STUDIES ON ISOCYANIDES. 2-ISOCYANOTHIOANISOLE, A SYNTHETIC EQUIVALENT OF THE BENZOTHIAZOL-2-YL ANION

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Abstract— A synthesis of 2-isocyanothioanisole (**3**) is described. The reaction between **3** and electrophilic reagents took place easily to give 2-functionalized benzothiazoles (**6**).

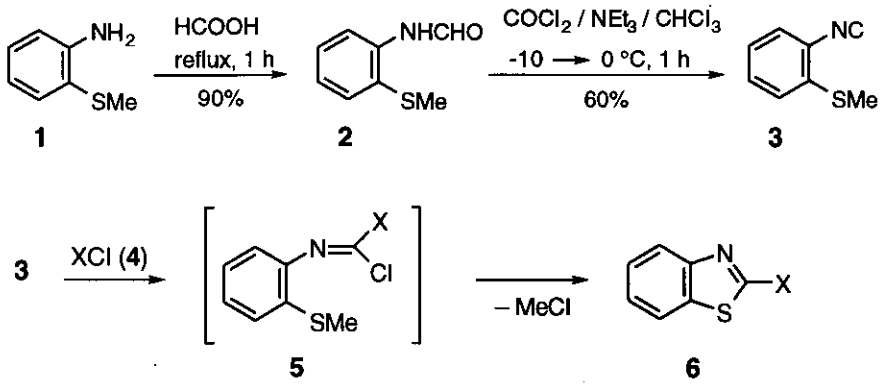
As is well-known the 2-position of the benzothiazole ring has a low electronic density, consequently, the introduction of substituents or functional groups in this position can not be achieved by reacting benzothiazole itself with electrophilic reagents.[1] The synthesis of benzothiazoles bearing functional groups in 2-position is usually accomplished by cyclizing suitable reagents[2] or by nucleophilic displacement on benzothiazoles having good leaving groups in 2-position.[3] Other methods consist in the reaction of electrophiles with benzothiazol-2-yllithium[4,5] or 2-trimethylsilylbenzothiazole.[6]

In the present note we report on an alternative method based on the chemistry of the isocyano group.[7]

Upon heating 2-aminothioanisole (**1**) with formic acid, 2-formylaminothioanisole (**2**) was obtained in high yield. Dehydration of **2** with phosgene/triethylamine afforded 2-isocyanothioanisole (**3**). On prolonged heating compound (**3**) undergoes a decomposition, so, acceptable yields were obtained only by distilling the crude product in small portions. The distilled product can be stored at –50 °C for 3–4 weeks without appreciable decomposition.

2-Isocyanothioanisole appears to be a starting product for the synthesis of 2-functionalized benzothiazoles.

In fact the reaction of **3** with arenesulfenyl chlorides (**4a,b**) and acid chlorides (**4c,d**) took place under mild conditions to give, in almost quantitative yields, 2-arylthiobenzothiazoles (**6a,b**) and 2-acylbenzothiazoles (**6c,d**), respectively. The elimination of chloromethane from the adducts (**5**) took place very quickly and attempts to perform their isolation failed.



4, 5, 6 **a** X = 2-$NO_2C_6H_4S$; **b** X = 2-NO_2-4Cl-C_6H_3S; **c** X = MeCO; **d** X = EtCO

EXPERIMENTAL

2-Aminothioanisole (**1**),[8] 2-nitrobenzenesulfenyl chloride (**4a**),[9] and 4-chloro-2-nitrobenzenesulfenyl chloride (**4b**)[10] were prepared following literature procedures. All the other chemicals were obtained commercially. Infrared spectra were recorded on a Perkin-Elmer 881 spectrophotometer. ^{1}H Nmr spectra were recorded on a Varian Gemini 200 apparatus. Microanalyses were obtained using a Perkin-Elmer 240 Elemental Analyzer. Melting points were obtained in open capillary tubes using a Büchi 512 apparatus and are uncorrected.

2-Formylaminothioanisole (2).

A mixture of 2-aminothioanisole (**1**) (27.87 g, 0.2 mol) and formic acid (100 ml, 2.65 mol) was refluxed for 1 h and then evaporated to dryness under reduced pressure. The residue was stirred with chloroform (100 ml) and saturated aq., 7.8% $NaHCO_3$ until the effervescence ceased. The aqueous layer was discarded and the organic phase was washed with water, separated, and then dried with $CaCl_2$. Removal of the solvent left a glass-like residue which solidified upon stirring with petroleum ether (40-70 °C) to give **2** (30.15 g, 90%): mp 52– 53 °C (*i*-Pr_2O); lit.,[11] 52-54 °C, lit.,[12] 53-54 °C.

2-Isocyanothioanisole (3).

A well-stirred solution of **2** (20.07 g, 0.12 mol) and triethylamine (24.29 g, 0.24 mol) in dry chloroform (150 ml) was treated dropwise with phosgene (11.87 g, 0.12 mol) in toluene (a 20% solution available from Fluka was employed), maintaining the temperature at -10 °C. The reaction mixture was allowed to react, without removing the cooling bath, until the temperature rose to 0 °C, and then treated with water (80 ml). The organic layer was separated, dried over Na_2SO_4, and then evaporated to dryness (bath temperature 35 °C). The resulting residue was distilled in three portions to give **3** (10.76 g, 60%): bp 100 °C / 0.3 Torr.; ir (film) ν 2125 cm^{-1}.

Anal. Calcd for C_8H_7NS: C, 64.40; H, 4.73; N, 9.39. Found: C, 64.72; H, 4.58; N, 9.21.

2-(2-Nitrophenylthio)benzothiazole (6a).

A solution of 2-nitrobenzenesulfenyl chloride (**2a**) (1.27 g, 6.7 mmol) in dichloromethane (10 ml) was added dropwise to a well-stirred solution of **3** (1.0 g, 6.7 mmol) in dichloromethane (10 ml), maintaining the temperature at –50 °C. The reaction mixture was allowed to react, without removing the cooling bath, until the temperature rose to 10 °C. Removal of the solvent left **6a** in almost quantitative yield: mp 106-107 °C (EtOH); ^1H nmr (200 MHz, $CDCl_3$) δ, ppm 7.26–8.24 (8 H, m); ir (KBr) ν 1514, 1337 cm^{-1}.

Anal. Calcd for $C_{13}H_8N_2O_2S_2$: C, 54.15; H, 2.80; N, 9.72. Found: C, 54.01; H, 3.07; N, 9.98.

2-(4-Chloro-2-nitrophenylthio)benzothiazole (6b).

This compound was obtained in almost quantitative yields following the above procedure, except that 4-chloro-2-nitrobenzenesulfenyl chloride (**4b**) was employed in place of **4a**; mp 136–137 °C (EtOH/DMF); ^1H nmr (200 MHz, $CDCl_3$) δ, ppm 7.39–8.21 (7 H, m); ir (KBr) ν 1518, 1333, 750 cm^{-1}.

Anal. Calcd for $C_{13}H_7N_2O_2ClS_2$: C, 48.38; H, 2.19; N, 8.68. Found: C, 48.59; H, 2.37; N, 8.61.

2-Acetylbenzothiazole (6c).

Compound (**3**) (2.58 g, 17.3 mmol) was added dropwise, under vigorous stirring, to acetyl chloride (**4c**) (10 ml, 0.14 mol), maintaining the temperature at 0 °C. The resulting mixture was stirred at 0 °C for 2 h and then at room temperature for 20 h. Removal of the solvent left a residue which was stirred with benzene (30 ml). The resulting mixture was evaporated to dryness again to give **6c** (2.87 g, 97%): mp 109–110 °C (*i*-PrOH); lit.,[13] 112 °C.

2-Propionylbenzothiazole (6d).

This compound was obtained in almost quantitative yields following the above procedure, except that propionyl chloride (**4d**) was used in place of **4c**; mp 74-75 °C (*i*-PrOH); lit.,[5] 76-77 °C.

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