<https://helda.helsinki.fi>

Synthesis and crystallographic evaluation of diazenyl- and hydrazothiazoles. [5.5] sigmatropic rearrangement and formation of thiazolium bromide dihydrate derivatives

Hassan, Alaa A.

2019-01

Hassan , A A , Mohamed , N K , Aly , A A , Tawfeek , H N , Bräse , S & Nieger , M 2019 , ' Synthesis and crystallographic evaluation of diazenyl- and hydrazothiazoles. [5.5] sigmatropic rearrangement and formation of thiazolium bromide dihydrate derivatives ' , Journal of Molecular Structure , vol. 1176 , pp. 346-356 . <https://doi.org/10.1016/j.molstruc.2018.08.106>

<http://hdl.handle.net/10138/323944>

<https://doi.org/10.1016/j.molstruc.2018.08.106>

cc_by_nc_nd

acceptedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

Graphical abstract

Synthesis and crystallographic evaluation of diazenyl- and hydrazothiazoles. [5.5] Sigmatropic rearrangement and formation of thiazolium bromide dihydrate derivatives

Alaa A. Hassan,^{1*} Nasr K. Mohamed,¹ Ashraf A. Aly,¹ Hendawy N. Tawfeek,¹ Stefan Bräse,² Martin Nieger³

¹ Chemistry Department, Faculty of Science, Minia University, 61519-El-Minia, Egypt.

² Institute of Organic Chemistry, Karlsruhe Institute of Technology, Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany.

³ Laboratory of Inorganic Chemistry, Department of Chemistry, University of Helsinki, P.O.Box55 (A. I. Virtasenaudio I), 00014, Helsinki, Finland.

Synthesis and crystallographic evaluation of diazenyl- and hydrazothiazoles. [5.5] Sigmatropic rearrangement and formation of thiazolium bromide dihydrate derivatives

Alaa A. Hassan,^{1*} Nasr K. Mohamed,¹ Ashraf A. Aly,¹ Hendawy N. Tawfeek,¹ Stefan Bräse,² Martin Nieger³

¹ Chemistry Department, Faculty of Science, Minia University, 61519-El-Minia, Egypt.

² Institute of Organic Chemistry, Karlsruhe Institute of Technology, Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany.

³ Laboratory of Inorganic Chemistry, Department of Chemistry, University of Helsinki, P.O.Box55 (A. I. Virtasenaukio I), 00014, Helsinki, Finland.

✉ Corresponding Authors: Tel./fax: +20 862363011. alaahassan2001@mu.edu.eg

Abstract:

In this investigation the synthesis of diazenylthiazoles (**3a-e**) by the reaction of arylthiosemicarbazides with ω -bromoacetophenones *via* Eschenmoser-coupling reaction in acetonitrile and equimolar amounts of triethylamine and triphenylphosphine. Upon heating 1,4-disubstituted thiosemicarbazides with ω -bromoacetophenones in absolute ethanol, hydrazothiazoles (**16a-i**) were precipitated. On the other hand, the reaction of arylthiosemicarbazides with ω -bromoacetophenones in refluxing ethanol yielded 2-amino-5-[4-aminophenyl]-4-phenylthiazolium bromide dihydrate derivatives (**19a-g**) *via* [5.5] sigmatropic shift. The studied products were further characterized by IR, ¹H NMR, ¹³C NMR and mass spectrometry. X-ray single crystal of **3a** and **16h** showed that, the molecules crystallized in the triclinic crystal system, space group P2₁/c. Whereas the X-ray single crystal of **19b** showed the molecule crystalized in orthorhombic, space group P2₁2₁2₁. In the crystal of **19b**, the lattice water and bromide ion associated through hydrogen bonded with thiazole-NH₂.

Keywords: Diazenylthiazoles; Hydrazothiazoles; Thiazoliumbromidedihydrates; Thiosmicarbazides; X-Ray analyses.

1. Introduction

The azo-dyes of heterocyclic compounds are useful structural components, due to their applications in textiles, papers, leather additives, foodstuffs, cosmetic industries and as organic solar cells and chemosensors [1-6]. Thiazole-azo dyes were synthesized during the reaction of thiourea with *p*-methoxyphenyl- ω -bromoacetophenone followed by coupling with *N,N*-diethylaniline [7], whereas 1,3-thiazolyl diazenyl-3-naphthalene derivatives have been synthesized by diazotization of 4-[4-ethylphenyl]thiazole-2-amine and coupling to *N*-[4-chloro-2-methylphenyl]-3-hydroxynaphthalen-2-carboxamide [8]. Various derivatives of diazenyl-1,3-thiazoles were synthesized and their biological activities were evaluated [9,10].

Recently, we reported that the reaction of hydrazinecarbothioamides with tetracyanoethylene (TCNE) gave azothiazoles [11]. Azo-benzothiazole chromophores possess large molecular hyperpolarizability and showed that they are a good choice for nonlinear optics (NLO) materials [12,13].

2-(3-(1*H*-Indol-3-yl)-5-(*p*-tolyl-4,5-dihydro-1*H*-pyrazol-1-yl)-5-(aryldiazenyl)-4-thiazoles were synthesized from 3-(1*H*-indolyl)-5-(*p*-tolyl)-4,5-dihydropyrazole-1-carbothioamide and keto-hydrazonyl halides. The latter compounds have been evaluated for their antitumor activity against the MCF-7 human breast carcinoma cell line [14], also, indolylmethylidenehydrazinyl-4-aryl-5-(aryldiazenyl)-thiazoles also have been synthesized [15].

2,4,5-Trisubstituted-1,3-thiazole derivatives including a hydrazide-hydrazone moiety have been synthesized and evaluated towards antitumor activity against some human cancer [16].

The reaction of *o*-bromoacetophenones with ethylidene hydrazinecarbothioamides gave substituted ethylidene hydrazinylthiazoles which exhibited anti-bacterial activity [17]. (*E*)-2-(2-(2-Nitrobenzylidene)thiazoles and (*E*)-3,4-diaryl-2-(cycloalkylidene-hyrazono)-thiazoles were formed during the reaction of *o*-bromoacetophenones with 2-(1-alkyl-methylidene)hydrazinecarbothioamides and cycloalkylidene-*N*-phenylhydrazine-carbothioamides [18].

4-Methyl-(1-benzylidenehydrazinyl)-2-carbothioamide reacted with ethylbromopyruvate to give ethyl-2-(4-methyl-(2-benzylidenehydrazinyl)thiazole-4-carboxylates [19].

Gomha et al. reported that, 1,4-bis(1-(5-aryldiazenyl)thiazol-2-yl)-3-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-5-yl)benzene was formed during the reaction of 5,5'-(4,4-phenylene)-bis-(3-thiophen-2-yl)-4,5-dihydro-pyrazole-1-carbothioamide with hydrazonyl halides [20].

Heterocyclization of 2-(1-alkylethylidene)hydrazinecarbothioamides afforded the formation of monohydrated pyridinium bromide-1,3-thiazolidenehydrazinylidene ethyl, 1,3-thiazolylidenehydrazinium bromide and thiazolylidenehydrazines [21].

Hydrazine derivatives are known to undergo rearrangements with N-H bond fission [22].

It has been reported, that the addition of benzophenonephenylhydrazone to polyphosphoric acid (PPA) under heating, *o*-phenylenediamine and benzophenone was observed [22].

A [5.5]sigmatropic shift of bis-thiazolylhydrazines in acidic catalyzed rearranged to *p*-aminophenylthiazoles in addition to, bis(2-aminothiazoles) [23].

2. Experimental

2.1. Instrumentation

Gallenkamp melting point apparatus was used to determine the melting points. IR spectra were recorded with Alpha, Bruker FT-IR instruments using potassium bromide pellets. NMR spectra were recorded for ^1H NMR at 400 MHz and ^{13}C NMR at 100 MHz on a Bruker AM 400 spectrometry with TMS as internal standard ($\delta = 0$), and data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, m = multiplet, br = broad). For ^{13}C NMR, TMS ($\delta = 0$) was used as internal standard and spectra were obtained with complete proton decoupling. Finnigan MAT instrument was used to record the mass spectra (70 eV, EI-mode). Elemental analyses for C, H, N, and S were carried out using an Elmyer 306. Preparative layer chromatography (plc) was carried out on glass plates covered with a 1.0 mm thick layer of slurry-applied silica gel (Merck Pf₂₅₄).

2.2. Chemicals

2.2.1. *Starting materials*

Monosubstituted and disubstituted thiosemicarbazides were prepared according to literature methods (**1a** [23], **1b** [24], **1c** [11], **1d** [25], **15a-d** [26]). ω -Bromoacetophenone **2a,b** were prepared according to literature [27,28].

2.2.2. Synthesis of substituted diazenylthiazoles **3a-e**.

Equimolar amounts of thiosemicarbazides **1a-d** (**1a**, 0.167; **1b**, 0.201; **1c**, 0.245 and **1d**, 0.257g) and ω -bromoacetophenone **2a/b** (**2a**, 0.198; **2b**, 0.277 g) were stirred in 20 ml dry CH_3CN for 16 h at room temperature. The dried salt was redissolved in CH_3CN , followed

by adding other equivalents of triethylamine and triphenylphosphine. The mixture was refluxed for 10-16 h, H₂O (30 ml) was added and the resulting mixture was extracted with CH₂Cl₂. The organic extracts were dried over anhydrous CaCl₂, filtered and concentrated. The residue was subjected to chromatographic plates (plc) using toluene/ethyl acetate (10:1) to give an orange main zone which was extracted with acetone to give compounds **3a-e** (Scheme 1).

2.2.2.1. *(E)*-4-Phenyl-2-(phenyldiazenyl)thiazole (**3a**)

Orange crystals (acetonitrile); yield 217 mg (82%); Mp. 158-159 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.58 (m, 6H, Ar-H), 7.62 (s, 1H, thiazole-H), 8.03-8.88 (m, 4H, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 115.88 (thiazole-CH), 123.25, 125.62, 126.83, 128.75, 129.53, 130.81 (Ar-CH), 133.91, 134.23, (Ar-C), 155.85 (thiazole-C4), 168.46 (thiazole-C2) ppm; IR (KBr): ν = 3105 (Ar-CH), 1600 (C=N), 1585 (Ar-C=C), 1560, 1444 cm⁻¹ (N=N); MS (70 eV): m/z (%) = 265 (M⁺, 58), 189 (12), 160 (28), 105 (17), 77 (100); Anal. Calcd for C₁₅H₁₁N₃S (265.33): C 67.90, H 4.18, N 15.84, S 12.08; Found: C 67.78, H 4.11, N 16.02, S 11.97.

2.2.2.2. *(E)*-2-((3-Chlorophenyl)diazenyl)-4-phenylthiazole

(3b) Pale orange crystals (acetonitrile); yield 248 mg (83%); Mp. 148-149°C; ¹H NMR (400 MHz, CDCl₃): δ 7.30-7.45 (m, 5H, Ar-H), 7.55 (s, 1H, thiazole-H), 7.85-7.88 (m, 1H, Ar-H), 7.92-8.00 (m, 3H, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 116.69 (thiazole-CH), 123.98, 124.00, 127.20, 129.68, 129.86, 131.27, 133.48 (Ar-CH), 134.60, 136.43, 142.12 (Ar-C), 157.48 (thiazole-C4), 169.84 (thiazole-C2) ppm; IR (KBr): ν = 3080 (Ar-CH), 1608 (C=N), 1592 (Ar-C=C), 1562, 1442 cm⁻¹ (N=N); MS (70 eV): m/z (%) = 301/299 (M⁺, 38), 223 (13), 189 (67), 160 (100), 141 (17), 113 (12); Anal. Calcd for

C₁₅H₁₀ClN₃S (299.78): C, 60.10, H 3.36, Cl 11.83, N 14.02, S 10.70; Found: C 59.97, H 3.45, Cl 11.77, N 13.91, S 10.82.

2.2.2.3. *(E)*-4-Phenyl-2-(tosyldiazenyl)thiazole (**3c**)

Orange crystals (acetonitrile); yield 274 mg (80%); Mp. 175-176°C; ¹H NMR (400 MHz, CDCl₃): δ 2.50 (s, 3H, CH₃); 6.90-7.00 (m, 2H, Ar-H), 7.15-7.41 (m, 5H, Ar-H), 7.52 (s, 1H, thiazole-H), 7.62-7.79 (m, 2H, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 22.37 (CH₃), 116.75 (thiazole-CH), 123.77, 127.61, 128.54, 129.70, 130.12 (Ar-CH), 135.48, 141.01, 142.86 (Ar-C), 156.67 (thiazole-C4), 168.55 (thiazole-C2) ppm; IR (KBr): ν = 3085 (Ar-CH), 1605 (C=N), 1594 (Ar-C=C), 1568, 1450 cm⁻¹ (N=N); MS (70 eV): m/z (%) = 343 (M⁺, 100), 265 (46), 189 (58), 184 (30), 160 (23), 155 (43), 91 (17), 77 (51); Anal. Calcd for C₁₆H₁₃N₃O₂S₂ (343.42): C 55.96, H 3.82, N 12.24, S 18.67; Found: C 56.12, H 3.91, N 12.15, S 18.58.

2.2.2.4. *(E)*-2-((2,4-Dinitrophenyl)diazenyl)-4-phenylthiazole (**3d**)

Orange crystals (acetonitrile); yield 287 mg (81%); Mp. 193-195 °C; ¹H NMR (400 MHz, DMSO-d₆): δ 7.35-7.43 (m, 6H, Ar-H), 7.55 (s, 1H, thiazole-H), 7.94-8.03 (m, 1H, Ar-H), 8.30-8.40 (m, 1H, Ar-H) ppm, ¹³CNMR (100 MHz, DMSO-d₆): δ 115.59 (thiazole-CH), 121.73, 126.10, 128.48, 128.81, 129.16, 129.63 (Ar-CH), 133.49, 134.55, 140.12, 142.16 (Ar-C), 157.11 (thiazole-C4), 169.69 (thiazole-C2) ppm; IR (KBr): ν = 3078 (Ar-CH), 1612 (C=N), 1602 (Ar-C=C), 1558, 1448 cm⁻¹ (N=N); MS (70 eV): m/z (%) = 355 (M⁺, 100), 279 (38), 197 (53), 189 (71), 183 (80), 167 (28), 160 (56), 123 (22); Anal. Calcd for C₁₅H₉N₅O₄S (355.33): C 50.70, H 2.55, N 19.71, S 9.02; Found: C 50.61, H 2.49, N 19.83, S 8.89.

2.2.2.5. *(E)*-4-(4-Bromophenyl)-2-((2,4-dinitrophenyl)diazenyl)thiazole (**3e**)

Orange crystals (acetonitrile); yield 373 mg (86%); Mp. 182-183°C; ¹H NMR (400 MHz, DMSO-d₆): δ 7.24-7.55 (m, 4H, Ar-H), 7.58 (s, 1H, thiazole-H), 7.81-7.86 (m, 1H, Ar-H), 7.92-8.00 (m, 1H, Ar-H), 8.31-8.39 (m, 1H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 114.34 (thiazole-CH), 121.32, 125.98, 128.03, 130.12, 131.87 (Ar-CH), 132.71, 134.16, 138.73, 139.14, 141.82 (Ar-C), 156.35 (thiazole-C4), 167.91 (thiazole-C2) ppm; IR (KBr) ν: 3063 (Ar-CH), 1608 (C=N), 1596 (Ar-C=C), 1570, 1442 cm⁻¹ (N=N); MS (70 eV): m/z (%) = 437/435 (M⁺, 63), 279 (14), 267 (100), 238 (81), 197 (53), 167 (27), 155 (62), 123 (22); Anal. Calcd for C₁₅H₈BrN₅O₄S (434.22): C 41.49, H 1.86, Br 18.40, N 16.13, S 7.38; Found: C 41.61, H 1.72, Br 18.29, N 16.25, S 7.47.

2.2.3. Synthesis of substituted hydrazono-2,3-dihydrothiazoles **16a-i**

A mixture of ω-bromoacetophenone **2a/b** (1.0 mmol, **2a**, 0.198; **2b**, 0.277 g) and 1,4-disubstituted thiosemicarbazides **15a-e** (1.0 mmol, **15a**, 0.333; **15b**, 0.339; **15c**, 0.285; **15d**, 0.297 and **15e**, 0.335 g) in 30 ml absolute ethanol was heated under reflux with stirring for 4-6 h, the reaction was followed up by TLC analysis. The precipitate was allowed to stand, filtered, washed with 5 ml ethanol, dried and recrystallized from the mentioned solvent to give hydrazothiazoles **16a-i** (Scheme 4).

2.2.3.1. *(Z)*-2-(2-(2,4-Dinitrophenyl)hydrazono)-3,4-diphenyl-2,3-dihydrothiazole (**16a**)

Brown crystals (methanol); yield 390 mg (90%); Mp. 241-243°C; ¹H NMR (400 MHz, DMSO-d₆) δ 6.82 (s, 1H, thiazole-H), 7.12-7.50 (m, 10H, Ar-H), 7.96-8.08 (m, 1H, Ar-H), 8.24-8.26 (m, 1H, Ar-H), 8.83-8.85 (m, 1H, Ar-H), 10.54 (br, s, 1H, NH, exchange with

D₂O) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 116.15 (thiazole-CH), 124.17, 125.24, 126.82, 128.34, 129.07, 130.00, 130.90, 131.87, 132.50, (Ar-CH), 132.84, 135.66, 136.59, 140.85, 141.18 (Ar-C), 145.00 (thiazole-C4), 165.83 (thiazole-C2) ppm; IR (KBr): ν = 3254 (hydrazo-NH), 3015 (Ar-CH), 1621 (C=N), 1578 cm⁻¹ (Ar-C=C); MS (70 eV): m/z (%) = 433 (M⁺, 100), 357 (28), 251 (14), 167 (13), 137 (73), 123 (32); Anal. Calcd for C₂₁H₁₅N₅O₄S (433.44): C 58.19, H 3.49, N 16.16, S 7.40; Found: C 58.22, H 3.56, N 16.02, S 7.29.

2.2.3.2. *(Z)*-3-Cyclohexyl-2-(2-(2,4-dinitrophenyl)hydrazono)-4-phenyl-2,3-dihydrothiazole (**16b**)

Brown crystals (methanol); yield 386 mg (88%); Mp. 230-232°C; ¹H NMR (400 MHz, DMSO-d₆): δ 1.06-1.09 (m, 4H, cyclohexyl-CH₂), 1.76-1.78 (m, 6H, cyclohexyl-CH₂), 3.72-3.74 (m, 1H, cyclohexyl-CH), 6.91 (s, 1H, thiazole-H), 7.48-7.52 (m, 6H, Ar-H), 8.28-8.38 (m, 1H, Ar-H), 8.87-8.89 (m, 1H, Ar-H), 10.53 (br, s, 1H, NH, exchange with D₂O) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 24.68, 25.56, 27.78 (cyclohexyl-CH₂), 58.88 (cyclohexyl-CH), 115.45 (thiazole-CH), 123.48, 128.80, 128.94, 129.59, 130.16, 131.15 (Ar-CH), 135.62, 137.18, 139.00, 141.53 (Ar-C), 144.90 (thiazole-C4), 164.40 (thiazole-C2) ppm; IR (KBr): ν = 3263 (hydrazo-NH), 3007 (Ar-CH), 2927-2865 (Alk-CH), 1613 (C=N), 1585 cm⁻¹ (Ar-C=C) ppm; MS (70 eV): m/z (%) = 439 (M⁺, 16), 363 (34), 357 (32), 257 (55), 168 (8), 156 (100), 137 (73), 123 (47); Anal. Calcd for C₂₁H₂₁N₅O₄S (439.49): C 57.39, H 4.82, N 15.94, S 7.30; Found: C 57.27, H 4.91, N 16.08, S 7.44.

2.2.3.3. *(Z)*-2-(2-(2,4-Dinitrophenyl)hydrazono)-3-ethyl-4-phenyl-2,3-dihydrothiazole (**16c**)

Brown crystals (methanol); yield 335 mg (87%); Mp. 222-224°C; ¹H NMR (400 MHz, CDCl₃): δ 1.28 (t, 3H, CH₃, J = 7.66), 3.52 (q, 2H, CH₂, J = 7.66), 7.10 (s, 1H, thiazole-H), 7.45-7.75 (m, 6H, Ar-H), 8.22-8.30 (m, 1H, Ar-H), 8.92-8.94 (m, 1H, Ar-H), 10.32 (br, s, 1H, NH, exchange with D₂O) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 15.28 (CH₃), 38.78 (CH₂), 115.20 (thiazole-CH), 123.23, 126.71, 128.78, 129.81, 130.40, 131.20 (Ar-CH), 131.88, 134.96, 139.11, 141.32 (Ar-C), 145.61 (thiazole-C4), 164.86 (thiazole-C2) ppm; IR (KBr): ν = 3195 (hydrazo-NH), 3018 (Ar-CH), 2925-2860 (Alk-CH), 1611 (C=N), 1581 cm⁻¹ (Ar-C=C); MS (70 eV): m/z (%) = 385 (M⁺, 100), 307 (32), 285 (15), 204 (12), 183 (38), 167 (13), 137 (73), 123 (29); Anal. Calcd for C₁₇H₁₅N₅O₄S (385.40): C 52.98, H 3.92, N 18.17, S 8.32; Found: C 53.11, H 4.09, N 18.06, S 8.21.

2.2.3.4. *(Z)*-4-(4-Bromophenyl)-2-(2-(2,4-dinitrophenyl)hydrazono)-3-phenyl-2,3-dihydrothiazole (**16d**)

Brown crystals (methanol); yield 430 mg (84%); Mp. 252-254°C; ¹H NMR (400 MHz, DMSO-d₆): δ 6.86 (s, 1H, thiazole-H), 7.09-7.50 (m, 9H, Ar-H), 7.90-8.00 (m, 1H, Ar-H), 8.20-8.27 (m, 1H, Ar-H), 8.78-8.84 (m, 1H, Ar-H), 10.53 (br, s, 1H, NH, exchange with D₂O) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ 115.60 (thiazole-CH), 122.20; 123.31, 128.38, 128.56, 129.17, 129.41, 129.86, 130.12 (Ar-CH), 130.33, 131.33, 135.96, 136.79, 139.22, 140.89 (Ar-C), 146.29 (thiazole-C4), 166.04 (thiazole-C2) ppm; IR (KBr): ν = 3254 (hydrazo-NH), 3015 (Ar-CH), 1621 (C=N), 1578 cm⁻¹ (Ar-C=C); MS (70 eV): m/z (%) = 513/511 (M⁺, 100), 357 (38), 329 (70), 267 (64), 181 (44), 167 (33), 135 (76), 123 (25); Anal. Calcd for C₂₁H₁₄BrN₅O₄S (512.34): C 49.23, H 2.75, Br 15.60, N 13.67, S 6.26; Found: C 49.10, H 2.67, Br 15.73, N 13.59, S 6.39.

2.2.3.5. *(Z)*-3-Allyl-4-(4-bromophenyl)-2-(2-(2,4-dinitrophenyl)hydrazono)-2,3-

dihydrothiazole (16e)

Brown crystals (methanol); yield 409 mg (86%); Mp. 229-231°C; ¹H NMR (400 MHz, CDCl₃): δ 4.30-4.45 (m, 2H, allyl-CH₂N), 4.90-5.00 (m, 2H, allyl-CH₂=), 5.76-5.86 (m, allyl-CH=), 6.85 (s, 1H, thiazole-H), 7.41-7.45 (m, 2H, Ar-H), 7.69-7.73 (m, 2H, Ar-H), 7.76-7.79 (m, 1H, Ar-H), 8.25-8.29 (m, 1H, Ar-H), 8.82-8.92 (m, 1H, Ar-H), 10.58 (br, s, 1H, NH, exchange with D₂O) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 47.68 (allyl-CH₂N), 115.73 (thiazole-CH), 117.18 (allyl-CH₂=), 124.80, 128.65, 129.87, 130.47, 133.57 (Ar-CH), 134.28 (allyl-CH=), 135.96, 136.88, 138.11, 141.51, 142.92 (Ar-C), 145.15 (thiazole-C4), 165.36 (thiazole-C2) ppm; IR (KBr): ν = 3193 (hydrazo-NH), 3014 (Ar-CH), 1626 (C=N), 1602 cm⁻¹ (Ar-C=C); MS (70 eV): m/z (%) = 477/475 (M⁺, 100), 435 (29), 321 (61), 293 (15), 183 (12), 167 (64), 136 (71), 123 (54); Anal. Calcd for C₁₈H₁₄BrN₅O₄S (476.30): C 45.39, H 2.96, Br 16.78, N 14.70, S 6.73; Found: C 45.51, H 3.06, Br 16.69, N 14.81, S 6.61.

2.2.3.6. *(Z)-3-Allyl-2-(2-(2,4-dinitrophenyl)hydrazono)-4-phenyl-2,3-dihydrothiazole (16f)*

Brown crystals (methanol); yield 353 mg (89%); Mp. 235-237°C; ¹H NMR (400 MHz, CDCl₃): δ 4.30-4.34 (m, 2H, allyl-CH₂N), 5.11-5.20 (m, 2H, allyl-CH₂=), 5.75-5.88 (m, allyl-CH=), 7.12 (s, 1H, thiazole-H), 7.22-7.32 (m, 3H, Ar-H), 7.43-7.48 (m, 2H, Ar-H), 7.50-7.61 (m, 1H, Ar-H), 8.10-8.13 (m, 1H, Ar-H), 9.00-9.02 (m, 1H, Ar-H), 10.31 (br, s, 1H, NH, exchange with D₂O) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 46.95 (allyl-CH₂N), 116.76 (thiazole-C5), 118.38 (allyl-CH₂=), 124.42, 129.48, 130.65, 132.85, 132.94, 133.04 (Ar-CH), 134.53 (allyl-CH=), 134.72, 137.25, 138.12, 143.16 (Ar-C), 145.82 (thiazole-C4), 164.98 (thiazole-C2) ppm; IR (KBr): ν = 3223 (hydrazo-NH), 3018 (Ar-CH), 3018

(Ar-CH), 2975, 2852 (Ali-CH), 1619 (C=N), 1584 cm^{-1} (Ar-C=C); MS (70 eV): m/z (%) = 397 (M^+ , 100), 321 (58), 215 (23), 183 (23), 136 (84), 123 (65); Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_5\text{O}_4\text{S}$ (397.41): C 54.40, H 3.80, N 17.62, S 8.07; Found: C 54.29, H 3.87, N 17.78, S 7.91.

2.2.3.7. *(Z)*-4-(4-Bromophenyl)-2-(2-(2,4-dinitrophenyl)hydrazono)-3-ethyl-2,3-dihydrothiazole (**16g**)

Brown crystals (methanol); yield 413 mg (89%); Mp. 227-228°C; ^1H NMR (400 MHz, CDCl_3): δ 1.22 (t, 3H, CH_3 , $J = 7.77$), 3.84 (q, 2H, CH_2 , $J = 7.77$), 7.06 (s, 1H, thiazole-H), 7.25-7.32 (m, 2H, Ar-H), 7.42-7.65 (m, 2H, Ar-H), 7.85-7.92 (m, 1H, Ar-H), 8.35-8.42 (m, 1H, Ar-H), 8.80-8.94 (m, 1H, Ar-H), 10.30 (br, s, 1H, NH, exchange with D_2O) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 15.37 (CH_3), 39.56 (CH_2), 116.60 (thiazole-C5), 123.77, 125.54, 128.40, 129.60, 130.87 (Ar-CH), 131.25, 134.62, 136.51, 139.34, 141.32 (Ar-C), 145.90 (thiazole-C4), 164.48 (thiazole-C2) ppm; IR (KBr): $\nu = 3195$ (hydrazo-NH), 3018 (Ar-CH), 2925-2860 (Ali-CH), 1611 (C=N), 1581 cm^{-1} (Ar-C=C); MS (70 eV): m/z (%) = 465/463 (M^+ , 100), 308 (45), 283 (56), 204 (41), 183 (22), 176 (32), 167 (14), 156 (51), 136 (67), 123 (22); Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{BrN}_5\text{O}_4\text{S}$ (464.29): C 43.98, H 3.04, Br 17.21, N 15.08, S 6.91; Found: C 43.85, H 2.97, Br 17.09, N 14.96, S 6.87.

2.2.3.8. *(Z)*-*N'*-(3-Benzyl-4-phenylthiazol-2(3H)-ylidene)-4-methylbenzenesulfonylhydrazide (**16h**)

Violet crystals (methanol); yield 357 mg (82%); Mp. 212-214 °C; ^1H NMR (400 MHz, CDCl_3): δ 2.30 (s, 3H, CH_3), 4.82 (s, 2H, CH_2Ph), 6.75 (s, 1H, thiazole-H), 6.92-7.42 (m, 15H, Ar-H and NH, exchange with D_2O) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 21.60 (CH_3), 46.25 (CH_2Ph), 115.76 (thiazole-C5), 125.87, 126.52, 127.62, 128.32, 128.60,

128.74, 129.05, 129.23 (Ar-CH), 132.71, 133.66, 135.20, 139.00 (Ar-C), 146.86 (thiazole-C4), 163.45 (thiazole-C2) ppm; IR (KBr): ν = 3150 (hydrazo-NH), 3038 (Ar-CH), 2973 (Ali-CH), 1614 (C=N), 1553 and 1491 cm^{-1} (Ar-C=C); MS (70 eV): m/z (%) = 435 (M^+ , 100), 358 (52), 264 (36), 188 (25), 170 (87), 155 (54), 91 (73), 77 (60); Anal. Calcd for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_2\text{S}_2$ (435.56): C 63.42, H 4.86, N 9.65, S 14.72; Found: C 63.34, H 4.76, N 9.55, S 14.57.

2.2.3.9. *(Z)-3-Benzyl-2-(2-(2,4-dinitrophenyl)hydrazono)-4-phenyl-2,3-dihydrothiazole (16i)*

Brown crystals (methanol); yield 402 mg (90%); Mp. 226-228 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 5.08 (s, 1H, CH_2Ph), 6.98 (s, 1H, thiazole-H), 7.05-7.50 (m, 11H, Ar-H), 8.04-8.13 (m, 1H, Ar-H), 8.79-8.82 (m, 1H, Ar-H), 10.60 (br, s, 1H, NH, exchange with D_2O) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.50 (CH_2Ph), 115.51 (thiazole-C5), 123.36, 126.52, 126.62, 127.27, 128.53, 128.87, 129.55, 129.96, 130.83 (Ar-CH), 131.80, 135.35, 136.47, 138.64, 142.10 (Ar-C), 145.30 (thiazole-C4), 162.50 (thiazole-C2) ppm; IR (KBr) ν = 3117 (hydrazo-NH), 3058, 3027 (Ar-CH), 2944 (Ali-CH), 1616 (C=N), 1587 and 1491 cm^{-1} (Ar-C=C); MS (70 eV): m/z (%) = 447 (M^+ , 100), 371 (51), 265 (33), 189 (73), 183 (40), 167 (83), 123 (32); Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{N}_5\text{O}_4\text{S}$ (447.47): C 59.05, H 3.83, N 15.65, S 7.17; Found: C 58.98, H 3.76, N 15.48, S 7.03.

2.2.4. Synthesis of substituted thiazolium bromide dihydrate 19a-g.

ω -Bromoacetophenone **2a/b** (1.0 mmol, **2a**, 0.198; **2b**, 0.277 g) and substituted thiosemicarbazides **1a-d** (1.0 mmol, **1a**, 0.167; **1b**, 0.201; **1c**, 0.257 and **1d**, 0.245 g) in 30 ml absolute ethanol were stirred under reflux for 8-12 h. The reaction was follow up by TLC analysis. A precipitate from the salt **19a-g** was formed (Scheme 6), filtered, washed

with a little of ethanol, dried and recrystallized from the mentioned solvent.

2.2.4.1. *2-Amino-5-(4-aminophenyl)-4-phenylthiazol-3-ium bromide dihydrate (19a)*

Colorless crystals (ethanol); yield 426 mg (88%); Mp. 215-217°C; ¹H NMR (400 MHz, CDCl₃): δ 6.43-6.52 (br, s, 2H, NH₂), 6.68-6.74 (br, s, 2H, thiazole-NH₂), 7.05-7.10 (m, 2H, Ar-H), 7.18-7.32 (m, 4H, Ar-H), 7.47-7.52 (m, 3H, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 115.09, 122.37, 128.12, 128.79, 130.61 (Ar-CH), 123.24, 127.24 (Ar-C), 135.37 (thiazole-C4), 144.33 (Ar-C-NH₂), 149.84 (thiazole-C5), 168.51 (thiazole-C2) ppm; IR (KBr): ν = 3325-3343 (NH₂ s), 1607 (C=N), 1592 cm⁻¹ (Ar-C=C) ppm; MS (70 eV): m/z (%) = 387/385 (M⁺, 15), 365 (M⁺ - HBr, 23), 267 (M⁺ - (HBr + H₂O), 100), 190 (16), 176 (33), 92 (19), 81 (38); Anal. Calcd for C₁₅H₁₈BrN₃O₂S (384.29): C 46.88, H 4.72, Br 20.79, N 10.93, S 8.34; Found: C 46.97, H 4.83, Br 20.66, N 11.09, S 8.19.

2.2.4.2. *2-Amino-5-(4-amino-2-chlorophenyl)-4-phenylthiazol-3-ium bromide dehydrate (19b)*

Colorless crystals (ethanol); yield 334 mg (80%); Mp. 210-212 °C; ¹H NMR (400 MHz, DMSO-d₆): δ = 6.53-6.58 (br, s, 2H, NH₂), 6.72-6.76 (br, s, 2H, thiazole-NH₂), 7.05-7.10 (m, 2H, Ar-H), 7.23-7.49 (m, 6H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ = 113.49, 116.02, 125.60, 127.73, 128.61, 129.08 (Ar-CH), 129.41, 131.43, 133.65 (Ar-C), 134.26 (thiazole-C4), 143.89 (Ar-C-NH₂), 150.35 (thiazole-C5), 168.08 (thiazole-C2) ppm; IR (KBr): ν = 3298-3275 (NH₂ s), 1610 (C=N), 1588 cm⁻¹ (Ar-C=C); MS (70 eV): m/z (%) = 423/419 (M⁺, 8), 337 (M⁺ - HBr, 25), 302 (M⁺ - (HBr + H₂O), 100), 225 (10), 127(9), 81 (31); Anal. Calcd for C₁₅H₁₇BrClN₃O₂S (418.74): C 43.02, H 4.09, Br 19.08, Cl 8.47, N 10.03, S 7.66; Found: C 42.89, H 4.16, Br 18.96, Cl 8.58, N 9.91, S 7.59.

2.2.4.3. *2-Amino-5-(2-methyl-5-sulfamoylphenyl)-4-phenylthiazol-3-ium bromide dihydrate (19c)*

Colorless crystals (ethanol); yield 379 mg (82%); Mp. 232-234°C; ¹H NMR (400 MHz, CDCl₃): δ = 2.23 (s, 3H, CH₃), 6.72-6.80 (br, s, 2H, thiazole-NH₂), 7.09-7.15 (m, 2H, Ar-H), 7.22-7.30 (m, 4H, Ar-H), 7.42-7.50 (br, s, 2H, SO₂NH₂), [29,30] 7.65-7.75 (m, 2H, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 29.27 (CH₃); 123.36, 125.50, 127.47, 128.61, 129.55, 129.94 (Ar-CH), 133.13, 133.37 (Ar-C), 134.08 (thiazole-C4), 136.44 (Ar-C-SO₂NH₂), 144.82 (Ar-C-CH₃); 150.62 (thiazole-C5), 169.20 (thiazole-C2) ppm; IR (KBr, cm⁻¹): ν = 3332-3312 (NH₂`s), 1625 (C=N), 1585 (Ar-C=C); MS (70 eV): m/z (%) = 465/463 (M⁺, 7), 346 (M⁺ - (HBr + H₂O), 100), 175 (24), 171 (21), 157 (26), 91 (42), 81 (17); Anal. Calcd for C₁₆H₂₀BrN₃O₄S₂ (462.38): C 41.56, H 4.36, Br 17.28, N 9.09, S 13.87; Found: C 41.38, H 4.45, Br 17.19, N 8.88, S 14.04.

2.2.4.4. *2-Amino-5-(2-amino-3,5-dinitrophenyl)-4-phenylthiazol-3-ium bromide dihydrate (19d)*

Brown crystals (ethanol); yield 403 mg (85%); Mp. 245-247°C; ¹H NMR (400 MHz, DMSO-d₆): δ = 6.68-6.76 (br, s, 2H, thiazole-NH₂), 7.10-7.15 (br, s, 2H, NH₂), 7.40-7.65 (m, 3H, Ar-H), 8.10-8.18 (m, 2H, Ar-H), 8.60-8.70 (d, 1H, Ar-H), 8.96-9.10 (d, 1H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ = 120.43, 121.27, 126.04, 128.76, 129.06 (Ar-CH); 123.37, 127.84 (Ar-C), 135.74 (thiazole-C4), 145.79 (Ar-C-NH₂), 146.68, 148.63 (Ar-C-NO₂), 150.62 (thiazole-C5), 169.59 (thiazole-C2) ppm; IR (KBr): ν = 3332-3312 (NH₂`s), 1625 (C=N), 1585 cm⁻¹ (Ar-C=C); MS (70 eV): m/z (%) = 477/475 (M⁺, 12), 396 (M⁺ - HBr, 26), 358 (M⁺ - (HBr + H₂O), 100), 183 (24), 176 (22), 138 (69), 81 (17); Anal. Calcd for C₁₅H₁₆BrN₅O₆S (474.29): C 37.99, H 3.40, Br 16.85, N 14.77, S 6.76; Found: C

38.12, H 3.49, Br 16.73, N 14.64, S 6.94.

2.2.4.5. *2-Amino-5-(4-aminophenyl)-4-(4-bromophenyl)-thiazol-3-ium bromide dihydrate (19e)*

Colorless crystals (ethanol); yield 426 mg (88%); Mp. 228-230°C; ¹H NMR (400 MHz, CDCl₃): δ = 6.44-6.56 (br, s, 2H, NH₂), 6.66-6.74 (br, s, 2H, thiazole-NH₂), 7.12-7.17 (m, 2H, Ar-H), 7.20-7.30 (m, 4H, Ar-H), 7.38-7.46 (m, 2H, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 116.32, 123.44, 128.35, 132.22 (Ar-CH), 123.13, 124.57, 133.78 (Ar-C), 136.33 (thiazole-C4), 143.83 (Ar-C-NH₂), 149.73 (thiazole-C5), 168.30 (thiazole-C2) ppm; IR (KBr): ν = 3310-3243 (NH₂'s), 1623 (C=N), 1586 cm⁻¹ (Ar-C=C); MS (70 eV): m/z (%) = 467/463 (M⁺, 18), 381 (M⁺ - HBr, 23), 346 (M⁺ - (HBr + H₂O), 100), 225 (20), 191 (46), 92 (57), 81 (31); Anal. Calcd for C₁₅H₁₇Br₂N₃O₂S (463.19): C 38.90, H 3.70, Br 34.50, N 9.07, S 6.92; Found: C 39.04, H 3.61, Br 34.66, N 8.89, S 7.09.

2.2.4.6. *2-Amino-4-(4-bromophenyl)-5-(2-methyl-5-sulfamoylphenyl) thiazol-3-ium bromide dihydrate (19f)*

Colorless crystals (ethanol); yield 433 mg (80%); Mp. 241-243°C; ¹H NMR (400 MHz, CDCl₃): δ = 2.27 (s, 3H, CH₃), 6.60-6.72 (br, s, 2H, thiazole-NH₂), 7.00-7.15 (m, 2H, Ar-H), 7.32-7.38 (m, 3H, Ar-H), 7.45-7.52 (br, s, 2H, SO₂-NH₂), [30,31] 7.72-7.78 (m, 2H, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 29.72 (CH₃), 127.35, 128.52, 129.90, 130.09, 131.72 (Ar-CH), 124.63, 128.26, 135.50 (Ar-C), 134.82 (thiazole-C4), 136.28 (Ar-C-SO₂NH₂), 145.30 (Ar-C-CH₃), 150.43 (thiazole-C5), 170.18 (thiazole-C2) ppm; IR (KBr): ν = 3332-3312 (NH₂'s), 1625 (C=N), 1585 cm⁻¹ (Ar-C=C); MS (70 eV): m/z (%) = 545/541 (M⁺, 39), 460 (M⁺ - HBr, 20), 426 (M⁺ - (HBr + H₂O), 100), 255 (34), 171 (68), 157 (36), 91 (92); Anal. Calcd for C₁₆H₁₉Br₂N₃O₄S₂ (541.28): C 35.50, H 3.54, Br 29.52,

N 7.76, S 11.85; Found: C 35.39, H 3.62, Br 29.43, N 7.64, S 11.69.

2.2.4.7. *2-Amino-5-(2-amino-3,5-dinitrophenyl)-4-(4-bromophenyl)thiazol-3-ium bromide dihydrate (19g)*

Brown crystals (ethanol); yield 459 mg (83%); Mp. 256-258°C; ¹H NMR (400 MHz, DMSO-d₆): δ = 6.78-6.83 (br, s, 2H, thiazole-NH₂), 7.00-7.08 (br, s, 2H, NH₂), 7.28-7.40 (m, 4H, Ar-H), 8.23-8.65 (d, 1H, Ar-H), 8.82-8.98 (d, 1H, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-d₆) δ: 122.70, 129.47, 130.47, 131.59 (Ar-CH), 123.21, 125.81 (Ar-C), 135.75 (thiazole-C4), 145.60 (Ar-C-NH₂), 147.67, 148.70 (Ar-C-NO₂), 150.00 (thiazole-C5), 168.00 (thiazole-C2); IR (KBr): ν = 3332-3312 (NH₂'s), 1625 (C=N), 1585 cm⁻¹ (Ar-C=C); MS (70 eV): m/z (%) = 557/553 (M⁺, 32), 472 (M⁺ - HBr, 34), 436 (M⁺ - (HBr + H₂O), 100), 183 (51), 176 (22), 168 (26); Anal. Calcd for C₁₅H₁₅Br₂N₅O₆S (553.18): C 32.57, H 2.73, Br 28.89, N 12.66, S 5.80; Found: C 32.71, H 2.64, Br 29.03, N 12.76, S 5.69.

2.3. Single crystal X-ray structure determination of **3a**, **16h** and **19b**

The single crystal X-ray diffraction studies for **3a**, **16h** and **19b** were carried out on a Bruker D8 Venture diffractometer with Photon 100 detector at 123 K using CuKα radiation (λ = 1.54178 Å) for **3a** and **19b** or MoKα radiation (λ = 0.71073 Å) for **16h**. Direct methods (SHELXS-97)[31] were used for structure solution and refinement was carried out using SHELXS-2013/2014[32] (full-matrix least squares on F²). Hydrogen atoms were localized by difference **Fourier** synthesis map and refined using a riding model [H(N, O) free]. Semi-empirical absorption corrections were applied. For **16h** and **19b** extinction correction was applied. The absolute structure of **19b** is determined by refinement of Parsons Flack parameter.[33]

2.3.1. **Compound 3a:** $C_{15}H_{11}N_3S$, $M_r = 265.33 \text{ g mol}^{-1}$, orange blocks, crystal size = 0.22 x 0.10 x 0.05 mm, monoclinic space group $P2_1/c$ (no. 14), $a = 21.7180(5) \text{ \AA}$, $b = 5.1347(1) \text{ \AA}$, $c = 11.3211(3) \text{ \AA}$, $\beta = 92.280(1)^\circ$, $V = 1261.48(5) \text{ \AA}^3$, $Z = 4$, $D_{\text{calcd}} = 1.397 \text{ Mg m}^{-3}$, $F(000) = 552$, $\mu = 2.170 \text{ mm}^{-1}$, $T = 123 \text{ K}$, 14789 measured reflections ($2\theta_{\text{max}} = 144.0^\circ$), 2473 independent reflections [$R_{\text{int}} = 0.027$], 172 parameters, $R_1[\text{for } 2305 \text{ with } I > 2\sigma(I)] = 0.028$, $wR_2 \text{ (for all data)} = 0.073$, $S = 1.04$, largest diff. peak and hole = $0.327 \text{ e \AA}^{-3} / -0.184 \text{ e \AA}^{-3}$.

2.3.2. **Compound 16h:** $C_{23}H_{21}N_3O_2S_2$, $M_r = 435.55 \text{ g mol}^{-1}$, violet blocks, crystal size = 0.45 x 0.35 x 0.20 mm, monoclinic space group $P2_1/c$ (no. 14), $a = 9.3897(5) \text{ \AA}$, $b = 11.0215(5) \text{ \AA}$, $c = 20.0638(9) \text{ \AA}$, $\beta = 101.146(2)^\circ$, $V = 2037.21(17) \text{ \AA}^3$, $Z = 4$, $D_{\text{calcd}} = 1.420 \text{ Mg m}^{-3}$, $F(000) = 912$, $\mu = 0.288 \text{ mm}^{-1}$, $T = 123 \text{ K}$, 59879 measured reflections ($2\theta_{\text{max}} = 55.0^\circ$), 4684 independent reflections [$R_{\text{int}} = 0.033$], 276 parameters, 1 restraint, $R_1[\text{for } 4231 \text{ with } I > 2\sigma(I)] = 0.032$, $wR_2[\text{for all data}] = 0.079$, $S = 1.07$, largest diff. peak and hole = $0.499 \text{ e \AA}^{-3} / -0.431 \text{ e \AA}^{-3}$.

2.3.3. **Compound 19b:** $C_{15}H_{13}ClN_3S \cdot Br \cdot 2(H_2O)$, $M_r = 418.74 \text{ g mol}^{-1}$, colorless blocks, crystal size = 0.25 x 0.20 x 0.10 mm, orthorhombic space group $P2_12_12_1$ (no. 19), $a = 7.2127(2) \text{ \AA}$, $b = 10.7593(3) \text{ \AA}$, $c = 21.8730(5) \text{ \AA}$, $V = 1697.42(8) \text{ \AA}^3$, $Z = 4$, $D_{\text{calcd}} = 1.639 \text{ Mg m}^{-3}$, $F(000) = 848$, $\mu = 6.008 \text{ mm}^{-1}$, $T = 123 \text{ K}$, 17133 measured reflections ($2\theta_{\text{max}} = 144.2^\circ$), 3324 independent reflections [$R_{\text{int}} = 0.027$], 236 parameters, $R_1[\text{for } 3291 \text{ with } I > 2\sigma(I)] = 0.045$, $wR_2[\text{for all data}] = 0.045$, $S = 1.08$, largest diff. peak and hole = $0.382 \text{ e \AA}^{-3} / -0.252 \text{ e \AA}^{-3}$.

3. Results and Discussion

In our present studies arylthiosemicarbazides **1a-d** and ω -bromoacetophenones **2a,b** were selected as reagents under Eschenmoser-contraction method [34,35] (Scheme 1 and 2) to receive a new C-C bond and synthesize aminophenylpyrazoles **14** (Scheme 3) instead, 4-aryl (2-alkyldiazenylthiazole) **3a-e** were observed (Scheme 1).

(Scheme 1)

The mechanism for the formation of **3a-e** is illustrated in scheme 2. Upon adding different amounts of triphenylphosphine as a thiophile and triethylamine as the base, the reaction does not produce a significant change in the products **3a-e**, and the yields were roughly the same. Also, it was found that Et₃N plays an important role on the reaction efficiency and products **3a-e**, even in the absence of thiophile Ph₃P (Scheme 2 and Scheme 3).

(Scheme 2)

(Scheme 3)

The present study will discuss the **behavior** of ω -bromoacetophenones **2a,b** towards 1,4-disubstituted thiosemicarbazides **15a-e** and will be compared to the behavior of the same compounds towards **1a-d**. Hydrazinothiazoles **16a-i** was formed during the reaction of **2a,b** with **15a-e** (Scheme 4).

(Scheme 4)

The mechanism for the formation of the compounds **16a-i** is shown in scheme 5.

(Scheme 5)

In the present study, condensation of ω -bromoacetophenones **2a,b** with substituted thiosemicarbazides **1a-d** afforded 2-amino-5-(4-aminophenyl)-4-phenyl-thiazol-3-ium bromide dihydrate **19a-g** via [5.5] sigmatropic rearrangement (Scheme 6).

(Scheme 6)

The mechanism for the formation of **19a-g** is described in Scheme 7, whereas, the mechanism for the formation of **19c,f** is described in Scheme 8.

(Scheme 7)

(Scheme 8)

All the synthesized compounds have been characterized by means of both analytical and spectroscopic methods, as follows.

3.1. Infrared spectroscopy of **3a-e**, **16a-I** and **19a-g**.

Figure 1

All compounds **3a-e** exhibit orange colors: The IR spectrum of **3a** (Fig. 1 as an example of diazenylthiazoles) showed characteristic bands of aromatic groups were observed at 1585 cm^{-1} corresponding to Ar-C=C stretching vibration of benzene and thiazole rings. The

C=N stretching band at 1600 cm^{-1} . The IR spectrum of **3a** confirm the presence of azo group (N=N) at 1560 and 1444 cm^{-1} .

In the hydrazothiazoles **16a-i** the IR peaks showed at $3263\text{--}3193\text{ cm}^{-1}$ broad bands of hydrazo-NH group, C=N at $1626\text{--}1611\text{ cm}^{-1}$.

The IR spectrum of **19b** showed bands at $3298\text{--}3275\text{ cm}^{-1}$ due to NH_2 groups and bands at 1610 (C=N), 1588 cm^{-1} (Ar-C=C).

3.2. ^1H and ^{13}C NMR spectra of **3a-e**, **16a-i** and **19a-g**.

Figure 2

The NMR spectra (^1H and ^{13}C) of compound **3a** were recorded using CDCl_3 as solvent and TMS as an internal standard (Figure 2) which showed three multiplets corresponding to ten protons at $\delta = 7.40\text{--}7.58$ and $8.03\text{--}8.88$ ppm due to aryl protons.

The ^{13}C NMR of **3a** (Figure 3) contained three signals at $\delta = 168.46$ (thiazole-C2), 155.85

(thiazole-C4) and 115.88 ppm (thiazole-CH), with the absence of C=S group. The downfield shift of thiazole-C2,4 is due to the high conjugation of thiazole ring with respect to azo- and aryl groups. From the spectral data, it can be concluded that ^1NH , ^3NH , ^4NH and thioxo group are the nucleophilic sites to form the products **3a-e**.

Figure 3

The ^1H NMR spectrum of **16b** showed one broad signal at $\delta = 10.53$ ppm due to hydrazo-NH which was confirmed further by H_2O exchange experiment. Also, the aromatic protons observed in the expected region 7.48-7.52, 8.28-8.38 and 8.87-8.89 ppm. One singlet at $\delta = 6.91$ because of thiazole-CH. Signals at 1.06-1.09, 1.76-1.78 and 3.72-3.74 due to cyclohexyl- CH_2 and CH.

In the ^{13}C NMR spectra of **16b** signals at $\delta = 164.40$, 144.90 and 115.45 ppm were assigned to thiazole-C2, thiazole-C4 and thiazole-CH, respectively.

On the other hand, in the ^1H NMR spectrum of **19b**, two broad signals at 6.53-6.58 and 6.72-6.76 ppm are due to NH_2 attached to phenyl ring and the other for NH_2 attached to thiazole ring. Eight protons were observed at $\delta = 7.05$ -7.10 and 7.23-7.49 ppm because of aromatic protons.

The ^{13}C NMR spectra of **19b** showed downfield shifted signals at 168.08 (thiazole-C2) and 150.35 (thiazole-C5). Signals at 129.41, 131.43 and 133.65 (Ar-C), 143.89 (Ar-C- NH_2), 134.26 (thiazole-C4), in addition to the signals of Ar-CH.

3.3. Mass spectrometry of **3a-e**, **16a-I** and **19a-g**.

Elemental analyses and mass spectra of compounds **3a-e** clearly showed that the azothiazoles **3a-e** were formed during the addition equimolar amounts of thiosemicarbazides **1a-d** and acetophenones **2a,b** *via* elimination ($\text{HBr} + \text{H}_2\text{O}$).

Form the mass spectrometry of **16b**, the molecular ion peak at $m/z = 439$ (16%) with abstraction HBr and H_2O from the reactants.

The molecular ion peak of **19b** as an example of thiazolium bromide dihydrates at $m/z = 423/419$ (M^+ , 9%) with molecular formula $\text{C}_{15}\text{H}_{17}\text{BrClN}_3\text{O}_2\text{S}$ and fragmentation patterns at 337 ($\text{M}^+ - \text{HBr}$, 25), 302 ($\text{M}^+ - (\text{HBr} + \text{H}_2\text{O})$, 100).

3.4. X-ray structure determination of **3a**, **16h** and **19b**.

Suitable single crystals for X-ray analysis of compound **3a** were obtained by crystallization from acetonitrile. X-ray crystallography (Fig. 6, Tables S1-S6 in the supporting information) provided unambiguous proof that (*E*)-4-phenyl-2-(phenyldiazenyl)thiazole **3a** was formed exclusively during the reaction of **1a** with **2a**. The

X-ray analysis of **3a** confirms a *transiod* geometry with respect to the N7-N8 double bond.

Sum of angles around C2, C4 and C5 are 360° revealing the planarity of the thiazole ring (Figure 4).

Figure 4

For the hydrazonothiazoles **16a-i**, the overall structure including the Z-configuration was also confirmed by X-ray crystallography of one derivative **16h** (Figure 5, Tables S7-S13).

Figure 5

The molecular structure of 5-(4-amino-2-chlorophenyl)-4-phenylthiazol-2(3*H*)-iminium bromide dihydrate **19b** was established by single crystal X-ray analysis (Figure 6, Tables S14-S20).

Figure 6

The dihedral angle between S1/N3-C2-C5 thiazole and C6-C11 in phenyl rings is 75.0°. In the crystal, the lattice water and bromide ion associated through hydrogen bonded with thiazole-NH₂.

4. Conclusions

Novel diazenylthiazoles, hydrazothiazoles and substituted thiazolium bromide dihydrates have been synthesized from the nucleophilic addition followed by condensation between mono or disubstituted thiosemicarbazides and ω -bromoacetophenones.

Appendix A. Supplementary data

Crystallographic data (excluding structure factors) for the structure reported in this work have been deposited with Cambridge Crystallographic Data Center as supplementary

publication no CCDC 1583184 (**3a**), 1589939 (**16h**) and 1583185 (**19b**) contain the supplementary crystallographic data for this paper [36]. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Acknowledgement

Alaa A. Hassan is indebted to the AvH-Foundation for the donation of a Shimadzu 408 IR instrument.

References

- [1] A. Navarro, F. Sanz, "Dye aggregation in solution: study of C.I. direct red I". *Dyes Pig.* 40 (1999) 131-139. doi: S0143-7208(98)00048-5
- [2] R. Karpicz, V. Gulbinas, A. Undzenas, "Picosecond Spectroscopic Studies of Tautomers of a Bisazo Compound in Solutions". *J. Chin. Chem. Soc.* 47 (2000) 589-595. doi: 10.1002/jccs.200000081
- [3] M. Bhaskar, A. Gnanamani, R.J. Ganeshjeevan, R. Chandrasekar, S. Sadulla, G. Radhakrishnan, "Analyses of carcinogenic aromatic amines released from harmful azo colorants by *Streptomyces* SP. SS07". *J. Chromatogr. A* 1018 (2003) 117-123. doi:10.1016/j.chroma.2003.08.024
- [4] M. Dakiky, I. Nemcova, "Aggregation of O,O`-Dihydroxy azo Dyes III. Effect of cationic, anionic and non-ionic surfactants on the electronic spectra of 2-hydroxy-5-nitrophenylazo-4-[3-methyl-1-(400-sulfohenyl)-5-pyrazolone]". *Dyes Pig.* 44 (2000) 181-193. Doi: S0143-7208(99)00086-8
- [5] D. Zhang, M. Zhang, Z. Liu, M. Yu, F. Li, T. Yi, C. Huang, "Highly selective colorimetric sensor for cysteine and homocysteine based on azo derivatives". *Tetrahedron Lett.* 47 (2006) 7093-7096. doi:10.1016/j.tetlet.2006.07.080
- [6] J.A. Mikroyannidis, D.V. Tsagkournos, S.S. Sharma, A. Kumar, Y.K. Vijay, G.D. Sharma, "Efficient bulk heterojunction solar cells based on lowb and gap

- bisazodyes containing anthracene and/or pyrrole units". Sol. Energy mater. Sol. Cells 94 (2010) 2318-2327. doi:10.1016/j.solmat.2010.08.001
- [7] R.M. El-Shishtawy, F. Borbone, Z.M. Al-amshany, A. Tuzi, A. Barsella, A.M. Asiri, A. Roviello, "Thiazole azo dyes with lateral donor branch: Synthesis, structure and second order NLO properties". Dyes Pig. 96 (2013) 45-51. <http://dx.doi.org/10.1016/j.dyepig.2012.08.002>
- [8] P.M. Savanor, K. Jathi, R.A. Rajesha and Shoukat Ali, "Synthesis, characterization and solvatochromic spectra of novel thiazole based azo dye. Der Chemica Sinica 4 (2013) 49-54. Available online at www.pelagiaresearchlibrary.com
- [9] G.M. Malik, S. Patel Segal, H. Tailor Jitesh, "Synthesis, characterization, dyeing performance and fastness properties of 2-amino 4-phenyl thiazole based bisazo disperse dyes having different tertiary amine as a coupling component". Chemistry & Biology Interface 6 (2016) 83-91. <http://cbijournal.com/paper-archive/march-april-2016-vol-2/Research-Paper-4-synthesis-characterization-dyeing-performance-and-fastness-properties-of-2-amino-4-phenyl-thiazole.pdf>
- [10] A.K. Prajapati, V.P. Modi, "Synthesis and biological activity of *N*-[5-(4-methylphenyl)diazenyl-4-phenyl-1,3-thiazol-2-yl]benzamide derivatives". Quim. Nova 34 (2011) 771-774. <http://dx.doi.org/10.1590/S0100-40422011000500008>.
- [11] A.A. Hassan, N.K. Mohamed, K.M.-A. El-Shaieb, H.N. Tawfeek, S. Bräse, M. Nieger, "Reactivity of 2-substituted hydrazinecarbothioamides towards tetracyanoethylene and convenient synthesis of (5-amino-2-diazenylthiazolyl-methylene)malononitrile derivatives". Arkivoc (vi) (2016) 163-171. doi: <http://dx.doi.org/10.3998/ark.5550190.p009.872>
- [12] Liu, XJ, Leng, WN, Feng, JK, Ren, AM, Zhou, X "Second-order nonlinear optical properties of a series of benzothiazole derivatives". Chin. J. Chem. 21 (2003) 9-15. doi: 10.1002/cjoc.20030210105
- [13] L. Chen, Y. Cui, G. Qian, M. Wang, "Synthesis and spectroscopic characterization of an alkoxysilane dye containing azo-benzothiazole chromophore for nonlinear optical applications". Dyes Pig. 73 (2007) 338-343. doi:10.1016/j.dyepig.2006.01.023

- [14] A.O. Abdelhamide, S.M. Gomha, N.A. Abdelriheem, S.M. Kandeel, "Synthesis of New 3-Heteroarylindoles as Potential Anticancer Agents" *Molecules* 21 (2017) 929-943. doi:10.3390/molecules21070929
- [15] A.O. Abdelhamide, S.M. Gomha, S.M. Kandeel, " Synthesis of Certain New Thiazole and 1,3,4-Thiadiazole Derivatives *via* the Utility of 3-Acetylindole" *J. Heterocycl. Chem.* 59 (2017) 1529-1536. doi 10.1002/jhet.2740
- [16] H. He, X. Wang, L. Shi, W. Yin, Z. Yang, H. He, Y. Liang, "Synthesis, antitumor activity and mechanism of action of novel 1,3-thiazole derivatives containing hydrazide-hydrazone and carboxamide moiety". *Bioorg. Med. Chem. Lett.* 26 (2016) 3263-3270. doi: <http://dx.doi.org/10.1016/j.bmcl.2016.05.059>
- [17] A.A. Hassan, Y.R. Ibrahim, E.M. El-Sheref, M. Abdel-Aziz, S. Bräse, M. Nieger, "Synthesis and Antibacterial Activity of 4-Aryl-2-(1-substituted ethylidene)-thiazoles". *Arch. Pharma. Chem. Life Sci.* 346 (2013) 562-570. doi 10.1002/ardp.201300099
- [18] A.A. Hassan, S.K. Mohamed, N.K. Mohamed, K.M.-A. El-Shaieb, A.T. Abdel-Aziz, J.T. Mague, M. Akkurt, "Facile and convenient synthesis of 2,4-disubstituted and 2,3,4-trisubstituted 1,3-thiazoles". *J. Sulfur Chem.* 37 (2016) 162-175. doi: 10.1080/17415993.2015.1114621
- [19] M. Haroon, T. Akhtar, M. Yousuf, M.W. Baig, M.N. Tahir, L. Rasheed, " Synthesis, spectroscopic characterization and crystallographic behavior of ethyl 2-(4-methyl-(2-benzylidenehydrazinyl))thiazole-4-carboxylate: Experimental and theoretical (DFT) studies" *J. molecular structure* 1167 (2018) 154-160. <https://doi.org/10.1016/j.molstruc.2018.04.083>
- [20] S.M. Gomha, M.M. Edrees, F.M.A. Altalbawy, " Synthesis and Characterization of Some New Bis-Pyrazolyl-Thiazoles Incorporating the Thiophene Moiety as Potent Anti-Tumor Agents" *Int. J. Mol. Sci.* 17 (2016) 1499-1509. doi:10.3390/ijms17091499
- [21] A.A. Hassan, S.K. Mohamed, N.K. Mohamed, K.M.-A. El-Shaieb, A.T. Abdel-Aziz, M.R. Abdel-Rahman, "Synthesis and biological activity of 1,3-thiazolylidene-hydrazinylidene ethylpyridiniumbromide monohydrate, 1,3-thiazolylidenehydrazinium bromide and 1,3-thiazolylidenehydrazine derivatives". *Adv. Chem.* 11 ((2015) 3357-3366. <https://cirworld.com/index.php/jac/article/view/863>

- [22] R. Fusco, F. Sannicolo, "N-N Bond cleavage and rearrangements of arylhydrazones and arylhydrazides-recent developments". *Tetrahedron* 36 (1980) 161-170. [https://doi.org/10.1016/0040-4020\(80\)80002-0](https://doi.org/10.1016/0040-4020(80)80002-0)
- [23] B. W. Lee, S.D. Lee, "[5,5] Sigmatropic shift of *N*-phenyl-*N*-(2-thiazolyl)hydrazines and *N,N*-bis(2-thiazolyl)hydrazines into 2-amino-5-(paminophenyl)thiazoles and 5,5'-bis(2-aminothiazole) derivatives" *Tetrahedron Lett.* 41 (2000) 3883-3886. doi: S0040-4039(00)00493-7
- [24] V. Zaharia, A. Ignat, N. Palibroda, B. Ngameni, V. Kuete, C.N. Fokunang, M.L. Mounsang, B.T. Ngadjui, "Synthesis of some *p*-toluenesulfonyl-hydrazinothiazoles and hydrazino-bisthiazoles and their anticancer activity". *Eur. J. Med. Chem.* 45 (2010) 5080-5085. doi:10.1016/j.ejmech.2010.08.017
- [25] B. Folkert, H. Thomas, *Eur. Pat. Appl.* 1555264, 20 Jul. (2005).
- [26] B. Parashar, A. Jain, S. Bharadwaj, "Synthesis and pharmacological properties of some novel pyrazolidine and pyrazole derivatives". *Med. Chem. Res.* 21 (2012) 1692–1699. doi: 10.1007/s00044-011-9687-0
- [27] T. Nobuta, S.-I. Hirashima, N. Tada, T. Miura, A. Itoh, " Facile Aerobic Photo-Oxidative Synthesis of Phenacyl Iodides and Bromides from Styrenes Using I₂ or Aqueous HBr". *Synlett.* 15 (2010) 2335–2339.
- [28] T.A. Salama, Z. Novak, "*N*-Halosuccinimide/SiCl₄ as general, mild and efficient systems for the α -monohalogenation of carbonyl compounds and for benzylic halogenation". *Tetrahedron Lett.* 52 (2011) 4026-4029. doi:10.1016/j.tetlet.2011.05.135
- [29] B.T. Gowda, K. Jyothi, J.D. Souza, "Infrared and NMR spectra of arylsulphonamides". *Z. Naturforsch.* 57a (2002) 967-973. <https://www.degruyter.com/view/j/zna.2002.57.issue-12/zna.../zna-2002-1210.xml>
- [30] K. Rutkauskas, A. Zubrienė, I. Tumosienė, K. Kantminienė, M. Kažemėkaitė, A. Smirnov, J. Kazokaitė, V. Morkūnaitė, E. EditaČapkauskaitė, E. Manakova, S. Gražulis, J. Zigmuntas, Z.J. Beresnevičius, D. Matulis, "4-Amino-substituted Benzenesulfonamides as Inhibitors of Human Carbonic Anhydrases". *Molecules* 19 (2014) 17356-17380. doi:10.3390/molecules191117356

- [31] G.M. Sheldrick, "A short history of SHELX". Acta Crystallogr A64 (2008) 112-122. doi:10.1107/S0108767307043930
- [32] G.M. Sheldrick, "Crystal structure refinement with SHELXL". Acta Crystallogr C71 (2015) 3-8. doi:10.1107/S2053229614024218
- [33] S. Parson, H.D. Flack, T. Wagner, "Use of intensity quotients and differences in absolute structure refinement". Acta Crystallogr B69 (2013) 249-259. doi:10.1107/S2052519213010014
- [34] S. R. Hussaini, R.R. Chamala, Z. Wang, "The Eschenmoser sulfide contraction method and its application in the synthesis of natural products". Tetrahedron 71 (2015) 6017-6086. doi: <http://dx.doi.org/10.1016/j.tet.2015.06.026>
- [35] R. Kammel, D. Tarabová, Z. Růžicková, J. Hanusek, "Reaction of a brominated benzolactone/lactam with 4-methoxythiobenzamide and thiourea: an Eschenmoser coupling reaction, ring transformation, or dimerization". Tetrahedron Lett. 56 (2015) 2548-2550. doi: <http://dx.doi.org/10.1016/j.tetlet.2015.03.052>
- [36] Crystallographic data (excluding structure factors) for the structure reported in this work have been deposited with Cambridge Crystallographic Data center as supplementary publication no CCDC 1583184 (**3a**), 1589939 (**16h**) and 1583185 (**19b**). Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223) 336 033; e-mail: deposit@ccdc.cam.ac).

Figure captions:

Figure 1: FT-IR Spectrum of compound **3a**.

Figure 2: ¹H NMR of (*E*)-4-Phenyl-2-(phenyldiazenyl)thiazole (**3a**) obtained in CDCl₃.

Figure 3: ¹³C NMR of (*E*)-4-Phenyl-2-(phenyldiazenyl)thiazole (**3a**) obtained in CDCl₃.

Figure 4: The X-ray structure of compound **3a** in crystal (displacement parameters are drawn at 50% probability level).

Figure 5: The overall structure including the Z-configuration was also confirmed by X-ray crystallography of one derivative **16h** (displacement parameters are drawn at 50% probability level).

Figure 6: The hydrogen bonds formed *via* the bromide ion as well as H₂O molecules in compound **19b** (displacement parameters are drawn at 50% probability level).

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Scheme 1. Synthesis of 4-aryl-2-aryldiazenylthiazoles **3a-e**.

Scheme 3: The unreactivity of **1a-d** and **2a,b** towards Eschenmoser-contraction and formation of pyrazoles **14**.

Scheme 4: Synthesis of hydrazinothiazoles **16a-i**.

Scheme 5: Mechanism of the formation of hydrazinothiazoles **16a-i**.

Scheme 6: Synthesis of 2-amino-5-(4-aminophenyl)- 4-phenylthiazol-3-ium bromides dihydrates **19a-g**.

Scheme 7: Mechanism for the formation of compounds **19a-g**.

Scheme 8: Mechanistic considerations for the formation of compounds **19c,f**.

Highlights:

- Eschenmoser-coupling reaction and synthesis of diazenylthiazoles.
- Synthesis of hydrazothiazoles.
- Synthesis of thiazolium bromide dihydrate derivatives *via* [5.5] sigmatropic shift.
- Crystallographic behavior of the title compounds.
- Lattice water and bromide ion associated through hydrogen bonded with thiazole- NH_2 in thiazolium bromide.