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Short Note

5,5′-Thiobis(3-methoxy-4*H*-1,2,6-thiadiazin-4-one)

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Abstract: The reaction of 3-chloro-5-methoxy-4*H*-1,2,6-thiadiazin-4-one (**9**) with $Na_2S{\cdot}9H_2O$ (0.5 equiv) in tetrahydrofuran (THF) at ca. 20 °C for 20 h gives 5,5′-thiobis(3-methoxy-4*H*-1,2,6-thiadiazin-4-one) (**10**) in a 44% yield as yellow needles. The compound was fully characterized.

Keywords: heterocycle; 1,2,6-thiadiazine; sulfide; nucleophilic displacement

1. Introduction

4*H*-1,2,6-thiadiazines are a class of heterocycles that do not occur in nature but have interesting applications: some 5-substituted 3-chloro-4*H*-1,2,6-thiadiazines show plant antifungal activity [1–5], while others display liquid crystalline or near-infrared dye behavior [6,7]. Moreover, certain 4*H*-1,2,6-thiadiazines were proposed to be precursors to radical anions for organic magnetic and conducting materials [8]. π-conjugated polymers of 1,2,6-thiadiazines were proposed by both Woodward [9] and Rees [10–12] as potentially stable substitutes to the superconductor poly(sulfur nitride) $(SN)_x$. Recently, 4*H*-1,2,6-thiadiazines were characterized by resonance Raman (RR), absorption (UV-vis) and photoluminescence (PL) spectroscopies in order to better understand their optical properties [13]. Amino-substituted 1,2,6-thiadiazinones were shown to behave as narrow spectrum calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2) inhibitors [14], demonstrating potential applications of the system in medicinal chemistry. A recent review describes the chemistry of non-S oxidized 1,2,6-thiadiazines [15].

As part of our ongoing interest with 1,2,6-thiadiazines, we investigated the synthesis of a thioamide functional group onto the 1,2,6-thiadiazine ring. Thioamide-containing azaarenes including pyridines and pyrimidines have numerous uses in medicinal chemistry. For example, pyridine **1** was a weak AChE inhibitor [16], pyridine **2** was investigated as a metaloenzyme inhibitor [17], while pyridine **3** is a reverse transcriptase inhibitor and is useful as an anti-HIV agent [18] (Figure 1).

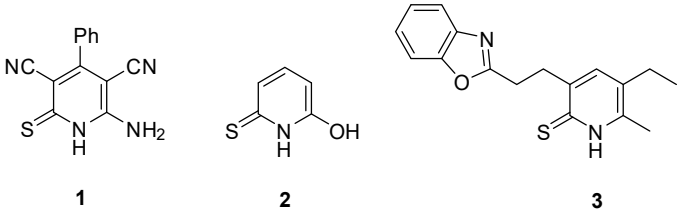
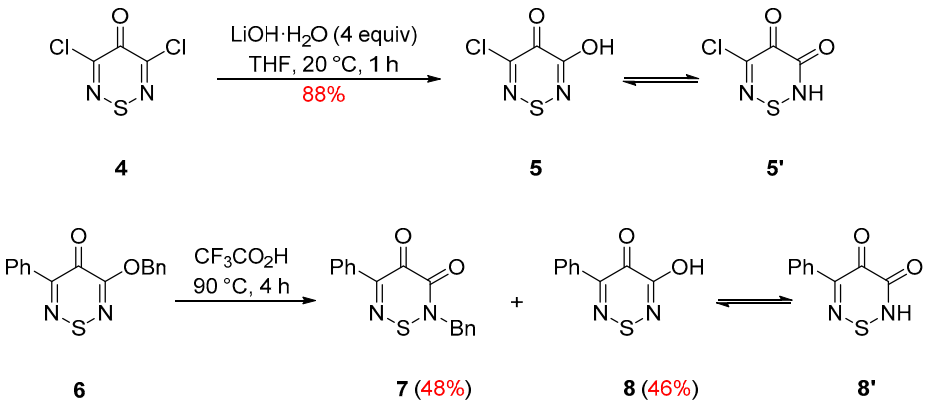


Figure 1. Biologically active thioamide-containing azaarenes.

1,2,6-thiadiazines could act as isosters to other 6-membered hetarenes; therefore, the formation of a thioamide onto the thiadiazine could offer a new scaffold for the synthesis of biologically active molecules. Some related amide-containing thiadiazines have been prepared, such as thiadiazinone **5**,

which can exist in the tautomeric form **5′** by the displacement of the C-5 chloride of dichlorothiadiazinone **4** with hydroxide [19] (Scheme 1). Moreover, an attempt to deprotect benzyloxy derivative **6** led to the benzyl group migration to the N-2 position, yielding amide **7** along with the deprotected thiadiazine **8′** [20] (Scheme 1).

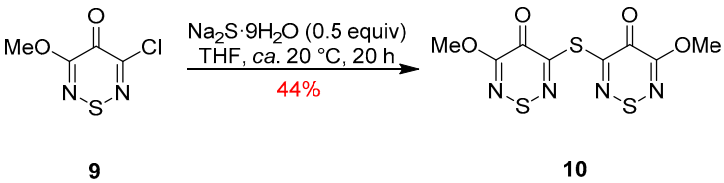


Scheme 1. Synthesis of amide-containing thiadiazines.

2. Results and Discussion

The above reactions showing the displacement of the C-5 chloride of dichlorothiadiazinone **4** with hydroxide [19], or other oxygen nucleophiles [15], prompted us to investigate the use of sulfide as a nucleophile that could afford the desired thiadiazine–thioamide. It is worthy of note that 3-chloro-1,2,6-thiadiazines are prone to ring-opening reactions in the presence of thiophilic reagents such as phosphines, halides and nucleophilic sulfur [15].

We chose 3-chloro-5-methoxy-4*H*-1,2,6-thiadiazin-4-one (**9**) as the starting material, as the electron donating ability of the methoxy group should make the ring sulfur less prone to thiophilic attack, while the methoxy group also acted as a protecting group to avoid the formation of oligomers or polymers. Methoxy-substituted thiadiazines can readily be transformed to analogous triflates [20]. In our efforts, we failed to obtain the desired thioamide; however, from the reaction of thiadiazine **9** with Na_2S in THF at ca. 20 °C, we isolated 5,5′-thiobis(3-methoxy-4*H*-1,2,6-thiadiazin-4-one) (**10**) as the only product in a 44% yield (Scheme 2, see Supplementary Materials for NMR spectra). This compound represents the first non-S-oxidized bis-1,2,6-thiadiazine sulfide. Moreover, compound **10** itself is a new chemotype with potential value in the medicinal chemistry sector. Several drugs contain heterocyclic sulfide moieties; e.g., the immunosuppressive Azathioprine.



Scheme 2. Synthesis of 5,5′-thiobis(3-methoxy-4*H*-1,2,6-thiadiazin-4-one) (**10**).

This study shows that thiadiazine sulfides can be readily synthesized, which can open up the investigation of their chemistry and properties.

3. Materials and Methods

The reaction mixture was monitored by thin layer chromatography (TLC) using commercial glass-backed TLC plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. Tetrahydrofuran (THF) was distilled over CaH_2 before use. 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 the 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 are referenced to the deuterated solvent peaks. Attached proton test (APT) NMR studies identified carbon multiplicities, which are indicated by (s), (d), (t) and (q) notations. The MALDI-TOF mass spectrum (+ve mode) was recorded on a Bruker Autoflex III Smartbeam instrument (Bruker). The elemental analysis was run by the London Metropolitan University Elemental Analysis Service. 3-chloro-5-methoxy-4*H*-1,2,6-thiadiazin-4-one (**9**) was prepared according to the procedure in the literature [21].

5,5′-Thiobis(3-methoxy-4H-1,2,6-thiadiazin-4-one) (**10**)

One portion of $Na_2S{\cdot}9H_2O$ (60.1 mg, 0.25 mmol) was added to a stirred mixture of 3-chloro-5-methoxy-4*H*-1,2,6-thiadiazin-4-one (**9**) (89.3 mg, 0.500 mmol) in THF (5 mL) at ca. 20 °C. The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until the complete consumption of the starting material (TLC, 20 h). Dichloromethane (DCM, 10 mL) was then added and the mixture adsorbed onto silica, and chromatography (*n*-hexane/*t*-BuOMe 50:50) gave the title compound **10** (35 mg, 44%) as yellow needles, mp 147–149 °C (from *c*-hexane); R_f 0.25 (*n*-hexane/*t*-BuOMe, 50:50); (found: C, 30.26; H, 1.92; N, 17.71. $C_8H_6N_4O_4S_3$ requires C, 30.18; H, 1.90; N, 17.60%); λ_{max}(DCM)/nm 304 (log ε 4.15), 362 (4.24); υ_{max}/cm^{-1} 2936 w (C-H), 1659 m, 1624 s, 1541 m, 1520 m, 1481 w, 1456 w, 1443 w, 1339 s, 1227 m, 1217 m, 1204 m, 1078 w, 991 s, 949 m, 914 w, 870 w, 833 m, 800 m, 791 m; δ_H(500 MHz; $CDCl_3$) 4.00 (3H, s, OCH_3); δ_C(125 MHz; $CDCl_3$) 158.9 (s), 156.1 (s), 155.0 (s), 55.0 (q); *m*/*z* (MALDI-TOF) 319 (MH^+, 100%), 318 (M^+, 22), 301 (59), 286 (57), 273 (42), 261 (49), 232 (48), 212 (67), 143 (48).

Supplementary Materials: The following are available online at http://www.mdpi.com/1422-8599/2019/2/M1064/s1, mol file, ^{1}H and ^{13}C NMR spectra.

Author Contributions: P.A.K. Koutentis conceived the experiments; A.S.K. Kalogirou designed and performed the experiments, analyzed the data and wrote the paper.

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Conflicts of Interest: The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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