


Short Note

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

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Received: 23 May 2019; Accepted: 8 June 2019; Published: 9 June 2019



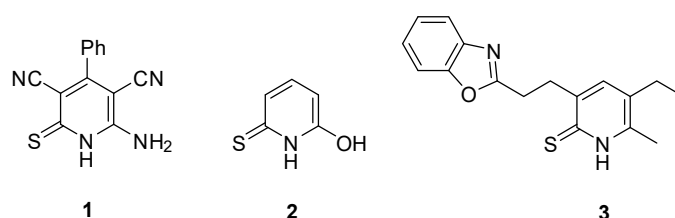
**Abstract:** The reaction of 3-chloro-5-methoxy-4*H*-1,2,6-thiadiazin-4-one (**9**) with Na<sub>2</sub>S·9H<sub>2</sub>O (0.5 equiv) in tetrahydrofuran (THF) at ca. 20 °C for 20 h gives 5,5'-thiobis(3-methoxy-4*H*-1,2,6-thiadiazin-4-one) (**10**) in a 44% yield as yellow needles. The compound was fully 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].  $\pi$ -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)<sub>x</sub>. 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].

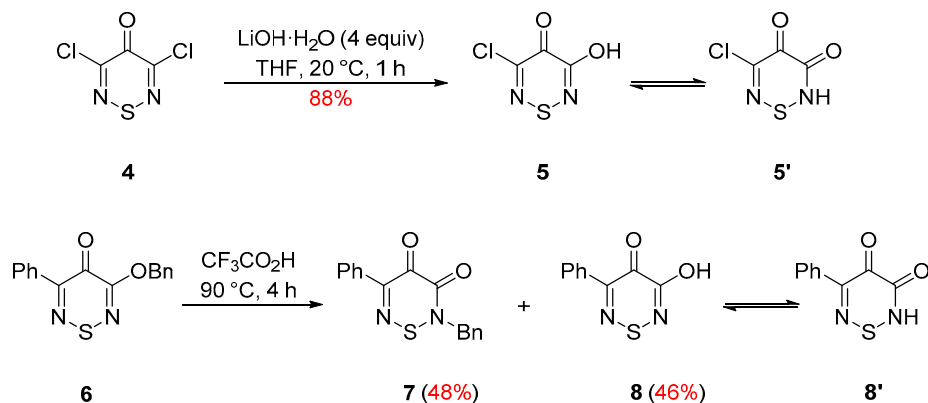
As part of our ongoing interest with 1,2,6-thiadiazines, we investigated the synthesis of a thioamide functional group onto the 1,2,6-thiadiazine ring. Thioamide-containing azaarenes including pyridines and pyrimidines have numerous uses in medicinal chemistry. For example, pyridine **1** was a weak AChE inhibitor [16], pyridine **2** was investigated as a metalloenzyme 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).

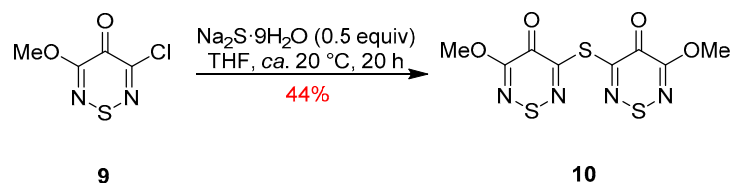


**Scheme 1.** Synthesis of amide-containing thiadiazines.

## 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<sub>2</sub>S 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<sub>254</sub>). The plates were observed under UV light at 254 and 365 nm. Tetrahydrofuran (THF) was distilled over CaH<sub>2</sub> 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.  $^1\text{H}$  and  $^{13}\text{C}$  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-4*H*-1,2,6-thiadiazin-4-one) (**10**)

One portion of  $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$  (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  $\text{CaCl}_2$  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.  $\text{C}_8\text{H}_6\text{N}_4\text{O}_4\text{S}_3$  requires C, 30.18; H, 1.90; N, 17.60%);  $\lambda_{\text{max}}$ (DCM)/nm 304 (log  $\epsilon$  4.15), 362 (4.24);  $\nu_{\text{max}}/\text{cm}^{-1}$  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*;  $\delta_{\text{H}}$ (500 MHz;  $\text{CDCl}_3$ ) 4.00 (3H, *s*,  $\text{OCH}_3$ );  $\delta_{\text{C}}$ (125 MHz;  $\text{CDCl}_3$ ) 158.9 (*s*), 156.1 (*s*), 155.0 (*s*), 55.0 (*q*); *m/z* (MALDI-TOF) 319 ( $\text{MH}^+$ , 100%), 318 ( $\text{M}^+$ , 22), 301 (59), 286 (57), 273 (42), 261 (49), 232 (48), 212 (67), 143 (48).

**Supplementary Materials:** The following are available online, mol file,  $^1\text{H}$  and  $^{13}\text{C}$  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.

**Funding:** This research was funded by the Cyprus Research Promotion Foundation (Grants: ΣTPATHII/0308/06, NEKYP/0308/02 ΥΤΕΙΑ/0506/19 and ENΙΣΧ/0308/83).

**Acknowledgments:** The authors thank the following organizations and companies in Cyprus for generous donations of chemicals and glassware: the State General Laboratory, the Agricultural Research Institute, the Ministry of Agriculture, MedoChemie Ltd., Medisell Ltd. and Biotronics Ltd. Furthermore, we thank the A. G. Leventis Foundation for helping to establish the NMR facility at the University of Cyprus.

**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.

## References

1. Peake, C.J.; Harnish, W.N.; Davidson, B.L. Mono-5-substituted-3-chloro-4*H*-1,2,6-thiadiazin-4-one antifungal agents. U.S. Patent 4,097,594A, 27 June 1978.
2. Peake, C.J.; Harnish, W.N.; Davidson, B.L. Mono-5-substituted-thio-3-chloro-4*H*-1,2,6-thiadiazin-4-one antifungal agents. U.S. Patent 4,100,281A, 27 June 1978.
3. Peake, C.J.; Harnish, W.N.; Davidson, B.L. 3-Chloro-5-(optionally substituted heterocycloxy)-4*H*-1,2,6-thiadiazin-4-one antifungal agents. U.S. Patent 4,143,138, 3 March 1979.
4. Peake, C.J.; Harnish, W.N.; Davidson, B.L. Mono-5-substituted-3-chloro-4*H*-1,2,6-thiadiazin-4-one antifungal agents. U.S. Patent 4,201,780, 6 May 1980.

5. Portnoy, R.C. Thiadiazinone Plant Disease Control Agents. U.S. Patent 4,497,807A, 5 February 1985.
6. Gómez, T.; Macho, S.; Miguel, D.; Neo, A.G.; Rodríguez, T.; Torroba, T. Cyclopentathiadiazines, Cyclohepta- and Cyclopentadithiazoles: New Materials and a Rich Heterocyclic Chemistry of Cyclic Enaminonitriles. *Eur. J. Org. Chem.* **2005**, 5055–5066. [[CrossRef](#)]
7. Macho, S.; Miguel, D.; Neo, A.G.; Rodríguez, T.; Torroba, T. Cyclopentathiadiazines, new heterocyclic materials from cyclic Enaminonitriles. *Chem. Commun.* **2005**, 334–336. [[CrossRef](#)] [[PubMed](#)]
8. Lonchakov, A.V.; Rakitin, O.A.; Gritsan, N.P.; Zibarev, A.V. Breathing Some New Life into an Old Topic: Chalcogen-Nitrogen  $\pi$ -Heterocycles as Electron Acceptors. *Molecules* **2013**, *18*, 9850–9900. [[CrossRef](#)] [[PubMed](#)]
9. Cava, M.P.; Lakshmikantham, M.V.; Hoffmann, R.; Williams, R.M.R.B. Woodward's unfinished symphony: Designing organic superconductors (1975–79). *Tetrahedron* **2011**, *67*, 6771–6797. [[CrossRef](#)]
10. Koutentis, P.A.; Rees, C.W.; White, A.J.P.; Williams, D.J. Reaction of tetracyanoethylene with  $\text{SCl}_2$ ; new molecular rearrangements. *Chem. Commun.* **2000**, 303–304. [[CrossRef](#)]
11. Koutentis, P.A.; Rees, C.W. Reaction of tetracyanoethylene with  $\text{SCl}_2$ ; new molecular rearrangements. *J. Chem. Soc. Perkin Trans. 1* **2000**, 1089–1094. [[CrossRef](#)]
12. Koutentis, P.A.; Rees, C.W. Cyclisation chemistry of 4*H*-1,2,6-thiadiazines. *J. Chem. Soc. Perkin Trans. 1* **2000**, 2601–2607. [[CrossRef](#)]
13. Theodorou, E.; Ioannidou, H.A.; Ioannou, T.A.; Kalogirou, A.S.; Constantinides, C.P.; Manoli, M.; Koutentis, P.A.; Hayes, S.C. Spectroscopic characterization of C-4 substituted 3,5-dichloro-4*H*-1,2,6-thiadiazines. *RSC Adv.* **2015**, *51*, 18471–18481. [[CrossRef](#)]
14. Asquith, C.R.M.; Godoi, P.H.; Couñago, R.M.; Laitinen, T.; Scott, J.W.; Langendorf, C.G.; Oakhill, J.S.; Drewry, D.H.; Zuercher, W.J.; Koutentis, P.A.; et al. 1,2,6-Thiadiazinones as Novel Narrow Spectrum Calcium/Calmodulin-Dependent Protein Kinase Kinase 2 (CaMKK2) Inhibitors. *Molecules* **2018**, *23*, 1221. [[CrossRef](#)] [[PubMed](#)]
15. Kalogirou, A.S.; Koutentis, P.A. The chemistry of non-S-oxidised 4*H*-1,2,6-thiadiazines. *Targets Heterocycl. Syst.* **2018**, *22*, 82–118. [[CrossRef](#)]
16. Samadi, A.; Marco-Contelles, J.; Soriano, E.; Álvarez-Pérez, M.; Chioua, M.; Romero, A.; González-Lafuente, L.; Gandía, L.; Roda, J.M.; López, M.G.; et al. Multipotent drugs with cholinergic and neuroprotective properties for the treatment of Alzheimer and neuronal vascular diseases. I. Synthesis, biological assessment, and molecular modeling of simple and readily available 2-aminopyridine-, and 2-chloropyridine-3,5-dicarbonitriles. *Bioorg. Med. Chem.* **2010**, *18*, 5861–5872. [[CrossRef](#)] [[PubMed](#)]
17. Adamek, R.N.; Credille, C.V.; Dick, B.L.; Cohen, S.M. Isosteres of hydroxypyridinethione as drug-like pharmacophores for metalloenzyme inhibition. *J. Biol. Inorg. Chem.* **2018**, *23*, 1129–1138. [[CrossRef](#)] [[PubMed](#)]
18. Hoffman, J.M.; Smith, A.M.; Rooney, C.S.; Fisher, T.E.; Wai, J.S.; Thomas, C.M.; Bamberger, D.L.; Barnes, J.L.; Williams, T.M.; Jones, J.H.; et al. Synthesis and Evaluation of 2-Pyridinone Derivatives as HIV-1-Specific Reverse Transcriptase Inhibitors. 3-[2-(Benzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2(1*fl*)-one and Analogues. *J. Med. Chem.* **1993**, *36*, 953–966. [[CrossRef](#)] [[PubMed](#)]
19. Ioannidou, H.A.; Kizas, C.; Koutentis, P.A. Selective Stille Coupling Reactions of 3-Chloro-5-halo(pseudohalo)-4*H*-1,2,6-thiadiazin-4-ones. *Org. Lett.* **2011**, *13*, 5886–5889. [[CrossRef](#)] [[PubMed](#)]
20. Ioannidou, H.A.; Koutentis, P.A. Synthesis of asymmetric 3,5-diaryl-4*H*-1,2,6-thiadiazin-4-ones via Suzuki–Miyaura and Stille coupling reactions. *Tetrahedron* **2012**, *68*, 7380–7385. [[CrossRef](#)]
21. Geever, J.; Trompen, W.P. Synthesis and reactions of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 270–272. [[CrossRef](#)]

