# A SYNTHESIS OF 2-SUBSTITUTED PHENYLBENZOTHIAZOLES

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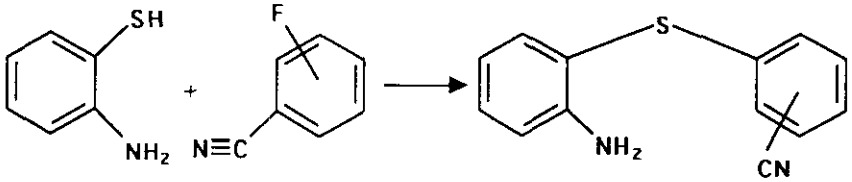
**Abstract**-A one-pot synthesis of 2-substituted phenylbenzothiazoles is achieved when 2-aminobenzenethiol is treated with an excess of sodium hydride and aromatic nitriles in THF. This method allows to obtain substituted products (F, $CF_3$, Cl or $OCH_3$) in each *ortho*, *meta* and *para* position and plurisubstituted products.

2-Halogenophenylbenzothiazoles exhibit various interesting biological activities : anthelmintic,[1,2] acaricide,[3-6] herbicide[7] and induction of increased hydroxylase activity.[8,9] Due to their interest, numerous synthetic routes were described.[9-15] Bromo and chloro derivatives were largely studied, but few papers report the synthesis of compounds containing fluorine. However, fluorine may have pharmacologic properties, so we were interested in synthesis of such compounds.

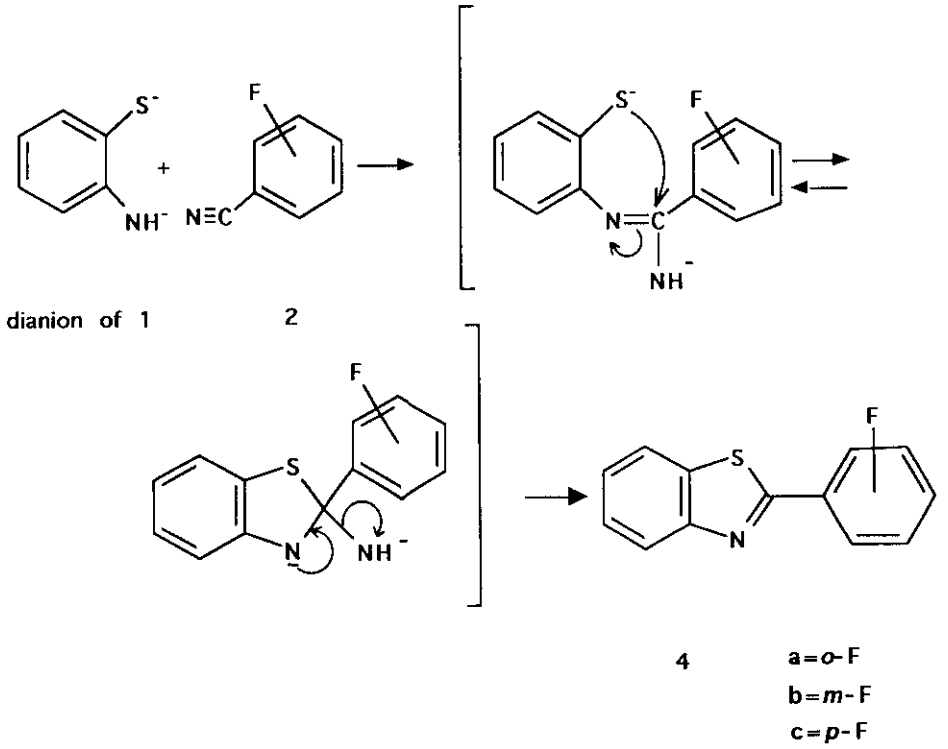
*Meta* and *para* fluorophenyl- substituted derivatives are obtained in a reaction from 2-aminobenzenethiol (AT) and acid chlorids,[9,14] but *ortho*-fluorophenyl compounds are synthesized in three steps : preparation of a thiobenzanilide which is then cyclised.[11] We investigated new experimental conditions to obtain - in one step - *ortho*, *meta* and *para* substituted derivatives and we condensed free AT with fluoroaromatic nitriles. It was found[13] AT reacts with aromatic nitriles under drastic conditions (8000 kg/cm$^2$, 140°C, 20 h) to give phenylbenzothiazoles. In a recent paper,[16] we report the reaction of AT with halogenobenzonitriles in the presence of NaH in DMF to give amino cyanodiphenylsulfides (**3**), which, *via* a Smiles rearrangement, lead to cyanophenothiazines.




1 2 3

a= *o*-C N
b= *m*-C N
c= *p*-C N

When THF was used as solvent, we observed a concurrent reaction : nucleophilic addition on C≡N took place instead of substitution of the halogen, acccording to the next scheme :




4 **a**=*o*-F
**b**=*m*-F
**c**=*p*-F

The yields of compound (**4**) regularly increased with the amount of NaH (Table I).

Table I

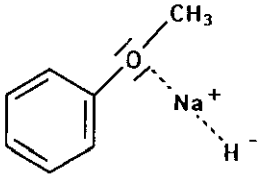
| NaH (mol for one mol of AT) | **3a** (yields %) | **4a** (yields %) |
|---|---|---|
| 1 | 15 | 0 |
| 2 | 5 | 20 |
| 3 | 2 | 60 |
| 4 | 2 | 80 |

Surprisingly, with THF as solvent and NaH (4 eq.), AT with benzonitrile gives a very poor yield of 2-phenylbenzothiazole. This reaction requires a substituent on the phenyl ring to give satisfactory yields. We tested different substituted nitriles : monofluoro, trifluoromethyl, chloro, methoxy and methyl nitriles. The yields were generally good or excellent (Table II) except for the *ortho*-tolunitrile which gave no benzothiazole

Table II

| 2-substituted phenylbenzothiazole | 4 | Yield (%) |
|---|---|---|
| 2'-fluoro | **a** | 80 |
| 3'-fluoro | **b** | 80 |
| 4'-fluoro | **c** | 88 |
| 2'-trifluoromethyl | **d** | 60 |
| 3'-trifluoromethyl | **e** | 81 |
| 4'-trifluoromethyl | **f** | 73 |
| 3', 5'-difluoro | **g** | 40 |
| 2'-chloro | **h** | 70 |
| 3'-chloro | **i** | 78 |
| 4'-chloro | **j** | 76 |
| 2'-methoxy | **k** | 65 |
| 3'-methoxy | **l** | 45 |
| 4'-methoxy | **m** | 52 |
| 3', 5'-dimethoxy | **n** | 65 |

DMF and THF are well known as dipolar aprotic solvents and facilitate nucleophilic reactions, especially aromatic substitutions. DMF is a better coordinating agent than THF, and no nucleophilic addition was observed in DMF. On the other hand, THF is efficient for nucleophilic additions and allows the addition of a relatively hard nucleophile ($NH^-$) with the hard carbonitrile. The nature of the solvent is not the only factor, the proportion of NaH is also determinant for this benzothiazole synthesis (Table I). There is no SNAr for 3 and 4 equivalents of NaH in THF, and only addition of $NH^-$ on the nitrile group is obtained. To explain the usefulness of the excess of NaH, formation of weak complexes with CN, F, Cl or $OCH_3$ may be considered. Complexes of carbonitrile and different metals are well known, and the interaction between nitrile and alkali metals ions was reported.[17] For the other substituents of the benzonitrile, a coordination of the electron deficient base (NaH) with the nonbonding electrons of the substituents F, Cl or $OCH_3$ may occur



This coordination may explain why the methoxy group does not exhibit a + M effect on the benzonitrile, but only a - I effect, which increases the nucleophilic addition on the carbonitrile. When + I effect ($CH_3$) group is used, no benzothiazole is isolated.

## EXPERIMENTAL

Melting points were measured by using a Kofler apparatus and are uncorrected. $^1H$ Nmr spectra were recorded on a Varian EM 360 spectrometer. Mass spectral data were obtained on a VG 70-70F spectrometer. Elemental analysis were performed on a Perkin Elmer 240 apparatus. THF was distilled in the presence of benzophenone and sodium. AT was distilled under reduced pressure and kept under nitrogen. Sodium hydride was a 80% dispersion in mineral oil.

**General procedure** : Sodium hydride (2.40 g, 0.08 mol) in THF (15 ml) was slowly added, under nitrogen, to a solution of freshly distilled AT (2.50 g, 0.02 mol) in THF (50 ml). The mixture was stirred for 15 min at room temperature to yield a pink mixture and then it was warmed to 60°C. The nitrile (0.02 mol) in THF (15 ml) was added dropwise, and the mixture was stirred at 60°C for 3 h, then cooled at 5°C and quenched with aqueous saturated ammonium chloride solution. The organic layer was dried over anhydrous sodium sulfate and evaporated. The product was chromatographed on a silica gel column with toluene as eluent, or it was recrystallised.

**2-(2'-fluorophenyl)benzothiazole (4a) :**

white powder (3.67 g, 80%); mp 80°C (ethanol) (lit.,[11] mp 77-77.5°C).

**2-(3'-fluorophenyl)benzothiazole (4b) :**

white powder (3.65 g, 80%); mp 92°C (methanol) (lit.,[11] mp 90-91°C, lit.,[14] mp 89-90°C).

**2-(4'-fluorophenyl)benzothiazole (4c) :**

white powder (4.03 g, 88%); mp 100°C (methanol) (lit.,[9] mp 102.5-103.5 °C; lit.,[11] mp 99.5-100°C; lit.,[14] mp 99-100°C).

**2-(2'-trifluoromethylphenyl)benzothiazole (4d) :**

pale yellow oil (3.35 g, 60%); $^1H$ nmr ($CDCl_3$) δ : 7.6-6.5 (m); ms m/z (%) : 279 ($M^+$, 100), 260 (9), 108 (33), 69 (27). Anal. Calcd for $C_{14}H_8NSF_3$ : C, 60.21; H, 2.89; N, 5.01. Found : C, 60.12; H, 2.97; N, 5.00

**2-(3'-trifluoromethylphenyl)benzothiazole (4e) :**

white powder (4.52 g, 81%); mp 92°C(methanol) (lit.,[14] mp 90°C).

**2-(4'-trifluoromethylphenyl)benzothiazole (4f) :**

white powder (4.07 g, 73%); mp 161°C (lit.,[14] mp 160-161°C)

**2-(3',5'-difluorophenyl)benzothiazole (4g) :**

white powder (1.97 g, 40%); mp 121°C; $^1H$ nmr ($CDCl_3$) δ : 8.0-7.6 (2 H, m), 7 4-7.1 (4 H, m), 6.8-6.5 (1 H, m). Anal. Calcd for $C_{13}H_7NSF_2$ : C, 63.14; H, 2 85; N, 5.66. Found : C, 63.13; H, 2.96; N, 5.71

**2-(2'-chlorophenyl)benzothiazole (4h) :**

white powder (3.42 g, 70%); mp 86°C (ethanol) (lit.,[2] mp 85-86°C; lit.,[7] mp 81-82°C; lit.,[9] mp 83-84°C).

**2-(3'-chlorophenyl)benzothiazole (4i) :**

white powder (3.80 g, 78%); mp 100°C (ethanol) (lit ,[2] mp 99-100°C; lit.,[9] mp 97 5-99.0°C; lit.,[14] mp 97-98°C).

**2-(4'-chlorophenyl)benzothiazole (4j) :**

white powder (3.75 g, 76%); mp 119°C (ethanol) (lit.,[2] mp 124-125°C; lit.,[7] mp 117-118°C; lit ,[9] mp 120-121°C).

**2-(2'-methoxyphenyl)benzothiazole (4k) :**

white powder (3.13 g, 65%), mp 110°C (lit.,[2] mp 105-106°C).

**2-(3'-methoxyphenyl)benzothiazole (4l) :**

white powder (2.16 g, 45%); mp 84-85°C (lit.,[14] mp 83-84°C).

**2-(4'-methoxyphenyl)benzothiazole (4m) :**

white powder (2.52 g, 52%); mp 125°C (ethanol) (lit.,[2] mp 132°C; lit.,[9] mp 121.5-122 0°C; lit.,[14] mp 122-123°C).

**2-(3',5'-dimethoxyphenyl)benzothiazole (4n) :**

white powder (3 53 g, 65%); mp 88°C; $^1$H nmr ($CDCl_3$) δ : 8 2-7.8 (2 H, m), 7.5-7.1 (4 H, m), 6.7-6.6, (1 H, t), 4.0-3.8 (6H,s) Anal. Calcd for $C_{15}H_{13}NO_2S$ : C, 66.40; H, 4.83, N, 5.16. Found : C, 66.22; H, 4.97; N, 5.11.

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