A Facile Synthesis of Cyanophenothiazines

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A one-pot synthesis of 1, 3 and 4-cyanophenothiazines and a two-step approach to 2-cyanoisomer have been developed. The condensation of 2-aminobenzenethiol and 2,3 or 3,4-dihalogenobenzonitriles followed by Smiles rearrangement or by intramolecular aromatic substitution gave the desired ring systmes.

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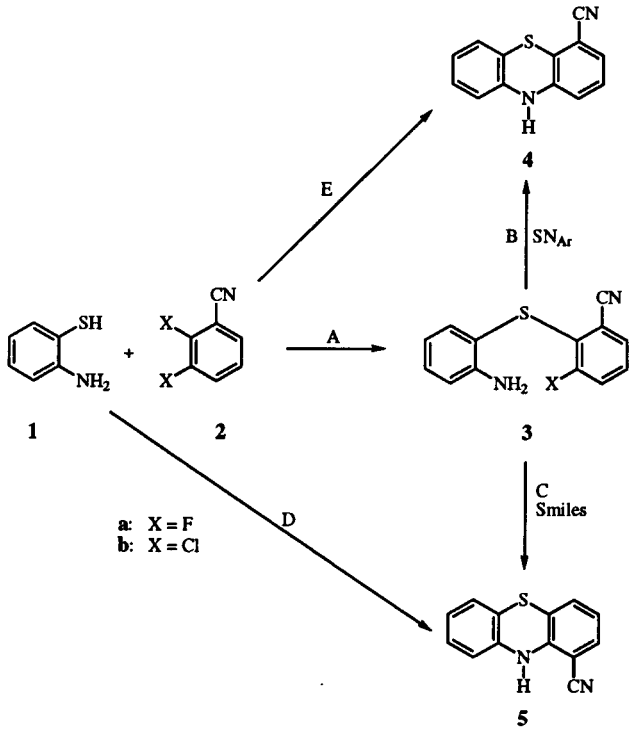
Because of important biological properties of phenothiazines [1], we were interested in the synthesis of cyanophenothiazines. We recently described a general method in four steps leading to the four possible cyanophenothiazines from 2-aminothiophenol and monohalogenobenzonitriles [2]. Here we are going to report a two-step and "one pot" synthesis from 2-aminothiophenol **1** and dihalogenobenzonitriles. Two types of compounds were used: 2,3 and 3,4-dihalogenobenzonitriles.

When 2,3-difluoro or dichlorobenzonitriles **2** were reacted in dimethylformamide with 2-aminothiophenol and sodium hydride (1 equivalent) at 0°, (Scheme 1, pathway A) the diphenyl sulfides **3** were obtained in very good yields, 88% for **3a** and 90% for **3b**.

Scheme 1



From compounds **3a** or **b**, two cyanophenothiazines could selectively be prepared: the 4-cyano **4** and the 1-cyano isomer **5** (Scheme 1). Compound **4** was isolated *via* a nucleophilic substitution (SN_{Ar}) of the halogen, by heating **3** in dimethylformamide at 140° (pathway B). The attempted substitution occurred with fluoro derivative **3a**, but curiously failed with chloro isomer **3b**. To obtain **5**, the only route from diphenyl sulfides **3** was a Smiles rearrangement (pathway C). This was achieved by heating **3a** or **b** in dimethylformamide, at 100° with sodium hydride (2 equivalent). The yields of compounds **4** and **5**, prepared from **3a** and **3b**, are given in Table I.

Table I

Preparation of 4 and 1-Cyanophenothiazines

Diphenyl sulfides	Pathway*	4 (yield%) (SN_{Ar})		5 (yield%) (Smiles)
3a	B	40	+	0
3b	B	0	+	2
3a	C	15	+	62
3b	C	0	+	73

*Pathway B: dimethylformamide, 140°, 48 hours; Pathway C: dimethylformamide, 100°, NaH (2 equivalents), 3 hours.

Similarly 3,4-difluoro or dichlorobenzonitriles **6** were reacted with 2-aminothiophenol and sodium hydride (1 equivalent) at 0° (Scheme 2), to give the diphenyl sulfides **7** in good yields (81% and 78%). Only the compound **7a** (X = F) allowed the formation of 2-cyanophenothiazine **8** (pathway B), but **7a** or **b**, gave rise to 3-cyanophenothiazine **9**, *via* a Smiles rearrangement (pathway C). These results are summarized in Table II. These results suggest a

Table II

Preparation of 2 and 3-Cyanophenothiazines

Diphenyl sulfides	Pathway	8 (yield%) (SN_{Ar})		9 (yield%) (Smiles)
7a	B	30	+	0
7b	B	0	+	0
7a	C	24	+	52
7b	C	2	+	66

possible "one-pot" synthesis of the four cyanophenothiazines **4**, **5**, **8** and **9** (Pathways D and E). For this purpose, 2-aminothiophenol was reacted with sodium hydride and 2,3 or 3,4-dihalogenobenzonitriles in dimethylformamide for 12 hours. Then the mixture was heated with sodium hydride (pathway D) or without (pathway E). However, the purification of compound **8** failed and we preferred to use the two-step method to obtain the 2-cyanophenothiazine. The yields are given in Table III.

Table III

"One pot" Synthesis of Cyanophenothiazines

Compound	Pathway	4 (yield, %)		5 (yield, %)	8 (yield, %)		9 (yield, %)
1 + 2a	D	16	+	60			
1 + 2b	D			72			
1 + 2a	E	40					
1 + 6a	D				19	+	67
1 + 6b	D						70
1 + 6a	E				*		

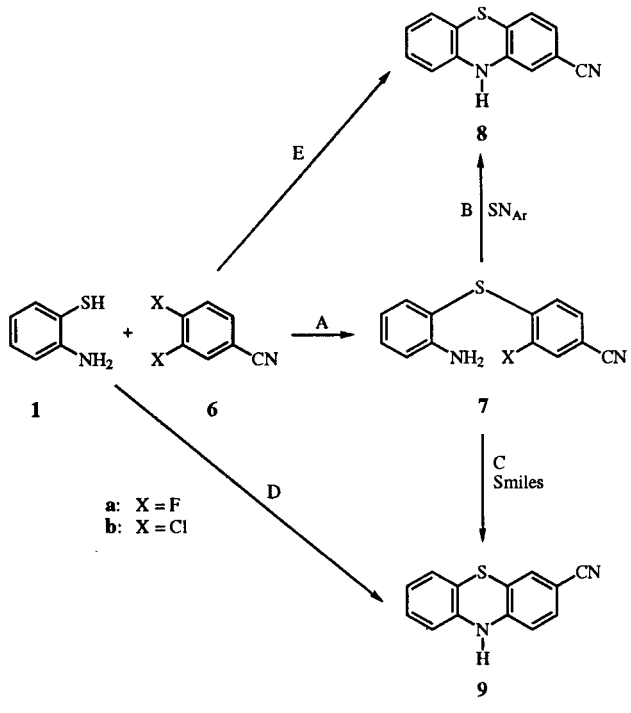
* Could not be isolated in a pure state.

Discussion.

In pathway A, the substitution occurred with the halogen atom in the *ortho* or *para* position to the cyano group with excellent yields, as well for fluoro compounds (88 and 81%) as for chloro compounds (90 and 78%). In contrast, with pathway B, the aromatic substitution of the halogen in diphenyl sulfides **3** and **7** was only carried out with fluorine. Chlorine did not react under these conditions. In pathway C, the Smiles rearrangement was observed for the compounds **3** and **7a** or **b**. We had previously shown that the cyano was a good electron attracting group to promote such intramolecular displacement [2]. Moreover as halogens are known to induce this rearrangement [3], we might anticipate that the presence in the *ortho*, or in the *ortho* and *para* positions to sulfur, that these two active groups (cyano and halo), will greatly facilitate intramolecular displacement of sulfur. However, the chloro derivatives **3b** or **7b** only led to the Smiles rearrangement while the fluoro compounds **3a** and **7a** gave the Smiles rearrangement and SN_{Ar} at the same time. For the "one pot" procedure (Pathway D or E), the 1 and 3-cyanophenothiazines **5** and **9** were synthesized from 2,3 or 3,4-dichlorobenzonitriles **2b** or **6b**, in good yields (Table III) with easy purification. The 4-cyanophenothiazine **4** was prepared in a "one pot" reaction from 2,3-difluorobenzonitrile **2a**. However, for the 2-cyanophenothiazine **8** from 3,4-difluorobenzonitrile **6a**, we could not isolate the compound in a pure state. For this reason, we preferred the two-step route A+B (Scheme 2).

In summary, we propose a "one pot" synthesis for the 1, 3 and 4-cyanophenothiazines and a two-step preparation for the 2-cyanophenothiazine.

Scheme 2



EXPERIMENTAL

Melting points were measured by using a Köfler apparatus and are uncorrected. The ^1H nmr spectra were recorded on a Varian EM 360 spectrometer. Elemental analyses [4] were performed on a Perkin Elmer 240 apparatus. Dimethylformamide was distilled and dried over molecular sieves. 2-Aminobenzenethiol was distilled under reduced pressure and kept under nitrogen. Sodium hydride was an 80% dispersion in mineral oil. Grace Amicon silica gel 60 A, 20-45 μ*M* and Merck aluminium oxide 90, 63-200 μ*M* (70-230 mesh ASTM) were employed for column chromatographies.

General Procedure for Compounds **3a-b** (Pathway A).

Sodium hydride (0.60 g, 0.02 mole) in 10 ml of dimethylformamide was slowly added at 0° under nitrogen to a solution of freshly distilled 2-aminobenzenethiol (2.50 g, 0.02 mole) in 10 ml of dimethylformamide. After stirring for 0.5 hour, 2,3-difluoro (2.78 g, 0.02 mole) or 2,3-dichlorobenzonitrile (3.44 g, 0.02 mole) was added at once and the mixture was stirred at 0° during 12 hours, then water was added dropwise. A yellowish solid separated and purified by column chromatography on silica gel with toluene as the eluent, or by recrystallization from toluene or ethanol.

2-Aminophenyl 2'-Cyano-6'-fluorophenyl Sulfide (**3a**).

This compound was obtained as a pale yellow powder (4.30 g, 88%), mp 98° (ethanol) (lit [5] mp 98°).

2-Aminophenyl 2'-Cyano-6'-chlorophenyl Sulfide (**3b**).

This compound was obtained as a white powder (4.69 g, 90%), mp 148° (toluene); ^1H nmr (deuteriochloroform): δ

7.70-7.00 (m, 5H), 6.90-6.50 (m, 2H), 4.25 (s, 2H, NH_2); ir (potassium bromide): ν 3440, 3351 (NH_2), 2232 (CN) cm^{-1}.

Anal. Calcd. for $C_{13}H_9ClN_2S$: C, 59.88; H, 3.48; N, 10.74. Found: C, 59.98; H, 3.65; N, 10.71.

General Procedure for Compounds **7a-b** (Pathway A).

Following the procedure described for the synthesis of **3a-b**, but 2,3-dihalogenobenzonitriles were replaced by 3,4-difluoro and 3,4-dichlorobenzonitriles.

2-Aminophenyl 4'-Cyano-2'-fluorophenyl Sulfide (**7a**).

This compound was obtained as a cream colored powder (3.95 g, 81%), mp 115° (toluene); ^1H nmr (deuteriochloroform): δ 7.45-7.00 (m, 4H), 6.85-6.45 (m, 3H), 4.20 (s, 2H, NH_2); ir (potassium bromide): ν 3500, 3371 (NH_2), 2233 (CN) cm^{-1}.

Anal. Calcd. for $C_{13}H_9FN_2S$: C, 63.92; H, 3.71; N, 11.47. Found: C, 63.76; H, 3.85; N, 11.35.

2-Aminophenyl 2'-Chloro-6'-cyanophenyl Sulfide (**7b**).

This compound was obtained as a pale yellow powder (4.07 g, 78%), mp 122° (toluene); ^1H nmr (deuteriochloroform): δ 7.60-7.15 (m, 4H), 6.95-6.55 (m, 3H), 4.15 (s, 2H, NH_2); ir (potassium bromide): ν 3452, 3350 (NH_2), 2228 (CN) cm^{-1}.

Anal. Calcd. for $C_{13}H_9ClN_2S$: C, 59.88; H, 3.48; N, 10.74. Found: C, 59.78; H, 3.65; N, 10.67.

General Procedure for Compounds **4** and **8** (Pathway B).

Diphenyl sulfide **3a** or **7a** (2.44 g, 0.01 mole) was added at once in dimethylformamide (12 ml) previously heated to 140°. After stirring 48 hours at this temperature, the reaction mixture was cooled to 0° and water was added. A greenish solid separated, which was dissolved in ether, and the reaction mixture was extracted with three 50 ml portions of ether. The combined ether phases were washed with water, dried (sodium sulfate), filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel (compound **4**) or aluminium oxide (compound **8**) column with toluene as the eluent.

4-Cyanophenothiazine **4**.

This compound was obtained as a yellow powder (0.89 g, 40%), mp 160° (lit [2] mp 160°).

2-Cyanophenothiazine **8**.

This compound was obtained as a yellow powder (0.67 g, 30%), mp 204° (lit [6] mp 204°).

General Procedure for Compounds **5** and **9** (Pathway C).

Diphenyl sulfides **3a** or **7a** (2.44 g, 0.01 mole) or **3b** or **7b** (2.61 g, 0.01 mole) in dimethylformamide (10 ml) was heated at 100°, and then sodium hydride (0.6 g, 0.02 mole) in dimethylformamide (10 ml) was slowly added under nitrogen. The mixture was stirred for 3 hours at 100°, cooled to 0° and water (200 ml) was droped in. A yellow solid was separated, filtered and dissolved in methylene chloride. The solution was washed with water, dried (sodium sulfate) and evaporated. The residue was chromatographed on a silica gel column with toluene (for **5**) or methylene chloride (for **9**) as the eluent.

1-Cyanophenothiazine **5**.

This compound was obtained as a bright yellow powder (1.39 g, 62% from **3a**, 1.63 g, 73% from **3b**), mp 171° (lit [7] mp 171°).

3-Cyanophenothiazine **9**.

This compound was obtained as a bright yellow powder (1.16 g, 52% from **7a**, 1.48 g (66%) from **7b**), mp 184° (lit [8] mp 184°).

"One-pot" Procedure for Compound **4** (Pathway E).

Sodium hydride (0.60 g, 0.02 mole) in 10 ml of dimethylformamide was slowly added at 0° under nitrogen to a solution of freshly distilled 2-aminobenzenethiol (2.50 g, 0.02 mole) in 10 ml of dimethylformamide. After stirring for 0.5 hour, 2,3-difluoro (2.78 g, 0.02 mole) was added at once and the mixture was stirred at 0° during 12 hours, then it was brought in a silicone oil bath at 140° and heated during 48 hours. The yield was 40%.

"One-pot" Procedure for **5** and **9** (Pathway E).

Following the procedure described for the preparation of **4**, but using 2,3 and 3,4-dichlorobenzonitriles. After 12 hours at 0°, the temperature raised to 100° and sodium hydride (0.6 g, 0.02 mole was slowly added under nitrogen. After 3 hours at 100°, the mixture was hydrolyzed. The yields were 72% (**5**) and 70% (**9**).

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