

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

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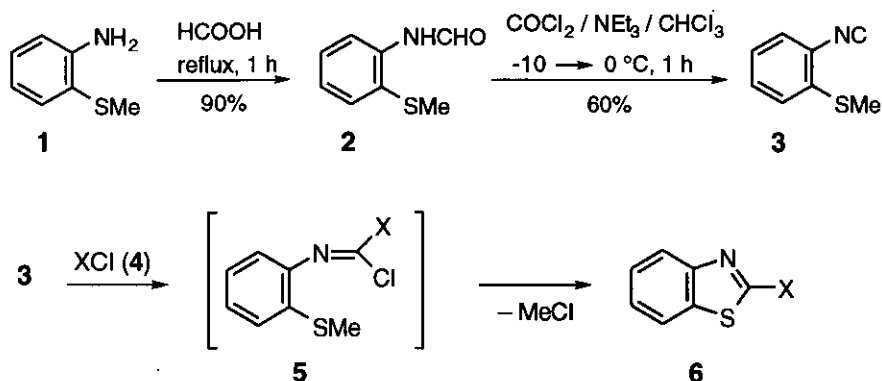
Abstract— A synthesis of 2-isocyanothioanisole (**3**) is described. The reaction between **3** and electrophilic reagents took place easily to give 2-functionalized benzothiazoles (**6**).

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 reagents² 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-yl lithium^{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 arenesulfonyl 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-NO₂C₆H₄S; **b** X = 2-NO₂-4Cl-C₆H₃S; **c** X = MeCO; **d** X = EtCO

EXPERIMENTAL

2-Aminothioanisole (**1**),⁸ 2-nitrobenzenesulfonyl chloride (**4a**),⁹ and 4-chloro-2-nitrobenzenesulfonyl 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. ¹H 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% NaHCO₃ until the effervescence ceased. The aqueous layer was discarded and the organic phase was washed with water, separated, and then dried with CaCl₂. 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*-Pr₂O); 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 Na₂SO₄, 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 C₈H₇NS: 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-nitrobenzenesulfonyl 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, CDCl₃) δ , ppm 7.26-8.24 (8 H, m); ir (KBr) ν 1514, 1337 cm⁻¹.

Anal. Calcd for C₁₃H₈N₂O₂S₂: 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-nitrobenzenesulfonyl chloride (**4b**) was employed in place of **4a**; mp 136-137 °C (EtOH/DMF); ¹H nmr (200 MHz, CDCl₃) δ , ppm 7.39-8.21 (7 H, m); ir (KBr) ν 1518, 1333, 750 cm⁻¹.

Anal. Calcd for C₁₃H₇N₂O₂ClS₂: 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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REFERENCES

1. J. V. Metzger, 'Comprehensive Heterocyclic Chemistry', Vol. 6, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, p. 255.
2. J. V. Metzger, 'Comprehensive Heterocyclic Chemistry', Vol. 6, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, p. 321.
3. J. V. Metzger, 'Comprehensive Heterocyclic Chemistry', Vol. 6, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, p. 291.
4. H. Gilman and J. A. Beel, *J. Am. Chem. Soc.*, 1949, **71**, 2328.
5. H. Chikashita, M. Ishibaba, K. Ori, and K. Itoh, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 3637.
6. F. H. Pinkerton and S. F. Thames, *J. Heterocycl. Chem.*, 1971, **9**, 257.
7. See for example: C. Grundmann, 'Houben-Weyl: Carbonsäuren und Carbonsäure-Derivate', Vol. E5, Part 2, ed. by J. Falbe, Georg Thieme Verlag, Stuttgart, 1985, s. 1648. P. Hoffmann, D. Marquarding, H. Kliemann, and I. Ugi, 'The Chemistry of the Cyano Group', ed. by S. Patai, Interscience Publishers, London - New York - Sydney - Toronto, 1971, p. 860. S. Marcaccini and T. Torroba, *Org. Prep. Proced. Int.*, 1993, **25**, 141.
8. S. E. Livingstone, *J. Chem. Soc.*, 1956, 437.
9. M. H. Hubacher, *Org. Synth., Coll. Vol. II*, 1943, 455.
10. T. Zincke, *Liebigs Ann. Chem.*, 1918, **416**, 86
11. L. Di Nunno and A. Scilimati, *Tetrahedron*, 1986, **42**, 3913.
12. G. Tobias, *Ber.*, 1882, **15**, 2443.
13. V. M. Zubarovsky, *Zhur. Obshchei Khim.*, 1951, **21**, 2199 (*Chem. Abstr.*, 1952, **46**, 8098g).