J = 1.7 Hz, 1 H), 6.75 (dd, J = 10.0 and 1.7 Hz, 1 H), 7.02-7.27 (m, 10H); ir ($CHCl_3$) ν_{max} 2219 (CN), 1595, 1517 cm^{-1}. *Anal.* Calcd for $C_{29}H_{23}N_2O_2FS$: C, 72.18 ; H, 4.80; N, 5.81. Found: C, 72.25; H, 4.90; N, 5.89.

1-Cyano-10-(4'-fluorobenzyl)-2-(3'-methoxybenzyl)phenothiazine (10j): Thick oil; ^1H nmr ($CDCl_3$) δ 3.79 (s, 3 H), 4.08 (s, 2 H), 5.36 (s, 2 H), 6.70-7.43 (m, 14 H); ir ($CHCl_3$) ν_{max} 2220 (CN), 1600, 1522, 1453, 1423 cm^{-1}. *Anal.* Calcd for $C_{28}H_{21}N_2OFS$: C, 74.23; H 4.78; N 6.18. Found: C, 74.33; H, 4.88; N, 6.29.

1-Cyano-10-(4'-fluorobenzyl)-2-(3',4',5'-trimethoxybenzyl)phenothiazine (10k): Colorless crystals (EtOAc); mp 113-115 °C; ^1H nmr ($CDCl_3$) δ 3.81 (s, 6 H), 3.83 (s, 3 H), 4.03 (s, 2 H), 5.35 (s, 2 H), 6.41 (s, 2H) 6.81-7.27 (m, 10H) ; ir ($CHCl_3$) ν_{max} 2220 (CN), 1590 cm^{-1}. *Anal.* Calcd for $C_{30}H_{25}N_2O_3FS$: C, 70.29; H, 4.92; N, 5.46. Found: C, 70.22; H, 5.01; N, 5.50.

1-Cyano-10-(4'-fluorobenzyl)-2-(3'-[(trifluoromethyl)benzyl]phenothiazine (10l): Colorless needles (hexane); mp 113-115 °C; ^1H nmr ($CDCl_3$) δ 4.14 (s, 2H), 5.32 (s, 2H), 6.85-7.45 (m, 14H); ir ($CHCl_3$) ν_{max} 2220, (CN), 1598, 1521, 1470 cm^{-1}. *Anal.* Calcd for $C_{28}H_{18}N_2F_4S$: C, 68.56; H, 3.70; N, 5.71. Found: C, 68.70 ; H, 3.80; N, 5.80.

General Procedure for the Reaction of 1,2, and 18 with Lithium Amides in Amine Solvents. To a cooled (-50 °C) solution of the amine (50 ml) contained in a 250 ml round-bottom flask equipped with balloon filled with dry nitrogen was added butyllithium (30 mmol, 12 ml of 2.5 M solution in hexane) dropwise. After the solution was stirred for 10 min, **1** or **2** (30 mmol) in THF (40 ml) was added, and the solution was allowed to warm to room temperature, during which time the solution developed a deep red color. The solution was stirred overnight, and then was quenched with a 2 ml of ethanol, and the quenched solution was worked-up in the same manner as that described for the reaction of **1** and **2** with nitriles.

10-Benzyl-2-N,N-diisopropylaminophenothiazine (11a): Colorless needles (hexane); mp 85-87 °C; ^1H nmr ($CDCl_3$) δ 0.99 (d, J = 6.7 Hz, 12H), 3.53 (m, septet, J = 6.7 Hz, 2H), 5.11 (s, 2H), 6.23 (d, J = 2.2 Hz, 1H), 6.45 (dd, J = 8.0 and 2.2 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.85-7.34 (m, 9H). *Anal.* Calcd for $C_{25}H_{28}N_2S$: C, 77.28; H, 7.26; N, 7.21. Found: C, 77.34; H, 7.34; N, 7.30.

10-Benzyl-2-N,N-diethylaminophenothiazine (11b): Thick oil; ^1H nmr ($CDCl_3$) δ 0.94 (t, J = 7.0 Hz, 6H), 3.13 (q, J = 7.0 Hz, 4 H), 5.14 (s, 2H), 6.05 (d, J = 2.4 Hz, 1H), 6.27 (dd, J = 8.5 and 2.4 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 6.87-7.16 (m, 4H), 7.38 (m, 5H). *Anal.* Calcd for $C_{23}H_{23}N_2S$: C, 76.84; H, 6.49; N, 7.79. Found: C, 76.90; H, 6.59; N, 7.84.

10-Benzyl-2-N, N-di-*sec*-butylaminophenothiazine (11c): Colorless needles (hexane); mp 78-80 °C; ^1H nmr ($CDCl_3$) δ 0.79-1.70 (m, 16H), 2.73 (m, 2H), 3.36 (s, 3H), 6.80-7.30 (m, 6H). *Anal.* Calcd for $C_{27}H_{32}N_2S$: C, 77.83; H, 7.74; N, 6.72. Found: C, 77.66; H, 7.64; N, 6.82.

10-Benzyl-2-N-*t*-butylaminophenothiazine (11d): Colorless crystals (hexane); mp 130-132 °C; ^1H nmr ($CDCl_3$) δ 1.15 (s, 9H), 3.25 (br s, 1H), 5.14 (s, 2H), 6.19 (d, J = 1.6 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.90-7.02 (m, 3H), 7.14 (d, J = 7.8 Hz, 1H), 7.38 (m, 5H). *Anal.* Calcd for $C_{23}H_{23}N_2S$: C, 77.83; H, 7.74; N, 6.72. Found: C, 76.91; H, 6.70; N, 7.80.

10-(4'-Fluorobenzyl)-2-N,N-diisopropylaminophenothiazine (12a): Thick oil; ^1H nmr ($CDCl_3$) δ 1.02 (d, J = 6.5 Hz, 12H), 3.53 (m, septet, J = 6.5 Hz, 2H), 5.09 (s, 2H), 6.67 (d, J = 1.2 Hz, 1H), 6.93

(dd, J = 8.4 and 2.0 Hz, 1H), 7.01 (t, J = 4.9 Hz, 1H), 7.08-7.32 (m, 8H). *Anal.* Calcd for $C_{25}H_{27}N_2SF$: C, 77.83; H, 7.74; N, 6.72. Found: C, 77.66; H, 7.64; N, 6.82.

2-N,N-Diethylamino-10-(4'-fluorobenzyl)phenothiazine (12b): Thick oil; ^1H nmr ($CDCl_3$) δ 0.95 (t, J =7.0 Hz, 6H), 3.14 (q, J = 7.0 Hz, 4H), 5.11 (s, 2H), 6.68 (d, J = 1.2 Hz, 1H), 6.97 (dd, J = 8.4 and 2.0 Hz, 1H), 7.03 (d, J = 3.9 Hz,1 H), 7.05-7.34 (m, H). *Anal.* Calcd for $C_{23}H_{22}N_2FS$: C, 73.18 H, 5.87 N, 7.42. Found: C, 73.30; H, 5.84; N, 7.46.

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