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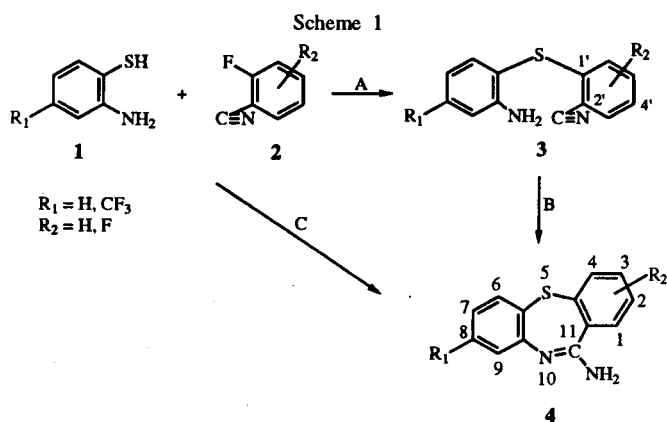
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The reaction of halogenobenzonitriles with 2-aminobenzenethiol is a new route, in a "one-pot" or two-step approach, to 11-aminodibenzo[*b,f*][1,4]thiazepine and fluoro derivatives.

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Dibenzo[*b,f*][1,4]thiazepines are useful compounds as intermediates for the preparation of drugs or as therapeutics like analgesics, antihistaminics, adrenolytics, neuroleptics [1] and anti HIV [2]. Different syntheses, in several steps, are described for these compounds [1a-b, 1e, 3a-b].

We report here the two-step (pathways A+B) or "one pot" (pathway C) synthesis of 11-aminodibenzo[*b,f*][1,4]thiazepine and some fluoro derivatives according to Scheme 1. We developed the reaction with 2-amino-



benzenethiol (1, $\text{R}_1 = \text{H}$) or with a trifluoro derivative 1, ($\text{R}_1 = \text{CF}_3$) and various *ortho*-fluorobenzonitriles. When R_1 was a CF_3 group, the yield of diphenyl sulfide **3b** decreased. In the case of difluorobenzonitriles, nucleophilic substitution was selectively observed in the *ortho* position to the nitrile group with **2c**, **2e**, **2f** and in the *para* position with 2,4-difluorobenzonitrile **2d**. When the reaction was run with sodium hydride in DMF at room tempera-

Table I
Preparation of Diphenyl Sulfides **3a-f**

| Compound | benzonitrile | Compound | R_1 | R_2 | $\text{C}\equiv\text{N}$ | Yield % |
|-----------|--------------|-----------|---------------|--------------|--------------------------|---------|
| 2a | 2-fluoro | 3a | H | H | 2' | 80 |
| 2b | 2-fluoro | 3b | CF_3 | H | 2' | 50 |
| 2c | 2,3-difluoro | 3c | H | 6'-F | 2' | 88 |
| 2d | 2,4-difluoro | 3d | H | 3'-F | 4' | 85 |
| 2e | 2,5-difluoro | 3e | H | 4'-F | 2' | 80 |
| 2f | 2,6-difluoro | 3f | H | 3'-F | 2' | 80 |

ture, the yields (Table I) were good. However, by heating, disubstituted benzonitriles were isolated.

When a compound **3** was allowed to react with sodium hydride in THF as solvent (pathway B), the major product was 11-aminodibenzo[*b,f*][1,4]thiazepine (**4**). Under these conditions, the nucleophilic addition of NH^- on the carbonitrile to form an amidine and a seven membered ring was obtained. If DMF was used in place of THF, a Smiles rearrangement occurred and a cyanophenothiazine was isolated [4]. In the "one-pot" synthesis, intermediate **3** was prepared in the same way, with sodium hydride in DMF, then the solvent was evaporated and the residue was dissolved with sodium hydride in THF and refluxed. The results are summarized in Table II. This synthesis

Table II
Dibenzo[*b,f*][1,4]thiazepines Prepared

| Compound | R_1 | R_2 | pathway B yield % | pathway A+B yield % | pathway C yield % |
|-----------|---------------|--------------|----------------------|------------------------|----------------------|
| 4a | H | H | 80 | 64 | 54 |
| 4b | CF_3 | H | 55 | 27 | 25 |
| 4c | H | 4F | 64 | 56 | 72 [a] |
| 4e | H | 2F | 78 | 62 | 72 |
| 4f | H | 1F | 52 | 41 | 40 65 [a] |

[a] "One pot" with sodium hydride in THF as solvent.

requires the following comments: the intermediate **3** was prepared with sodium hydride in DMF at 20° (reaction A) but when this reaction is run at a higher temperature, poly-substituted benzonitriles were obtained. On the other hand, thiazepines **4** were obtained from diphenyl sulfides **3** with sodium hydride only in THF (pathway B). Curiously, two compounds **3c** and **3f** could be prepared in THF and it was very easy to obtain **4c** and **4f** in "one pot" reaction with only THF as the solvent. However, under the same conditions isomer **2e** gave the compound **4e** in a poor yield.

The structures were supported by ^1H nmr and ir spectra as well as by microanalysis and was confirmed by comparison with spectral data and physical constants previously published [1c].

In summary, dibenzo[*b,f*][1,4]thiazepines **4** and their fluoro derivatives were easily available by formation of a

cyclic seven-membered ring amidine, either in two-step or in "one pot" reaction sequences in good yields.

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 [5] were performed on a Perkin Elmer 240 apparatus. DMF was distilled and dried over molecular sieves. THF was distilled in the presence of benzophenone and sodium. 2-Aminobenzenethiol was distilled under reduced pressure and kept under nitrogen. Sodium hydride was an 80% dispersion in mineral oil.

General Procedure for Compounds 3a-f.

Sodium hydride (0.66 g, 0.022 mole) in 10 ml of DMF was slowly added at 0° under nitrogen to a solution of freshly distilled 2-aminobenzenethiol (2.75 g, 0.022 mole) in 10 ml of DMF. After stirring for 0.5 hour, fluorobenzonitrile (2.42 g, 0.02 mole) was added and the mixture was allowed to reach to room temperature and stirred during 12 hours, then water was added. The mixture was evaporated to dryness and the residue was dissolved in chloroform, the solution was dried (sodium sulfate), evaporated and separated by column chromatography on silica gel with toluene as the eluent.

2-Aminophenyl 2'-Cyanophenyl Sulfide (3a)

This compound was obtained as a white powder (3.62 g, 80%), mp 92° (lit [4] mp 92°).

2-Amino-4-trifluoromethylphenyl 2'-Cyanophenyl Sulfide (3b)

Following the procedure described for the preparation of 3a with heating the reaction at 120° during four hours, the product was a pale yellow powder (2.94 g, 50%), mp $90-92^\circ$; ^1H nmr (deuteriochloroform): δ 7.45-6.95 (m, 4H, C3'-H, C4'-H, C5'-H, C6'-H), 6.90-6.60 (m, 3H, C3-H, C5-H, C6-H), 4.40 (s, 2H, NH_2); ir (potassium bromide): ν 3454, 3359 (NH_2), 2221, (CN) cm^{-1} .

Anal. Calcd. for $\text{C}_{14}\text{H}_9\text{F}_3\text{N}_2\text{S}$: C, 57.13; H, 3.08; N, 9.52. Found: C, 57.17; H, 3.20; N, 9.56.

2-Aminophenyl 2'-Cyano-6'-Fluorophenyl Sulfide (3c)

This compound was obtained as a pale yellow powder (4.30 g, 88%), mp 98° (ethanol); ^1H nmr (deuteriochloroform): δ 7.50-6.80 (m, 5H, C3'-H, C4'-H, C5'-H, C4-H, C6-H), 6.70-6.40 (m, 2H, C3-H, C5-H), 4.20 (s, 2H, NH_2); ir (potassium bromide): ν 3424, 3337 (NH_2), 2226 (CN) cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{FN}_2\text{S}$: C, 63.92; H, 3.71; N, 11.47. Found: C, 63.79; H, 3.85; N, 11.45.

2-Aminophenyl 3'-Fluoro-4'-cyanophenyl Sulfide (3d)

This compound was isolated as a white syrup (4.15 g, 85%); ^1H nmr (deuteriochloroform): δ 7.50-6.90 (m, 3H), 6.80-6.20 (m, 4H), 4.20 (s, 2H, NH_2); ir (potassium bromide): ν 3464, 3365 (NH_2), 2230 (CN) cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{FN}_2\text{S}$: C, 63.92; H, 3.71; N, 11.47. Found: C, 63.71; H, 3.89; N, 11.28.

2-Aminophenyl 4'-Fluoro-2'-cyanophenyl Sulfide (3e)

This compound was obtained as a pale yellow powder (3.90 g, 80%), mp $92-94^\circ$ (ethanol); ^1H nmr (deuteriochloroform): δ

7.00-6.50 (m, 4H), 6.50-6.00 (m, 3H), 3.60 (s, 2H, NH_2); ir (potassium bromide): ν 3451, 3356 (NH_2), 2228 (CN) cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{FN}_2\text{S}$: C, 63.92; H, 3.71; N, 11.47. Found: C, 64.05; H, 3.85; N, 11.54.

2-Aminophenyl 2'-Cyano-3'-fluorophenyl Sulfide (3f)

This compound was obtained as a pale yellow powder (3.90 g, 80%), mp $92-93^\circ$; ^1H nmr (deuteriochloroform): δ 7.40-6.90 (m, 3H, C4'-H, C5'-H, C6'-H), 6.90-6.60 (m, 2H, C4-H, C6-H), 6.60-6.30 (m, 2H, C3-H, C5-H), 4.20 (s, 2H, NH_2); ir (potassium bromide): ν 3478, 3378 (NH_2), 2230 (CN) cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{FN}_2\text{S}$: C, 63.92; H, 3.71; N, 11.47. Found: C, 64.10; H, 3.90; N, 11.52.

General Procedure for Compounds 4a-f (Pathway B)

Sodium hydride (0.90 g, 0.03 mole) in 25 ml of THF, was slowly added under nitrogen, to a solution of 3 (0.02 mole) in 50 ml of THF at room temperature. The mixture was warmed to 70° and became orange coloured. After stirring for 2 hours, the mixture was cooled to 10° and water was added dropwise. A white solid separated, was dried and chromatographed on a silica gel column with ethyl acetate as the eluent.

"One-pot" Procedure for 4c and 4f (Pathway C)

Sodium hydride (0.66 g, 0.022 mole) in 10 ml of DMF or THF, was slowly added at 0° under nitrogen to a solution of freshly distilled 2-aminobenzenethiol (2.75 g, 0.022 mole) in 5 ml of DMF or THF. After stirring during 0.5 hour, difluorobenzonitrile (2.78 g, 0.02 mole) was added rapidly and the mixture was allowed to reach room temperature and was allowed to stand for twelve hours. Then DMF was evaporated under vacuum, and replaced by 50 ml of THF. Sodium hydride (0.90 g, 0.03 mole) was added and the mixture was refluxed for two hours.

11-Aminodibenzo[b,f][1,4]thiazepine (4a)

This compound was obtained as a white powder (3.60 g, 80%), route B, (2.45 g, 54%), route C, mp 176° (lit [1c] mp $176-178^\circ$).

8-Trifluoromethyl-11-aminodibenzo[b,f][1,4]thiazepine (4b)

This compound was obtained as a white powder (3.23 g, 55%), route B or (1.47 g, 25%), route C, mp 187° ; ^1H nmr (deuteriochloroform): δ 7.70-7.00 (m, 7H), 5.25 (s, 2H, NH_2); ir (potassium bromide): ν 3517, 3305 (NH_2), 3089 cm^{-1} .

Anal. Calcd. for $\text{C}_{14}\text{H}_9\text{F}_3\text{N}_2\text{S}$: C, 57.14; H, 3.08; N, 9.52. Found: C, 56.95; H, 3.20; N, 9.35.

4-Fluoro-11-aminodibenzo[b,f][1,4]thiazepine (4c)

This compound was obtained as a white powder (3.12 g, 64%), route B, (3.51 g, 72%), route C in DMF then THF, (2.97 g, 61%), route C in THF; mp 228° ; ^1H nmr ($\text{DMSO}-d_6$): δ 7.50-7.20 (m, 4H), 7.20-6.90 [m, 5H (3H+ NH_2)]; ir (potassium bromide): ν 3470, 3291 (NH_2), 3066 cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{FN}_2\text{S}$: C, 63.92; H, 3.71; N, 11.47. Found: C, 63.36; H, 4.07; N, 11.14.

2-Fluoro-11-aminodibenzo[b,f][1,4]thiazepine (4e)

This compound was isolated as a white powder (3.81 g, 78%), route B, (3.51 g, 72%), route C, mp 180° ; ^1H nmr ($\text{DMSO}-d_6$): δ 7.50-7.20 (m, 4H), 7.20-6.90 [m, 5H (3H+ NH_2)]; ir (potassium bromide): ν 3484, 3469 (NH_2), 3280, 3051 cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{FN}_2\text{S}$: C, 63.92; H, 3.71; N, 11.47. Found: C, 63.99; H, 3.75; N, 11.46.

1-Fluoro-11-aminodibenzo[*b,f*][1,4]thiazepine (4f).

This compound was obtained as a pale yellow powder (2.54 g, 52%), route B, (1.95 g, 40%), route C in DMF then THF, (3.17 g, 65%), route C in THF, mp 194°; ¹H nmr (DMSO-*d*₆): δ 7.50-7.25 (m, 4H), 7.20-6.80 [m, 5H (3 H+NH₂)]; ir (potassium bromide): ν 3497, 3469, 3302 (NH₂), 3082 cm⁻¹.

Anal. Calcd. for C₁₃H₉FN₂S: C, 63.92; H, 3.71; N, 11.47. Found: C, 63.80; H, 3.80; N, 11.39.

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