A NOVEL SYNTHETIC ROUTE TO CYANOPHENOTHIAZINES.
FIRST EXAMPLE OF SMILES REARRANGEMENT FROM HALOGENOBENZONITRILES

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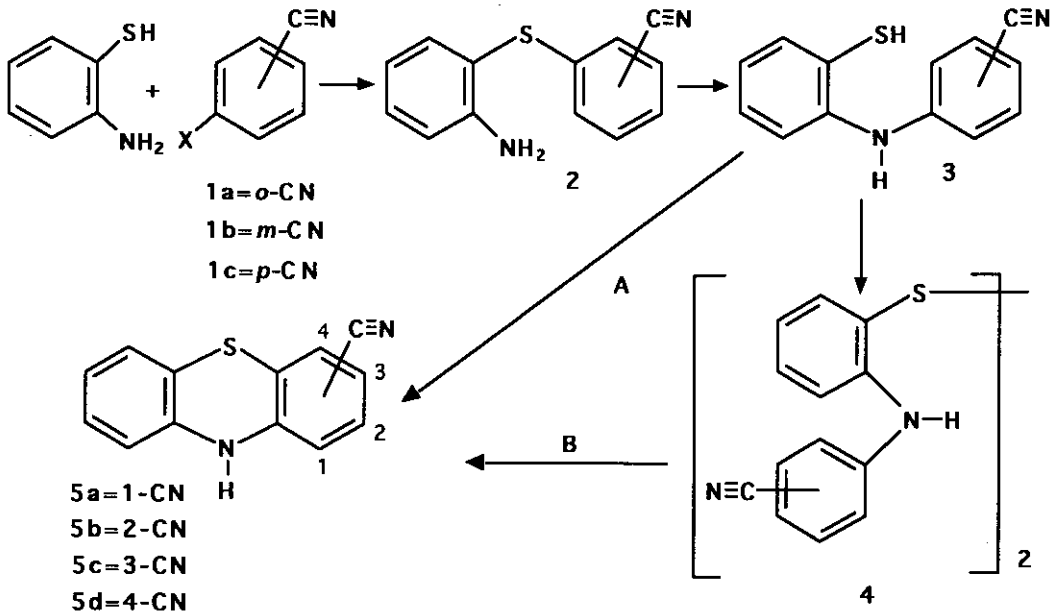
Abstract - The reaction of halogenobenzonitriles with 2- aminobenzenethiol gave, by a Smiles rearrangement 2-mercaptocyanodiphenylamines which are cyclised to cyanophenothiazines *via* a disulfide intermediate. A mechanism is proposed.

Cyanophenothiazines are useful intermediates[1] for the synthesis of a wide range of psychotics, antihistaminics, analgesics, antihypertensives, neoplasm inhibitors. The 2- and 3-cyanophenothiazines have been known for a long time,[2,3] whereas 1-cyanoisomer was recently[4] obtained in 34 % yield. The 4-cyanophenothiazine was not known. We have studied a new route to these derivatives by condensing 2-aminobenzenethiol (AT) with halogenobenzonitriles. These compounds exhibit some electronic analogy with halogenonitrobenzenes and we report a new example of Smiles rearrangement where cyano replaces nitro as the activating group.
Initially, we condensed AT with *o*-chlorobenzonitrile in the presence of NaH and DMF as solvent and warming to 100°C during 2 h. The analysis of the reaction products showed four compounds (**2a**, **3a**, **4a** and **5a**). The influence of the concentration of NaH was tested (Table I).

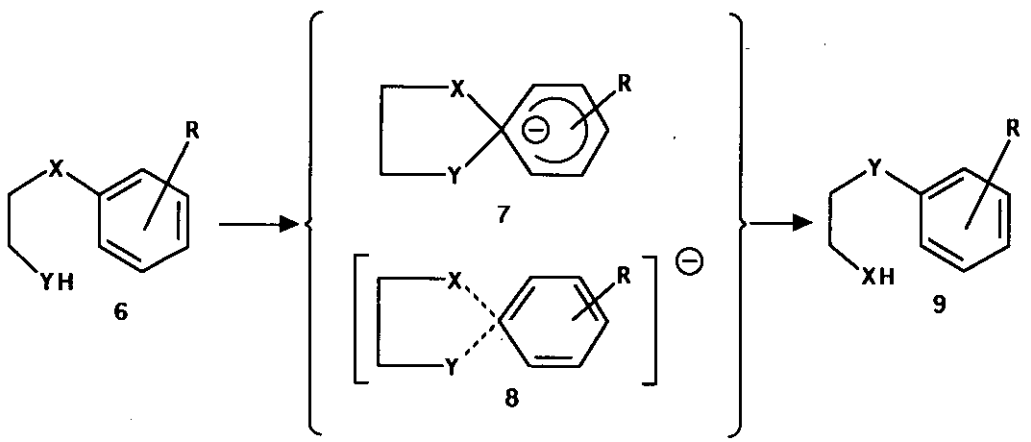
TABLE I

NaH	**2a**	**3a + 4a**	**5a**
1 mol	90	0	0
2 mol	46	5	1
3 mol	18	12	5
4 mol	0	20	10



Scheme 1

Compound (**2a**) was isolated in very good yield with 1 mol of NaH, and yields decreased progressively with high concentrations. In contrast, the yields of compounds (**5a** and **3a+4a**) increased. Evidently, the product (**3**) is issued from a Smiles rearrangement. This reaction[5,6] is an intramolecular displacement involving an activated nucleophilic aromatic substitution :



The group R is an electron-attracting substituent; the most common activating group is nitro, with or without other substituents. To our knowledge the cyano group has not been tested. The reaction occurred *via* unsymmetrical spiro Meisenheimer complex (**7**) either *via* a transition state (**8**).[5,7] Compound (**3a**) appeared to us, as the first example of the Smiles rearrangement with a nitrile substituent.

We investigated the ability of compounds (**2 a-c**) to undergo the Smiles rearrangement.

By heating at 110°C with two molar equivalents of NaH in DMF, we obtained the diphenylamines (**3 a-c**) in good yields (75-85 %). The explanation of the formation of compounds (**3a** and **3c**) by a Meisenheimer complex (**7**) is resonable, but for **3b** a transition state such as **8** is necessary. For these experimental conditions the C ≡ N is an efficient activating group in the Smiles rearrangement in each position ortho, meta, or para. The compound (**4a**) resulted from spontaneous oxidation of the thiol (**3a**).

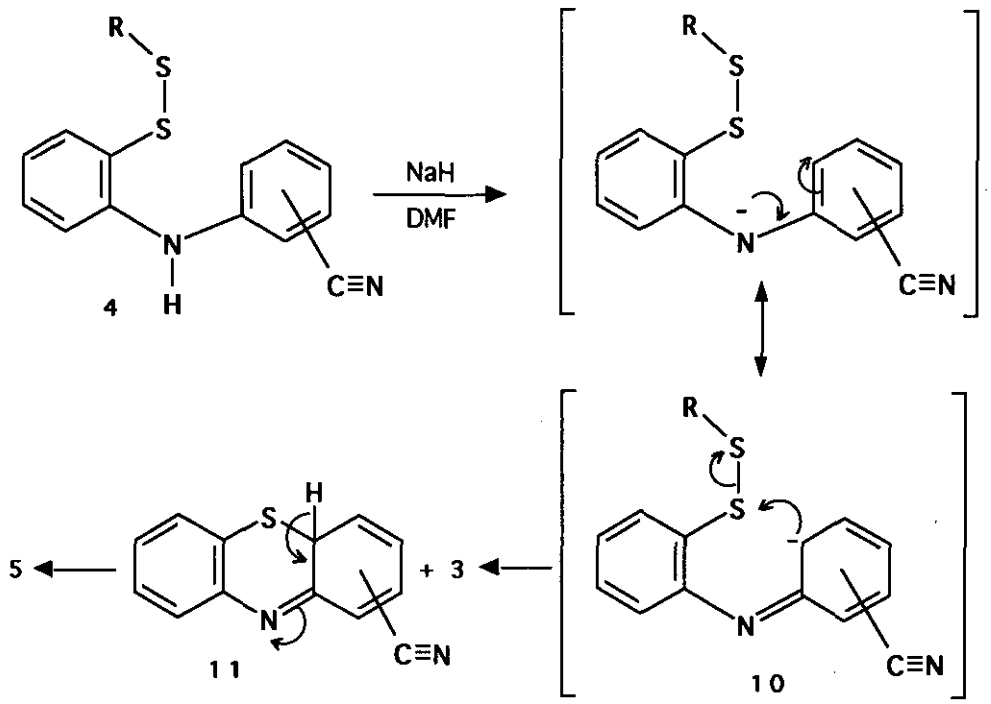
At this time, the problem concerning the formation of the phenothiazine (**5a**) is to know if it comes from diphenylamine (**3a**) or from disulfide (**4a**). In order to answer this question, the diphenylamine (**3a**) was dissolved in DMF and warmed to 100° C under N_2 atmosphere and NaH (1 mol) was added. We observed no appreciable phenothiazine formation. But, when dry air was bubbled in the reaction mixture, compound (**5a**) was isolated in good yield. Non ambiguously, in this reaction, the phenothiazine (**5a**) was formed from disulfide (**4a**). To test this last step, NaH (2 mol) was added to compound (**4a-c**) (1 mol) prepared by bubbling dry air in a solution of the thiol (**3**). The DMF mixture was heated at 110°C for 30 min to give phenothiazines (**5 a-c**) with compounds (**3 a-c**) + (**4 a-c**) according to Table II.

TABLE II

compounds **4**	**5** (yield, %)*	**3** + **4** (yield, %)*
a	**a** = 54	20
b	**b** = 8 **d** = 31	9
c	**c** = 60	10

* Yields related to compound (**3**).

We propose a mechanism according to Scheme 2 : The anion (**10**) arises from the disulfide (**4**), intramolecular nucleophilic attack at the S-S group, gives intermediate (**11**) which leads to the phenothiazine (**5**). This reaction may be compared with the cyclisation in 4*H*-1,4-benzothiazine, from AT and ß-diketones, which proceeds *via* an enamine ketone intermediate.[8] The isolation of compounds (**5b** and **5d**) from **4b** confirms the mechanistic pathway shown in Scheme 2. The formation of the transitory intermediate (**11**) from **10** is realised with elimination of one mol of diphenylamine (**3**).



Scheme 2

We have precedently shown that compound (**3a**) gives only few phenothiazine (**5a**), according to route A (Scheme 1). On the other hand, para derivative (**3c**), in the same conditions (route A) leads to **5c** with 21 % yield. So, the addition of the two routes (A and B) can explain the yields shown in Table II.
Keeping in view this Smiles rearrangement and the disulfide pathway to cyanophenothiazines, we now investigate a one-pot synthesis of cyanophenothiazines.

EXPERIMENTAL

Melting points were measured by using a Köfler apparatus and are uncorrected. ^{1}H Nmr spectra were recorded on a Varian EM 360 and a Bruker 200 A.C. spectrometers. ^{13}C Nmr spectra were realised on a Bruker 200 A.C. spectrometer. Mass spectral data were obtained on a VG 70-70F spectrometer. Elemental analyses were performed on a Perkin Elmer 240 apparatus.
DMF was distilled and dried over molecular sieves. Sodium hydride was a 80% dispersion in mineral oil.

General procedure for compounds (2a, 2b and 2c) : Sodium hydride (1.20 g, 0.04 mol) in DMF (20 ml), was slowly added, under nitrogen, to a hot solution (80°C) of freshly distilled 2-aminobenzenethiol (5 g, 0.04 mol) in DMF (15 ml). Hydrogen evolved and the mixture was stirred for 15 min at 80°C, followed by addition of chlorobenzonitrile (5.5 g, 0.04 mol) in DMF (10 ml). After stirring for 1 h at 100°C, the mixture was cooled to 10°C and water (200 ml) was added. An oil was separated which was solidified on standing. The yellow solid was dissolved in $CHCl_3$ and dried (Na_2SO_4). $CHCl_3$ was evaporated and the product was chromatographed on a silica gel column with toluene as eluent.

2-amino 2'-cyanodiphenylsulfide (**2a**):

Pale yellow powder (8.14 g, 90%); mp 92°C; ^1H nmr ($CDCl_3$) δ : 7.50 (1H, dd, J=7.5 Hz, J'=1.5 Hz), 7.35 (1H, dd, J=7.5 Hz, J'=1.5 Hz), 7.30-7.15 (2H, m), 7.10-7 00 (1H, m), 6.75-6.65 (3H, m), 4.25 (2H, s, NH_2); ^{13}C nmr ($CDCl_3$) δ : 148.1, 142.4 (2s), 137.7, 133.4, 133, 132.1, 126.4, 125.4, 119 (7d), 116.9 (s, CN), 115.7 (d, C3), 111.5, 110.4 (2s); ir (ν cm^{-1}) (KBr): 3560, 3440 (NH_2), 2240 (CN); ms m/z (%) : 226 (M^+, 100), 194 (M^+ - S, 27), 124 (M - C_6H_4CN, 20). Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found : C, 68.93; H, 4.49; N, 12.35.

2-amino 3'-cyanodiphenylsulfide (**2b**):

Identical procedure, but the reaction mixture was heated at 115°C for 5 h.

Pale yellow powder (5.61 g, 62 %); mp 60 °C; ^1H nmr ($CDCl_3$) δ : 7.45 (1H, dd, J=8 Hz, J'=1 Hz), 7.35-7.30 (5H, m), 6.81-6.72 (2H, m), 4.31 (2H, s, NH_2); ^{13}C nmr ($CDCl_3$) δ : 148.9, 139.3 (2s), 137.5, 131.9, 130, 129.3, 128.6, 128.5, 118.8 (7d), 118.3 (s, CN), 115.5 (d), 112.9, 111.6 (2s); ir (ν cm^{-1}) (KBr) : 3550, 3450 (NH_2), 2240 (CN). Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found : C, 68.89; H, 4.51; N, 12.23.

2-amino 4'-cyanodiphenylsulfide (**2c**):

Pale yellow powder (7.24 g, 80%); mp 100°C; ^1H nmr ($CDCl_3$) δ :7.45-7.40 (3H, m), 7.35-7.25 (1H, t, J = 6.8 Hz), 7.15-7.05 (2H, m), 6.85-6.75 (2H, m), 4.35 (2H, s, NH_2); ^{13}C nmr ($CDCl_3$) δ : 148.9, 144 (2s), 137.5 (d), 132.1 (2d, C'3 and C'5), 132 (d), 125.5 (2d, C'2 and C'6), 118.7, 115.4 (2d), 111, 107.9 (2s); ir (ν cm^{-1}) (KBr) : 3540, 3430 (NH_2), 2240 (CN). Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found : C, 69.09; H, 4.41; N, 12.31.

General procedure for compounds (3a, 3b and 3c): Compound (**2**) (2.26 g, 0.01 mol) in DMF (20 ml) was heated to 115°C and then sodium hydride (0.6 g, 0.02 mol) in DMF (10 ml) was added to the mixture. The mixture was stirred for 15 min at 130°C, cooled to 0°C and water (20 ml) was added. The solution was evaporated to dryness and the residue was dissolved in water, neutralised by CH_3COOH, and extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. Compound (**3**) was rapidly separated by chromatography on a silica gel column, elution with toluene.

2-mercapto 2'-cyanodiphenylamine (**3a**):

Cream powder (1.69 g, 75%); ^1H nmr ($CDCl_3$) δ : 7.25-6.40 (8H, m), 6.20 (1H, s, NH), 3.20 (1H, s, SH); ir (ν cm^{-1}) (KBr) : 3380 (NH), 2250 (CN) ·

2-mercapto 3'-cyanodiphenylamine (**3b**):

Cream powder (1.81 g, 80%); ^1H nmr ($CDCl_3$) δ : 7.30-6.60 (8H, m), 5.90 (1H, s, NH), 3.10 (1H, s, SH); ir (ν cm^{-1}) (KBr) : 3380 (NH), 2220 (CN).

Thiols (**3a** and **3b**) were not obtained in the pure form owing to rapid conversion to the disulfide.

2-mercapto 4'-cyanodiphenylamine (**3c**):

Cream powder (1.81 g, 80%); ^{1}H nmr ($CDCl_3$) δ : 7.10-6.35 (8H, m), 6.05 (1H, s, NH), 3.20 (1H, s, SH); ir (ν cm^{-1}) (KBr) : 3400 (NH), 2240 (CN). Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found : C, 69.12; H, 4.46; N, 12.30.

Compounds (**3**) rapidly converted into the disulfide (**4**) on standing in air at room temperature.

2-(2'-cyanophenylaminophenyl) disulfide (**4a**):

Pale yellow cristals; mp 137-138°C; ^{1}H nmr ($CDCl_3$) δ : 7.55-7.45 (2H, m), 7.40 (1H, d, J = 7 Hz), 7.25-7.15 (3H, m), 7.00-6.80 (2H, m), 6.85 (1H, s, NH); ^{13}C nmr ($CDCl_3$) δ: 145.6 (s, C'1), 141 (s, C1), 134.9, 133.6, 133, 130.4 (4d), 126.3 (s, C2), 123.3, 120.5, 119.4 (3d), 116.9 (s, CN), 116 (d), 100.7 (s, C'2); ir (ν cm^{-1}) (KBr) : 3430 (NH), 2240 (CN); ms m/z (%) : 450 (M^+, 7), 225 (M/2, 95), 224 (100), 192 (44). Anal. Calcd for $C_{26}H_{18}N_4S_2$: C, 69.31; H, 4.02; N, 12.44. Found : C, 68.82; H, 4.36; N, 12.42.

2-(3'-cyanophenylaminophenyl) disulfide (**4b**):

Pale yellow crystals; mp 128°C; ^{1}H nmr ($CDCl_3$) δ : 7.50 (1H, dd, J = 8 Hz J'=1.7 Hz), 7.35-7.05 (6H, m), 6.92-6.82 (1H, m), 6.55 (1H, s, NH); ^{13}C nmr ($CDCl_3$) δ : 143.2, 142.6 (2s, C1 and C'1), 136.4, 131.3, 130.1, 125 (4d), 123.8 (s, C2), 122.6, 121.8, 120.9 (3d), 118.5 (s, CN), 116.3 (d), 113 (s, C'3); ir (ν cm^{-1}) (KBr) : 3440 (NH), 2260 (CN). Anal. Calcd for $C_{26}H_{18}N_4S_2$: C, 69.31; H, 4.02; N, 12.44. Found : C, 69.30; H, 4.16; N, 12.41.

2-(4'-cyanophenylaminophenyl) disulfide (**4c**):

Pale yellow crystals; mp 149°C; ^{1}H nmr ($CDCl_3$) δ : 7.51 (1H, d, J = 7,5 Hz), 7.46-7.42 (2 H, dd, J = 8.8 Hz, J' = 1.1 Hz, H3' et H5'), 7.30-7.25 (2H, d), 6.97-6.89 (1H, m,), 6.88-6.83 (2H, dd, J = 8.8 Hz, J' = 1.1 Hz, H2' and H6'), 6.62 (1H, s, NH); ^{13}C nmr ($CDCl_3$) δ : 146.3 (s, C'1), 141.7 (s, C1), 135.7 (d), 133.5 (2d, C'3 and C'5), 131 (d), 126 (s, C2), 123, 119 (2d), 119.4 (s, CN), 116.4 (2d, C'2 and C'6), 103 (s, C4); ir ν cm^{-1}) (KBr) : 3410 (NH), 2230 (CN) . Anal. Calcd for $C_{26}H_{18}N_4S_2$: C, 69.31; H, 4.02; N, 12.44. Found : C, 69.08; H, 4.07; N, 12.46.

General procedure for compounds (5a, 5b and 5c): Compound (**4**) 2.25 g, 0.005 mol) was dissolved in DMF (30 ml) and heated to 110°C. Sodium hydride (0.3 g, 0.010 mol) was added and the mixture instantaneously became deep red colored. After stirring for 40 min at 110°C, the mixture was cooled to 0°C and water (300 ml) was droped in. An yellow solid was separated, which was filtered, dissolved with $CHCl_3$; this solution was washed with water, dried (Na_2SO_4) and the residue was evaporated to give pure product (**5**).

The DMF-H_2O mixture was evaporated to dryness and chromatographed on a silica gel column with toluene as eluent to give compound (**4**).

1-cyanophenothiazine (**5a**):

Bright yellow needles (1.21 g, 54%); mp 171°C (lit.,[4] mp 171°C).

2-cyanophenothiazine (**5b**):

Bright yellow powder (0.18 g, 8%); mp 204°C (lit.,[2] mp 204°C).

3-cyano phenothiazine (**5c**):

Bright yellow powder (1.35 g, 60%); mp 184 °C (lit.,[3] mp 182-184°C).

4-cyano phenothiazine (**5d**):

Bright yellow powder (0.36 g, 32%); mp 160°C; ^{1}H nmr ($CDCl_3$) δ : 8.95 (1H, s, NH), 7.17-6.95 (4H, m), 6.89-6.66 (3 H, m); ^{13}C nmr ($CDCl_3$) δ : 142.8, 140.6 (2s), 128.1, 127.9 (2d, C2 and C8), 126.3, 125.3 (2d, C3 and C6), 122.4 (d, C7), 120.7 (s), 117.8 (d, C1), 116.1, 113 (2s, CN and C4a), 114.5 (d, C9), 108 (s, C4); ir (ν cm^{-1}) (KBr) : 3400 (NH), 2250 (CN). Anal. Calcd for $C_{13}H_8N_2S$: C, 69.62; H, 3.60; N, 12.49. Found : C, 69.46; H, 3.78; N, 12.31.

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