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Short Note

5,5′-Thiobis(3-bromoisothiazole-4-carbonitrile)

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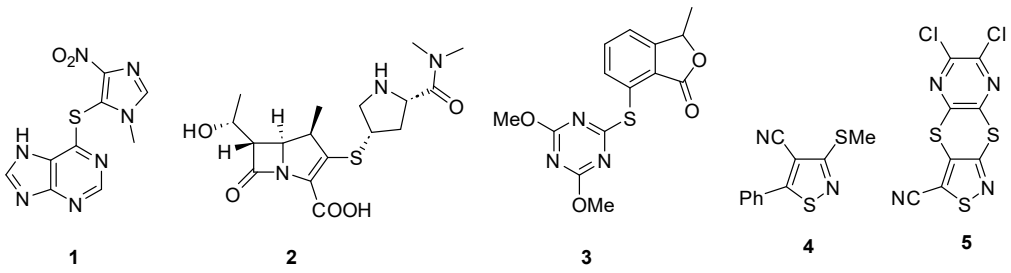
Abstract: The reaction of sodium 2,2-dicyanoethene-1,1-bis(thiolate) with bromine (2 equiv.) in CCl_4 gave 3,5-dibromoisothiazole-3-carbonitrile and 5,5′-thiobis(3-bromoisothiazole-4-carbonitrile) in 7% and 18% yields, respectively. The latter novel compound was fully characterized.

Keywords: heterocycle; isothiazole; polyfunctionalized

1. Introduction

Heterocycle sulfides are a particularly important group of compounds with numerous examples of biologically useful compounds such as the immunosuppressant Azathioprine **1** [1–3], the antibacterial drug meropenem **2** [4–6] and the herbicide pyriftalid **3** [7–9] (Figure 1). Focusing on isothiazole sulfides, there are several examples of biologically useful compounds such as the 4-cyanoisothiazole **4** that has shown antiviral activity against polio [10–12] and dithiine **5** which is active as an antifungal agent [13] (Figure 1).



1 **2** **3** **4** **5**

Figure 1. Biologically active isothiazole carbonitriles.

Isothiazoles are five-membered heterocycles that have found uses as agrochemicals [14], pharmaceuticals [15] and dyes [16]. Their applications, chemistry and synthesis have been reviewed [17–19]. Examples of biologically useful isothiazoles are the fungicide isotianil (Stout®) [20,21], active against rice blast, and the antibacterial drug sulfasomizole [22,23].

Our interest in isothiazoles focuses on their preparation from 1,2,3-dithiazoles **6** by treatment with gaseous HCl or HBr [24,25] (Scheme 1), halide or alkylamines [26]. Moreover, we were interested in the investigation of the chemistry of halo and cyano-substituted isothiazoles. Halogen atoms in the C-5 position were substituted by carbon nucleophiles in Suzuki [27], Stille and Sonogashira couplings [28] (Scheme 1), while the coupling chemistry of the C-3 [28] and later the C-4 positions [29] was also investigated. Interestingly, the isothiazole C-4 cyano group has been converted to a bromo group via a Hunsdiecker strategy or to an iodo group via a Hoffmann and Sandmeyer strategy [29].

An important isothiazole scaffold that we required in the course of our investigations is 3,5-dibromoisothiazole-3-carbonitrile (**8b**) (Scheme 1). The synthesis of this highly functionalized isothiazole that offers many options for functional group modifications is reported in the literature [30,31].

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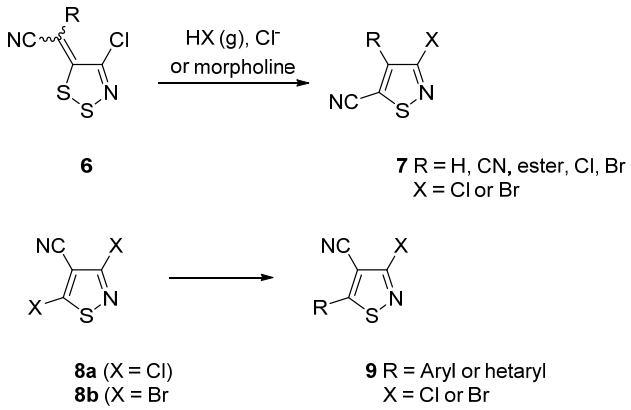


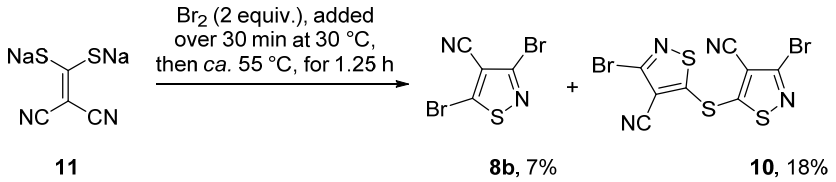
Scheme 1. Route to isothiazole-5-carbonitriles **7** from dithiazoles **6** and coupling chemistry of 3-haloisothiazoles **8**.

Herein, we report our findings in performing this reaction that led to the isolation of 5,5′-thiobis(3-bromoisothiazole-4-carbonitrile) (**10**). The formation of this compound through the treatment of 3,5-dibromoisothiazole-4-carbonitrile with sodium thiocyanate is mentioned in the patent literature [31], but no yield or characterization data are described.

The preparation of sulfide **10** differs from most reported methods of preparation of isothiazole sulfides that commonly involve the nucleophilic aromatic substitution of halo-isothiazoles with thiols [32] or palladium-catalyzed C-S coupling [33].

2. Results and Discussion

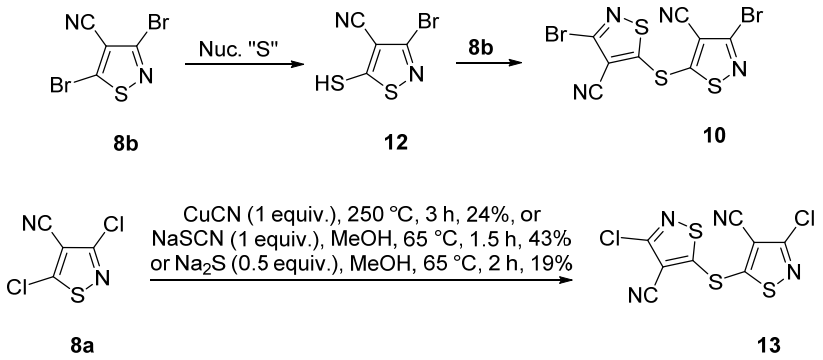
The reaction of sodium 2,2-dicyanoethene-1,1-bis(thiolate) (**11**) with bromine (2 equiv.) in CCl_4 at ca. 55 °C, by a modification of the reported method [30,31] gave, after workup and chromatography, 3,5-dibromoisothiazole-4-carbonitrile (**8b**) and 5,5′-thiobis(3-bromoisothiazole-4-carbonitrile) (**10**) in 7% and 18% yields, respectively (Scheme 2).



Scheme 2. Synthesis of 5,5′-thiobis(3-bromoisothiazole-4-carbonitrile) (**10**).

Product **10** was isolated as yellow plates, mp 141–142 °C (from PhH). UV-vis spectroscopy in dichloromethane supported an intact isothiazole ring [λ_{max}(DCM) 279 nm, log ε 4.18], while FTIR spectroscopy showed the presence of a ν(C≡N) stretch at 2334 cm^{-1}. Mass spectrometry revealed a molecular ion (MH^+) peak of m/z 407 (38%) along with a MH^+ + 2 isotope peak at 408 (85%) and a MH^+ + 4 at 411 (54%) that supported the presence of two bromine atoms. ^{13}C NMR spectroscopy showed the presence of four quaternary carbon resonances (see Supplementary Information), while a correct elemental analysis (CHN) was obtained for the molecular formula $C_8Br_2N_4S_3$. The multifunctional nature of isothiazole **10** makes it a potentially useful synthetic scaffold.

Mechanistically, we attribute the formation of sulfide **10** to a reaction of product **8b** with a source of nucleophilic sulfur. The initial displacement of the 5-bromide should lead to 3-bromo-5-mercaptoisothiazole-4-carbonitrile **12**, which could condense with another molecule of isothiazole **8b** to yield product **10** (Scheme 3). Interestingly, sulfide **13**, which is the chloro analogue of sulfide **10**, can be prepared by the reaction of 3,5-dichloroisothiazole-4-carbonitrile **8a** with either CuCN (1 equiv.), NaSCN (1 equiv.) or Na_2S (0.5 equiv.) [34] (Scheme 3). In the latter two methods, it is clear that nucleophilic sulfur is involved similarly to our proposal for the formation of sulfide **10**.



Scheme 3. Origins of sulfide **10** and reported syntheses of 5,5′-thiobis(3-chloroisothiazole-4-carbonitrile) (**13**).

3. Materials and Methods

The reaction mixture was monitored by TLC using commercial glass-backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The melting point was determined using a PolyTherm-A, Wagner & Munz, Kofler—Hotstage Microscope apparatus (Wagner & Munz, Munich, Germany). The solvent used for recrystallization is indicated after the melting point. The UV-vis spectrum was obtained using a Perkin-Elmer Lambda-25 UV-vis spectrophotometer (Perkin-Elmer, Waltham, MA, USA) and inflections are identified by the abbreviation "inf". The IR spectrum was recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer (Shimadzu, Kyoto, Japan) with Pike Miracle Ge ATR accessory (Pike Miracle, Madison, WI, USA), and strong, medium and weak peaks are represented by s, m and w, respectively. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 machine [at 500 and 125 MHz, respectively, (Bruker, Billerica, MA, USA)]. Deuterated solvents were used for homonuclear lock and the signals were referred to with the deuterated solvent peaks. Attached proton test (APT) NMR studies were used for the assignment of the ^{13}C peaks as *C*H$_3$, *C*H$_2$, *C*H and *C*q (quaternary). MALDI-TOF mass spectra were recorded on a Bruker Autoflex III Smartbeam instrument. Sodium 2,2-dicyanoethene-1,1-bis(thiolate) (**11**) [30] was prepared according to the literature procedure.

*5,5′-Thiobis(3-bromoisothiazole-4-carbonitrile) (**10**)*

A suspension of sodium 2,2-dicyanoethene-1,1-bis(thiolate) (**11**) (223.3 g, 1.20 mol) in CCl_4 (2.4 L) in a 5 L round bottom flask fitted with a mechanical stirrer, thermometer and condenser was added dropwise to bromine (123 mL, 2.40 mol) under stirring over 30 min. The temperature of the mixture rose to ca. 30 °C during the addition. The mixture was then heated in a heating mantle to ca. 55 °C and stirred for a further 1.25 h. The mixture was then filtered through a pad of silica to remove insoluble matter and washed with DCM (a total of 2 L); the filtrate was then adsorbed onto silica and chromatographed (*n*-hexane/DCM, 80:20) to give 3,5-dibromoisothiazole-4-carbonitrile (**8b**) (23.16 g, 7%) as colorless needles, mp 98–99 °C (sublimed, lit. [28] 98–98.5 °C); R_f 0.28 (*n*-hexane/DCM, 80:20); υ_{max}/cm^{-1} 2232m (C≡N), 1488s, 1369m, 1351w, 1313s, 1207w, 1071m, 965m, 955m, 935w, 912w, 803s, 766m, identical to the one reported [30]. A further elution (*n*-hexane/DCM, 50:50) gave the *title compound* **10** (44.87 g, 18%) as yellow plates, mp 141–142 °C, (from PhH); R_f 0.33 (*n*-hexane/DCM, 50:50); (found: C, 23.31; H, 0; N, 13.58. $C_8Br_2N_4S_3$ requires C, 23.54; H, 0; N, 13.73%); λ_{max}(DCM)/nm 230 (4.01), 279 (4.18), 319 inf (3.41); υ_{max}/cm^{-1} 2234m (C≡N), 1478m, 1346w, 1319s, 1086m, 949m, 937m, 824m, 812s; δ_C(125 MHz; $CDCl_3$) 163.3 (Cq), 140.2 (Cq), 116.7 (Cq), 109.8 (Cq); *m*/*z* (MALDI-TOF) 411 (MH$^+$ + 4, 54%), 409 (MH$^+$ + 2, 85), 407 (MH$^+$, 38), 402 (64), 329 (M-Br + 2, 100), 327 (M-Br, 63).

Supplementary Materials: The following supporting information can be downloaded online: mol file, ^{13}C NMR and IR spectra.

Author Contributions: A.S.K. and P.A.K. conceived the experiments; A.S.K. designed the experiments; A.S.K. wrote the paper; A.S.K. and P.A.K. edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Data are contained within the article and Supplementary Materials.

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Conflicts of Interest: The authors declare no conflicts of interest.

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