DE GRUYTER Heterocycl. Commun. 2017; 23(5): 359–363

Preliminary Communication

Franciszek Sączewski*, Maria Gdaniec and Krzysztof Data

A new imidazoline-containing Bunte salt: synthesis, molecular and electronic structure

https://doi.org/10.1515/hc-2017-0177
Received August 10, 2017; accepted August 23, 2017

Abstract: *S*-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]sulfothioate, a new imidazoline-containing Bunte salt **4** was prepared by reacting 2-chloromethylimidazoline **3** with sodium thiosulfate in aqueous solution at room temperature. The mechanism of the concerted S_N2 reaction pathway was studied by means of quantum chemical calculations at the B3LYP/6-31G** level of theory. The molecular structure of compound **4** incorporating a formal amidine moiety was confirmed by single crystal X-ray diffraction analysis, while its electronic structure was studied using quantum chemical calculations at the MP2/6-311++G** level of theory.

Keywords: Bunte salt; imidazoline; quantum chemical calculations; *S*-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl] sulfothioate; S_N2 reaction mechanism; synthesis; X-ray crystallographic structure.

Salts of *S*-alkylthiosulfuric acid (*S*-substituted thiosulfates, Bunte salts) have long been known as valuable reagents in synthetic organic chemistry [1] and in the industry [2]. Perspectives in the application of these sulfurating reagents have recently been defined in a versatile review article [3]. Thus, *S*-alkylsulfothioates are easily transformed into the corresponding sulfhydrides and sulfides [1, 4, 5], disulfides [6, 7], trisulfides [8, 9], as well as isothiocyanates and mercaptals [10]. They also serve as thiol precursors in the synthesis of 3-thioindoles [11] and in conjugated polymer self-assemblies on gold and silver surfaces [12]. Of special interest are alkylthiolation reactions, in which *S*-nucleophiles generated *in situ* from Bunte salts undergo a reaction with carbocations of isobenzofuranone and isoindolone [13], as well as the use of Bunte salts as the odorless thiol surrogates for the synthesis of α-sulfido carbonyl compounds via the thia-Michael addition [14]. Worth noting are also the biological activities of Bunte salts that include antimicrobial [15], antiradiation [16] and schistosomicidal [17] properties.

The most common methods developed for the preparation of *S*-alkyl thiosulfates include reactions of sodium or thalium thiosulfate with alkyl halides, alkenes or oxiranes [1], while some pharmacologically relevant, amino-containing analogs can be obtained by reacting aminothiols with chlorosulfonic acid [18]. Our continuous interest in the preparation of synthetically useful imidazolines containing the sulfate group of type **A** [19–21] prompted us to investigate the reactions of sodium thiosulfate with 2-chloro-4,5-dihydroimidazole and 2-chloromethyl-4,5-dihydroimidazole that were expected to provide new thiosulfates of type **B** and **C**, respectively (Figure 1).

First, 2-chloro-4,5-dihydroimidazole hemisulfate (**1**) [22] was subjected to a reaction with a 2-fold excess of sodium thiosulfate in aqueous solution at room temperature. An exothermic nucleophilic substitution reaction [23–26] took place with vigorous evolution of sulfur trioxide. As shown in Scheme 1, the initially formed internal Bunte salt **D** proved to be unstable and decomposed with the formation of imidazolidine-2-thione (**2**) in quantitative yields. The identity of product **2** was confirmed by comparison of its IR spectrum and melting point with data of the commercially available imidazolidine-2-thione (Experimental section). The facile dehalogenation of **1** bears resemblance to the previously described reaction of sodium thiosulfate with 2-chloro-1-methylquinolinium tetraborate (CQMT) that can be used as a tool in medical diagnostics for the determination of thiosulfate ion in human urine [27, 28].

Next, we attempted an analogous reaction of sodium thiosulfate with 2-chloromethyl-4,5-dihydroimidazole (**3**). As shown in Scheme 2, the reaction carried out in aqueous solution at ambient temperature led to the formation of the expected Bunte salt that precipitated from the reaction mixture in the form of the stable zwitterion **4**. The presence

---

***Corresponding author: Franciszek Sączewski,** Department of Chemical Technology of Drugs, Faculty of Pharmacy, Medical University of Gdańsk, 80-416 Gdańsk, Poland, e-mail: saczew@gumed.edu.pl
Maria Gdaniec: Faculty of Chemistry, A. Mickiewicz University, Poznań, Poland
Krzysztof Data: Department of Chemical Technology of Drugs, Faculty of Pharmacy, Medical University of Gdańsk, Gdańsk, Poland

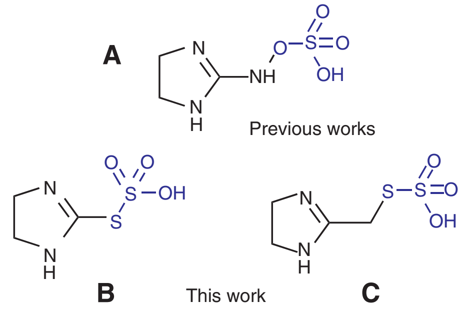
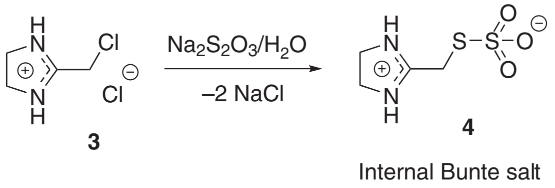


Figure 1 Imidazoline derivatives containing a sulfate or thiosulfate group. Imidazolines containing the sulfate group A and reactions of sodium thiosulfate with 2-chloro 4,5-dihydroimidazole and 2-chloromethyl-4,5-dihydroimidazole to provide thiosulfates B and C.

of the S-SO_3^- group in **4** was confirmed by a strong absorption at 1031 cm^{-1}, characteristic of Bunte salts, found in the IR spectrum. A protonated 2-methyleneimidazoline moiety was identified by the presence of two singlets in the ^1H NMR spectrum, corresponding to four protons of the imidazoline ring and two protons of the exocyclic CH_2 group at 3.78 and 3.89 ppm, respectively, as well as three signals in the ^{13}C NMR spectrum at 28.8 ppm (S-CH_2), 45.2 ppm (CH_2-CH_2 grouping) and 170.2 ppm (quaternary C2 atom of imidazoline ring).

The constitution of the thiosulfate **4** was further investigated by single crystal X-ray diffraction analysis. The crystal unit of **4** consists of zwitterionic molecules with a proton transferred from the sulfate group to the 4,5-dihydro-1*H*-imidazole fragment. The molecular structure features the typical characteristics of the thiosulfate group [29], with the S-S bond length of 2.1097(6) Å (Figure 2). The crystal packing is dominated by intermolecular hydrogen bonding N-H···O interactions, with the molecules arranged in a ‘head-to-tail’ manner within the hydrogen-bonded chain propagating along the z axis (Figure 3A). There are also numerous C-H···O interactions formed predominantly between the molecules forming (-102) layers (Figure 3B).



Scheme 2 Reaction of 2-chloromethyl-4,5-dihydroimidazole (**3**) with sodium thiosulfate.

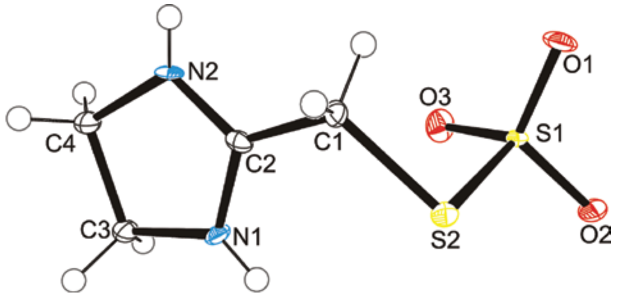
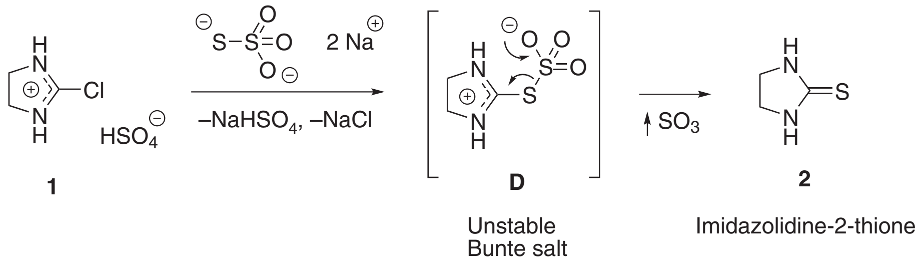


Figure 2 Molecular structure of **4**. Displacement ellipsoids are shown at the 50% probability level.

To gain a mechanistic insight into the reaction depicted in Scheme 2, we carried out DFT calculations (the B3LYP/6-31G** level of theory) on the concerted S_N2 reaction pathway. As shown in Figure 4, the displacement of the chloride ion with thiosulfate occurs in the plane perpendicular to the imidazoline ring, in a nearly linear manner (S2-C1-Cl angle = 170.32°), and is exothermic ($\Delta G = 26.7$ kcal/mol). The transition state $TS^‡$ has sufficiently low activation energy ($E_a = 3.5$ kcal/mol) to undergo a substitution reaction under mild reaction conditions (Figure 5). The geometry of the transition state shows a single imaginary frequency pertaining to the S-C bond formation and C-Cl bond breakage at 409 cm^{-1}.

To identify reactive sites at compound **4**, the electronic structure of this compound was studied using quantum chemical calculations at the MP2/6-311++G** level of theory. Bunte salts are defined as a class of sulfurating reagents bearing an SO_3^- ‘mask’ on the sulfur atom, which serves as a steric bulky group to prevent homocoupling and as a conjugated group to tune the electron effect on sulfur [3]. Shielding of the S(II) sulfur



Scheme 1 Reaction of 2-chloro-4,5-dihydroimidazole (**1**) with sodium thiosulfate.

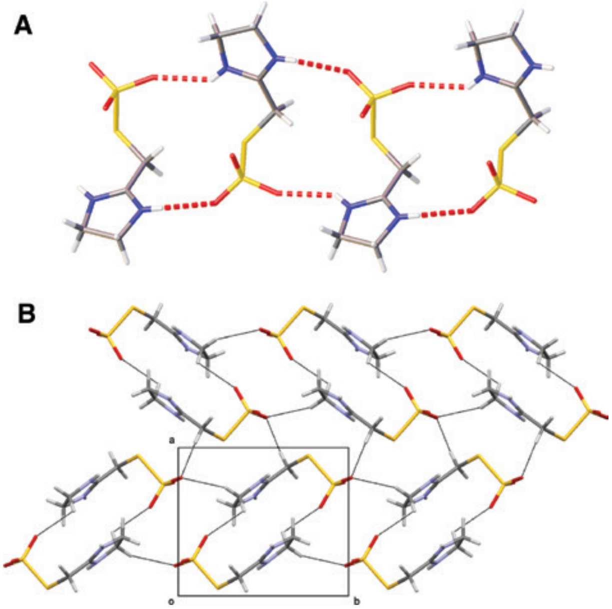


Figure 3 N-H···O and C-H···O interactions. (A) Hydrogen-bonded chain in **4**. (B) C-H···O interactions between the molecules in (-102) layers. Hydrogen bonds are shown with dashed lines.

atom is assured by a negative electrostatic potential that surrounds the SO_3^- mask (Figure 6). As shown in Figure 4, the HOMO orbital is mainly localized at the S(II) sulfur

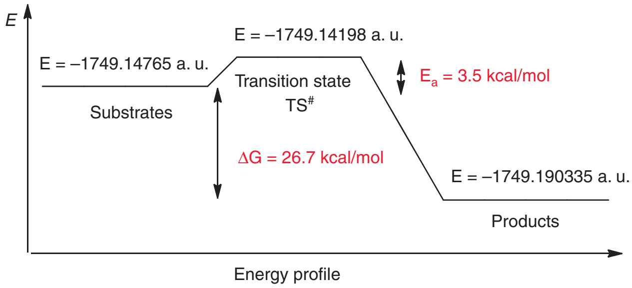


Figure 5 Energy profile computed at the B3LYP/6-31G** level for the transformation **3**→**4** (S_N2 reaction).

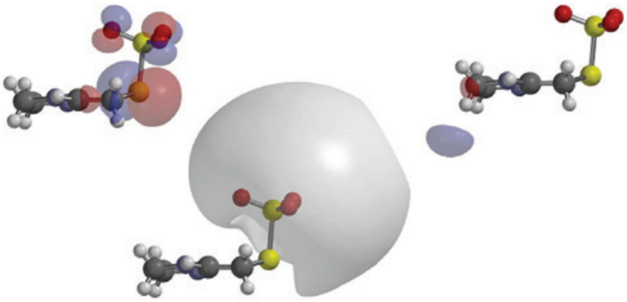


Figure 6 Electronic structure of thiosulfate **4**: localization of HOMO (top left), LUMO (top right) (isovalue = 0.032 e/au^3) and electrostatic potential (bottom) (isovalue = −83.68 kJ/mol).

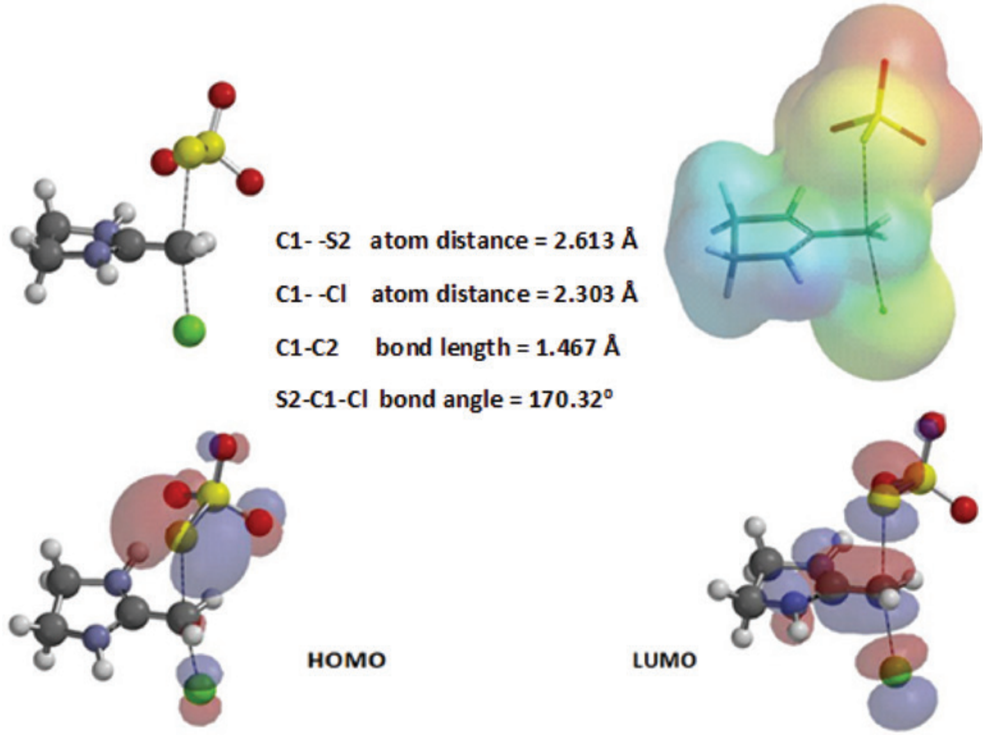


Figure 4 Structure of the transition state TS‡: N1-S2, C1-Cl and C1-C2 atom distances (Å), S2-C1-Cl bond angle (°), electrostatic potential mapped on the isodensity surface (0.002 e/au^3) and localization of frontier orbitals HOMO and LUMO (isovalue = 0.032 e/au^3).

atom of the thiosulfate moiety, which should be involved in the orbital-controlled reactions with electrophiles. On the other hand, scrutiny of the calculated charges in **4** suggests that electrostatically controlled reactions with electrophilic reagents should proceed preferentially at the C1 carbon atom. Studies of possible applications of **4** in the synthesis of new imidazoline-containing compounds are in progress.

Experimental

Melting points were determined on a Boetius apparatus and are uncorrected. FT-IR spectra were measured on a Nicolet 380 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in dimethyl sulfoxide-d_6 on a Varian Gemini instrument operating at 200 MHz and 50 MHz, respectively. Sodium thiosulfate ($Na_2S_2O_3 \times 5H_2O$) and imidazolidine-2-thione (**2**) were acquired from a commercial source and used as provided. 2-Chloro-4,5-dihydro-1*H*-imidazole (**1**) and 2-chloromethyl-4,5-dihydro-1*H*-imidazole (**3**) were prepared according to the literature procedures in [22] and in [30], respectively. The diffraction data for single crystals of **4** were collected with an Oxford Diffraction SuperNova diffractometer using Cu Kα radiation. The intensity data were collected and processed using the CrysAlisPro software [31]. The structure was solved by direct methods with the program SIR-2004 [32] and refined by a full-matrix least-squares method on F^2 with SHELXL-2016/6 [33]. Quantum chemical calculations were performed with the program Spartan v.8.0 (Wavefunction, Inc., Irvine, CA, USA).

Reaction of sodium thiosulfate with 2-chloro-4,5-dihydroimidazole

To a solution of **1** (5 g, 25 mmol) in water (10 mL) was added $Na_2S_2O_3 \times 5H_2O$ (12.4 mg, 50 mmol) with stirring. After an exothermic reaction had subsided, the mixture was kept at room temperature for 1 h, and then cooled to 5°C. The precipitated pure imidazolidine-2-thione (**2**) was collected by filtration, washed with cold water and dried; yield 2.1 g (82%), mp 197–200°C. Spectroscopic and physicochemical properties of product **2** were virtually identical to those of commercially available imidazolidine-2-thione.

Reaction of sodium thiosulfate with 2-chloromethyl-4,5-dihydroimidazole

To a solution of **3** (2 g, 13 mol) in water (5 mL) was added $Na_2S_2O_3 \times 5H_2O$ (6.45 g, 26 mol). The mixture was stirred for 10 min and then kept at ambient temperature for 12 h. The precipitated Bunte salt **4** was separated by suction, washed with cold water and dried; yield 1.6 g (64%); mp 147–149°C (dec.); FT-IR (KBr): ν 3376, 3282, 2970, 2928, 1604, 1596, 1254, 1220, 1196, 1031, 619 cm^{-1}; ^{1}H NMR: δ 3.78 (s, 4H, CH_2-CH_2), 3.89 (s, 2H, CH_2), 9.85 (s, 2H, 2×NH); ^{13}C NMR: δ 28.8 (S-CH_2), 45.2 (C4- and C5-imidazoline), 170.2 (C2-imidazoline).

Crystal data for Bunte salt 4

($C_4H_8N_2O_3S_2$; $M = 196.24$ g/mol): monoclinic, space group $P2_1/c$ (no. 14), $a = 8.22560(12)$ Å, $b = 9.45112(13)$ Å, $c = 9.75528(15)$ Å, $\beta = 99.6136(14)°$, $V = 747.736(19)$ Å^3, $Z = 4$, $T = 130.15$ K, $\mu(\mathrm{CuK}\alpha) = 6.186$ mm^{-1}, $D_{calc} = 1.743$ g/cm^3, 8294 reflections measured ($13.134° \leq 2\Theta \leq 148.946°$), 1526 unique ($R_{\mathrm{int}} = 0.0824$, $\mathrm{R}_{\mathrm{sigma}} = 0.0353$), which were used in all calculations. The final R_1 was 0.0404 [$I > 2\sigma(I)$] and wR_2 was 0.1065 (all data). Illustrations were prepared with the OLEX2 software [34].

CDC 1550367 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

References

[1] Distler, H. The chemistry of Bunte salts. *Angew. Chem. Int. Eng. Ed*. **1967**, *6*, 544–553.

[2] Watson, C. D. Bunte Salt Dyes. In *The Chemistry of Synthetic Dyes*; Venkataraman K., Ed. Academic Press: New York, 1974; Vol. 7, pp 35–68.

[3] Qiao, Z.; Jiang, X. Recent development in sulfur-carbon bond formation reaction involving thiosulfate. *Org. Biomol. Chem*. **2007**, *15*, 1942–1946.

[4] Reeves, J. T.; Camara, K.; Han, Z. S.; Xu, Y.; Lee, H.; Busacca, C. A.; Senanayake, C. H. The reaction of Grignard reagents with Bunte salts: a thiol-free synthesis of sulfides. *Org. Lett*. **2014**, *16*, 1196–1199.

[5] Zhang, R.; Yan, Z.; Wang, D.; Wang, Y.; Lin, S. NaI-mediated acetamido sulfenylation of alkenes with Bunte salts as thiolating reagent leading to β-acetamido sulfides. *Synlett* **2017**, *28*, 1195–1200.

[6] Milligan, B.; Swan, J. M. New synthesis of disulfides from Bunte salts. *J. Chem. Soc*. **1962**, 2172–2177.

[7] Xiao, X.; Feng, M.; Jiang, X. Transition-metal-free persulfuration to construct unsymmetrical disulfides and mechanistic study of sulfur redox process. *Chem. Commun*. **2015**, *51*, 4208–4211.

[8] Milligan, B.; Saville, B.; Swan, J. M. Trisulfides and tetrasulfides from Bunte salts. *J. Chem. Soc*. **1963**, 3608–3614.

[9] Milligan, B.; Swan, J. M. Cyclic trisulphides from Bunte salts. *J. Chem. Soc*. **1965**, 2901–2904.

[10] Westlake, H. E.; Dougherty, J. R. G. The use of Bunte salts in synthesis III. The preparation of aliphatic disulfides. *J. Am. Chem. Soc*. **1942**, *64*, 149–150.

[11] Qi, H.; Zhang, T.; Wan, K.; Luo, M. Catalytic synthesis of 3-thioindoles using Bunte salts as sulfur sources under metal-free conditions. *J. Org. Chem*. **2016**, *81*, 4262–4268.

[12] Kraft, M.; Adamczyk, S.; Polywka, A.; Zilberberg, K.; Weijtens, Ch.; Meyer, J.; Gorrn, P.; Reidl, T.; Scherf, U. Polyanionic alkylthiosulfate-based thiol precursors for conjugated polymer self-assembly onto gold and silver. *ACS Applied Mater. Interfaces* **2014**, *6*, 11758–11765.

[13] Ukhin, L. Y.; Akopova, A. R.; Bicherov, A. V.; Kuzmina, L. G.; Morkovnik, A. S.; Borodkin, G. S. Reaction of Bunte salts with carbocations of isobenzofuranone and isoindolone. *Tetrahedron Lett*. **2011**, *52*, 5444–5447.

[14] Kin, Y. M.; Lu, G.-P.; Cai, Ch.; Yi, W.-B. An odorless thia-Michael addition using Bunte salts as thiol surrogates. *RSC Adv*. **2015**, *5*, 27107–27111.

[15] Stefańska, J. Z.; Starościak, B. J.; Orzeszko, A.; Kazimierczuk, Z. Antimicrobal activity of organic thiosulfates (Bunte salts). *Pharmazie* **1998**, *53*, 190–192.

[16] Bauer, L.; Sandberg, K. R. α-Amidinium thiosulfates (Bunte Salts) as antiradiation drugs. *J. Med. Chem.* **1964**, *7*, 766–768.

[17] de Oliveira Penido, M. L.; Nelson, D. N.; Vieira, L. Q.; Marcos, P.; Coelho, Z. Schistosomicidal activity of alkylaminooctanethiosulfuric acids. *Mem. Inst. Oswaldo Cruz Rio de Janeiro*. **1994**, *89*, 595–602.

[18] Tanaka, T.; Nakamura, H.; Tamura, Z. A simple synthesis of amino-containing Bunte salts by the reaction of aminothiols with chlorosulfonic acid. *Chem. Pharm. Bull*. **1974**, *21*, 2725–2728.

[19] Sączewski, J.; Gdaniec, M. First tandem nucleophilic addition-electrophilic amination of Eschenmoser's salts: synthesis of cyclic and spiro-fused hydrazonium salts. *Tetrahedron Lett*. **2007**, *48*, 7624–7627.

[20] Sączewski, J.; Gdaniec, M. Synthesis of heterocycles by intramolecular nucleophilic substitution at an electron-deficient sp2 nitrogen atom. *Eur. J. Org. Chem*. **2010**, 2387–2394.

[21] Sączewski, J.; Korcz, M. Synthesis and reactivity of heterocyclic hydroxylamine-*O*-sulfonates. *Heterocycl. Commun*. **2014**, *20*, 133–147.

[22] Trani, A.; Belasio, E. Synthesis of 2-chloroimidazoline and its re-activity with aromatic amines, phenols and thiophenols. *J. Heterocycl. Chem*. **1974**, *11*, 257–261.

[23] Łączkowski, K. Z.; Jachowicz, K.; Misiura, K.; Biernasiuk, A.; Malm, A. Synthesis and biological evaluation of novel 2-(1*H*-imidazol-2-ylmethylidene)hydrazinyl-1,3-thiazoles as potential antimicrobial agents. *Heterocycl. Commun.* **2015**, *21*, 109–114.

[24] Krauze, A.; Grinberga, S.; Sokolova, E.; Domracheva, I.; Shestakova, I.; Duburs, G. Synthesis of polysubstituted pyridines as potential multidrug resistance modulators. *Heterocycl. Commun*. **2015**, *21*, 93–96.

[25] Vijay, T. A. J.; Sandhya, N. C.; Pavankumar, C. S.; Rangappa, K. S.; Kempegowda Mantelingu, K. Ligand- and catalyst-free intramolecular C-S bond formation: direct access to indalothiochromen-4-ones. *Heterocycl. Commun.* **2015**, *21*, 159–163.

[26] Arghiani, Z.; Seyedi, S. M; Bakavoli, M.; Nikpour, M. Synthesis of new derivatives of 10*H*-benzo[*b*]pyridazino[3,4-*e*][1,4] thiazines. *Heterocycl. Commun.* **2015**, *21*, 215–218.

[27] Chwatko, G.; Bald, E. Determination of thiosulfate in human urine by high performance liquid chromatography. *Talanta* **2009**, *79*, 229–234.

[28] Kubalczyk, P.; Chwatko, G.; Głowacki, R. Fast and simple MEKC sweeping method for determination of thiosulfate in urine. *Electrophoresis* **2016**, *37*, 1155–1160.

[29] Foust, A. S.; Janickis,V. Preparation and structure of Bunte salt *trans*-dichlorobis)ethylenediamine)cobalt(III) *S*-hydroxymethyl thiosulfate, $[Co(en)_2Cl_2]HOCH_2S_2O_3$. *Inorg. Chem.* **1980**, *19*, 1048–1050.

[30] Klarer, W.; Ucher, E. Uber Oxyalkyl- bzw. Halogenalkyl-formamidine und –imidazoline. *Helv. Chim. Acta*. **1944**, *27*, 1762–1776.

[31] Agilent Technologies. *CrysAlis Pro software*, ver. 1.171.34, Yarton, Oxfordshire, England (2014).

[32] Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Siliqi, D.; Spagna, R. *SIR2004*: an improved tool for crystal structure determination and refinement. *J. Appl. Cryst.* **2005**, *38*, 381–388.

[33] Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst*. **2015**, *C71*, 3–8.

[34] Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Cryst*. **2009**, *42*, 339–341.