molbank

MDPI

Short Note

(Z)-2-{[(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino](methylthio)methylene}malononitrile

Andreas S. Kalogirou [1,*] and Panayiotis A. Koutentis [2]

[1] Department of Life Sciences, School of Sciences, European University Cyprus, 6 Diogenis Str., Engomi, P.O. Box 22006, 1516 Nicosia, Cyprus
[2] Department of Chemistry, University of Cyprus, P.O. Box 20537, 1678 Nicosia, Cyprus; koutenti@ucy.ac.cy
* Correspondence: a.kalogirou@euc.ac.cy; Tel.: +357-22559655

Abstract: Reaction of 4,5-dichloro-1,2,3-dithiazolium chloride with 2-[amino(methylthio)methylene])malononitrile (1 equiv) in the presence of pyridine (2 equiv) gave (*Z*)-2-{[(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino](methylthio)methylene}malononitrile in 20% yield. The compound was fully characterized.

Keywords: heterocycle; polyfunctionalized; 1,2,3-dithiazole; imine

check for updates

Citation: Kalogirou, A.S.; Koutentis, P.A. (Z)-2-{[(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino](methylthio)methylene}malononitrile. *Molbank* **2022**, *2022*, M1354. https://doi.org/10.3390/M1354

Academic Editor: Luke R. Odell

Received: 25 February 2022
Accepted: 11 March 2022
Published: 13 March 2022

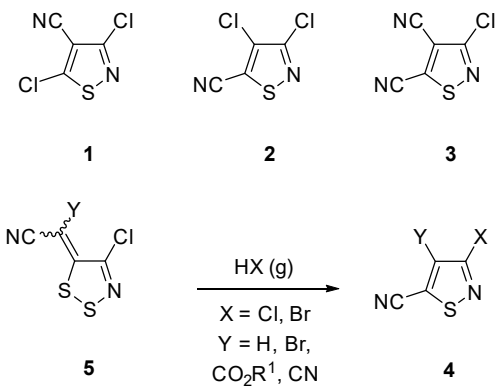
Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Isothiazoles are isomers of thiazoles that find uses in the medicinal (e.g., antirhinoviral, enteroviral [1–4] and anticancer activity [5], and as cathepsin C inhibitors [6]) and agrochemical (e.g., as fungicides, insecticides and acaricides [7–9]) sciences. Isothiazoles also have industrial applications, e.g., as dyes [10] and corrosion inhibitors [11], while they are also useful synthetic intermediates (e.g., Woodward's synthesis of colchicine [12]). The synthesis, chemistry and applications of isothiazoles have been extensively reviewed [13–15].

A group of important isothiazole scaffolds are isothiazole-carbonitriles [16–24]. For example, isothiazole-carbonitriles **1**–**3** (Scheme 1) are precursors for the preparation of insecticides [25], herbicides [9] and other potent biocides [26]. Recently, we developed the synthesis of isothiazole-carbonitriles **4** starting from (4-chloro-5*H*-1,2,3-dithiazolylidene)acetonitriles **5**, using gaseous HCl or HBr (Scheme 1) [27].

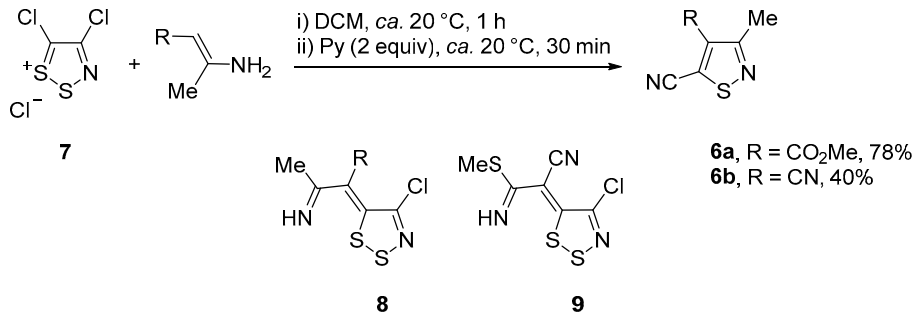


Scheme 1. Structure of isothiazole-carbonitriles **1**–**3** and synthesis of isothiazoles **4** from (4-chloro-5*H*-1,2,3-dithiazolylidene)acetonitriles **5**.

2. Results and Discussion

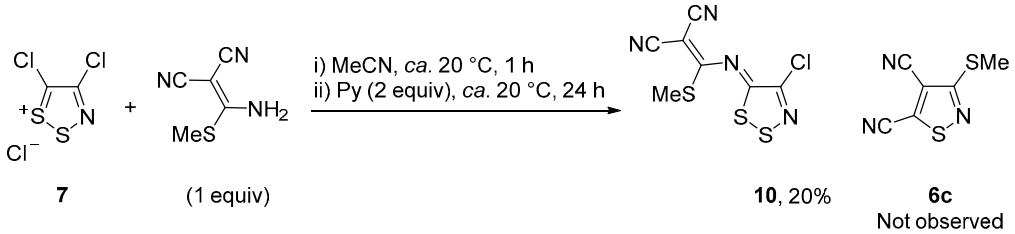
Another interesting synthesis of isothiazoles **6** directly from Appel's salt **7** and primary enamines was reported by Rees [28]. In this work, two examples were reported with medium to good yields, while the reaction was proposed to proceed via the dithiazole

ylidenes **8** (Scheme 2). Inspired by this work, we decided to investigate the same reaction with the analogous 2-[amino(methylthio)methylene]malononitrile that after nucleophilic addition to Appel's salt **7** and elimination of cyanogen chloride could give ylidene **9**.



Scheme 2. Synthesis of isothiazoles **6** from Appel's salt **7** and structures of intermediate dithiazole ylidenes **8** and **9**.

Nevertheless, the reaction of Appel's salt **7** with 2-[amino(methylthio)methylene] malononitrile (1 equiv) in MeCN, for 1 h, followed by addition of pyridine (2 equiv) and further stirring for 24 h gave the yellow colored product (*Z*)-2-{[(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino](methylthio)methylene}malononitrile (**10**) in 20% yield together with traces of the usual Appel's salt degradation products (Scheme 3). The desired isothiazole **6c** was not observed, indicating that either the enaminic reagent preferentially reacts with Appel's salt **7** via the nucleophilic nitrogen instead of the enamine carbon, and/or that isothiazole **6c** did form but was reactive and could not be isolated.



Scheme 3. Reaction of Appel's salt **7** with 2-[amino(methylthio)methylene]malononitrile.

Product **10** was isolated as yellow needles, mp 172–174 °C (from DCE/*c*-hexane). UV-vis spectroscopy supported an intact dithiazole ring (λ_{max} 374 nm, log ε 2.99). FTIR spectroscopy showed two cyano ν(C≡N) stretches at 2224 and 2216 cm^{-1}, while mass spectrometry revealed a molecular ion (MH^+) peak of *m/z* 275 (100%) along with a MH^++2 isotope peak at 277 (73%) that supported the presence of a single chlorine. ^{13}C NMR spectroscopy showed the presence of one CH_3 resonance and six quaternary carbon resonances (see Supplementary Materials for the complete spectra), while a correct elemental analysis (CHN) was obtained for the molecular formula $C_7H_3ClN_4S_3$. Tentatively, the imine geometry was assigned as *Z* owing to steric and electronic repulsion between the C-4 chloride and the sulfide group. Despite the low yield of its preparation, imine **10** is a multifunctional dithiazole and its chemistry will be investigated in the future. An example of the potential reactivity of this compound is the ring opening of the dithiazole by various thiophiles followed by ring closure on the cyano groups that could yield pyrimidines. Alternatively, Michael addition onto the acrylonitrile unit could then lead to cyclization on to the dithiazole C-4 position.

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 instrument [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 were used for the assignment of the ^{13}C peaks as CH_3, CH_2, CH and Cq (quaternary). The Matrix-Assisted Laser Desorption/Ionization-Time of Flight (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. 4,5-Dichloro-1,2,3-dithiazolium chloride (**7**) [29] and 2-[amino(methylthio)methylene]malononitrile [30] were prepared according to the literature procedures.

*(Z)-2-{[(4-Chloro-5H-1,2,3-dithiazol-5-ylidene)amino](methylthio)methylene}malononitrile (**10**)*

To a stirred suspension of 4,5-dichloro-1,2,3-dithiazolium chloride (**7**) (104.3 mg, 0.50 mmol) in DCM (2 mL) was added 2-[amino(methylthio)methylene]malononitrile (69.6 mg, 0.50 mmol) and the reaction mixture was stirred at ca. 20 °C for 1 h. Pyridine (81 µL, 1.00 mmol) was then added and the reaction mixture was stirred for another 24 h. The mixture was then adsorbed onto silica and chromatographed (*n*-hexane/DCM 20:80) to give the *title compound* **10** (27 mg, 20%) as yellow needles, mp 172–174 °C (from DCE/*c*-hexane); R_f 0.30 (*n*-hexane/DCM 20:80); (found: C, 30.73; H, 1.11; N, 20.33. $C_7H_3ClN_4S_3$ requires C, 30.60; H, 1.10; N, 20.39%); λ_{max}(DCM)/nm 295 (log ε 3.12), 374 (2.99), 389 inf (2.93); v_{max}/cm^{-1} 2933w (alkyl C–H), 2224m and 2216m (C≡N), 1572m, 1560m, 1557s, 1553s, 1528w, 1489m, 1470s, 1454w, 1416w, 1323w, 1252m, 1186m, 1123m, 988w, 935m, 924m, 901w, 870s, 839w, 810m, 716s; δ_H(500 MHz; $CDCl_3$) 2.44 (3H, s, CH_3); δ_C(125 MHz; $CDCl_3$) 181.4 (Cq), 163.6 (Cq), 147.2 (Cq), 112.2 (Cq), 111.5 (Cq), 66.9 (Cq), 15.0 (CH_3); *m/z* (MALDI-TOF) 277 (MH^++2, 73%), 275 (MH^+, 100), 239 (M^+-Cl, 3), 229 (M^+-SMe+2, 25), 227 (M^+-SMe, 60), 204 (MH^+-SMe-CN+2, 14), 202 (MH^+-SMe-CN, 37), 74 (26).

Supplementary Materials: The following supporting information can be downloaded online, mol file, ^{1}H and ^{13}C NMR spectra.

Author Contributions: A.S.K. and P.A.K. conceived the experiments; A.S.K. performed 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.

Funding: This research was funded by the Cyprus Research Promotion Foundation, grant numbers ΣΤΡΑΤΗΙΙ/0308/06, ΝΕΚΥΡ/0308/02 ΥΓΕΙΑ/0506/19 and ΕΝΙΣΧ/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 funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. Cutrì, C.C.C.; Garozzo, A.; Siracusa, M.A.; Sarvà, M.C.; Tempera, G.; Geremia, E.; Pinizzotto, M.R.; Guerrera, F. Synthesis and antiviral activity of a new series of 4-isothiazolecarbonitriles. *Bioorg. Med. Chem.* **1998**, *6*, 2271–2280. [CrossRef]
2. Cutrì, C.C.C.; Garozzo, A.; Siracusa, M.A.; Sarvà, M.C.; Castro, A.; Geremia, E.; Pinizzotto, M.R.; Guerrera, F. Synthesis of New 3,4,5-Trisubstituted Isothiazoles as Effective Inhibitory Agents of Enteroviruses. *Bioorg. Med. Chem.* **1999**, *7*, 225–230. [CrossRef]
3. Garozzo, A.; Cutrì, C.C.C.; Castro, A.; Tempera, G.; Guerrera, F.; Sarvà, M.C.; Geremia, E. Anti-rhinovirus activity of 3-methylthio-5-aryl-4-isothiazolecarbonitrile derivatives. *Antivir. Res.* **2000**, *45*, 199–210. [CrossRef]
4. Cutrì, C.C.C.; Garozzo, A.; Siracusa, M.A.; Castro, A.; Tempera, G.; Sarvà, M.C.; Guerrera, F. Synthesis of new 3-methylthio-5-aryl-4-isothiazolecarbonitriles with broad antiviral spectrum. *Antivir. Res.* **2002**, *55*, 357–368. [CrossRef]
5. Larson, E.R.; Noe, M.C.; Gant, T.G. Isothiazole Derivatives Useful as Anticancer Agents. U.S. Patent 6,235,764, 22 May 2001.
6. Bullion, A.M.; Busch-Petersen, J.; Evans, B.; Neipp, C.E.; McCleland, B.W.; Nevins, N.; Wall, M.D. Cathepsin C Inhibitors. WO Patent 2011,025,799, 3 March 2011.
7. Muelthau, F.A.; Bretschneider, T.; Fischer, R.; Fueslein, M.; Heil, M.; Hense, A.; Kluth, J.; Koehler, A.; Franken, E.-M.; Malsam, O.; et al. Novel Heterocyclic Compounds as Pesticides. U.S. Patent 62012,094,837, 19 April 2012.
8. Sagasser, I.; Menke, O.; Rack, M.; Hamprecht, G.; Puhl, M.; Reinhard, R.; Witschel, M.; Zagar, C.; Walter, H.; Westphalen, K.-O. 3-Arylisothiazoles and Their Use as Herbicides. U.S. Patent 623,807, 15 May 2004.
9. Hitoshi, S.; Yanase, Y.; Sekino, T.; Ishikawa, K.; Kuwatsuka, T.; Tanikawa, H.; Kawashima, H.; Tomura, N.; Kanemoto, Y. Isothiazolecarboxylic Acid Derivatives, Rice Blast Control Agents Containing the Same as Active Ingredients, and Rice Blast Control Method Applying the Control Agents. U.S. Patent 65,240,951, 31 August 1993.
10. Bradbury, R.; Butters, A.; Moscrop, C.; Slark, A. Ink Composition. WO Patent 9,634,916, 7 November 1996.
11. Pasch, N.F. Use of Corrosion Inhibiting Compounds to Inhibit Corrosion of Metal Plugs in Chemical-Mechanical Polishing. U.S. Patent 6,068,879, 30 May 2000.
12. Woodward, R.B. *A Total Synthesis of Colchicine*; The Harvey Lecture Series; Academic Press: New York, NY, USA, 1963; Volume 59, pp. 31–47.
13. Chapman, R.F.; Peart, B.J. *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Katritzky, A.R., Rees, C.W., Scriven, E.F.V., Eds.; Pergamon: Oxford, UK, 1996; ch. 3.05; pp. 319–372.
14. Potkina, V.I.; Kletskov, A.V.; Zubkov, F.I. *Comprehensive Heterocyclic Chemistry IV*; Black, D.S.C., Cossy, J., Stevens, C.V., Eds.; Pergamon: Oxford, UK, 2022; ch. 4.05; pp. 482–529.
15. Silva, A.D.A.; McQuade, J.; Szostak, M. Recent Advances in the Synthesis and Reactivity of Isothiazoles. *Adv. Synth. Cat.* **2019**, *361*, 3050–3067. [CrossRef]
16. Emayan, K.; English, R.F.; Koutentis, P.A.; Rees, C.W. New routes to benzothiophenes, isothiazoles and 1,2,3-dithiazoles. *J. Chem. Soc. Perkin Trans. 1* **1997**, 3345–3350. [CrossRef]
17. Christoforou, I.C.; Koutentis, P.A.; Rees, C.W. Reactions of 1,2,3-dithiazoles with halogenated malononitriles. *J. Chem. Soc. Perkin Trans. 1* **2002**, 1236–1241. [CrossRef]
18. Potkin, V.I.; Zubenko, Y.S.; Nechai, N.I.; Bykhovets, A.I.; Kurman, P.V. Synthesis of 4,5-dichloro-3-cyanoisothiazole and its functional derivatives. *Russ. J. Org. Chem.* **2008**, *44*, 1038–1042. [CrossRef]
19. Hatchard, W.R. The Synthesis of Isothiazoles. I. 3,5-Dichloro-4-isothiazolecarbonitrile and Its Derivatives. *J. Org. Chem.* **1964**, *29*, 660–665. [CrossRef]
20. Hatchard, W.R. The Synthesis of Isothiazoles. II. 3,5-Dimercapto-4-isothiazolecarbonitrile and Its Derivatives. *J. Org. Chem.* **1964**, *29*, 665–668. [CrossRef]
21. Ioannidou, H.A.; Koutentis, P.A. Regioselective hydrodehalogenation of 3,5-dihaloisothiazole-4-carbonitriles: Synthesis of 3-haloisothiazole-4-carbonitriles. *Tetrahedron* **2011**, *67*, 3348–3354. [CrossRef]
22. Christoforou, I.C.; Koutentis, P.A. New regiospecific isothiazole C–C coupling chemistry. *Org. Biomol. Chem.* **2006**, *4*, 3681–3683. [CrossRef] [PubMed]
23. Nakamura, T.; Kumagai, H.; Ogawa, M. Process for Producing Isothiazole Derivative. U.S. Patent 46,473, 23 February 2012.
24. Zborovskii, Y.L.; Smirnov-Zamkov, I.V.; Staninets, V.I. Heterocyclization of Acetylene Derivatives by the Action of Sulfur-Dioxide and Hydrogen Bromide. *Zh. Org. Khim.* **1984**, *20*, 1774–1784.
25. Turnbull, M.D.; Smith, A.M.; Salmon, R. Oxazoles and Their Agricultural Compositions. U.S. Patent 5,705,516, 6 January 1998.
26. Assmann, L.; Kitagawa, Y.; Ishikawa, K.; Yamazaki, D.; Sawada, H.; Araki, Y.; Sakuma, H.; Kinbara, T.; Imanishi, K. Isothiazole carboxylic acid amides. WO Patent 15,622, 23 March 2000.
27. Kalogirou, A.S.; Christoforou, I.C.; Ioannidou, H.A.; Manos, M.J.; Koutentis, P.A. Ring transformation of (4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitriles to 3-haloisothiazole-5-carbonitriles. *RSC Adv.* **2014**, *4*, 7735–7748. [CrossRef]
28. Clarke, D.; Emayan, K.; Rees, C.W. New synthesis of isothiazoles from primary enamines. *J. Chem. Soc. Perkin Trans. 1* **1998**, 77–82. [CrossRef]
29. Appel, R.; Janssen, H.; Siray, M.; Knoch, F. Synthese und reaktionen des 4,5-dichlor-1,2,3-dithiazoliumchlorids. *Chem. Ber.* **1985**, *118*, 1632–1643. [CrossRef]
30. Gibbons, L.K. 3-Aminoisothiazole Derivatives as Herbicides. U.S. Patent 4,075,001, 21 February 1978.