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Utility of Carbothiohydrazides in Synthesis of some New Heterocyclic Compounds with Five- and Six-Membered Rings

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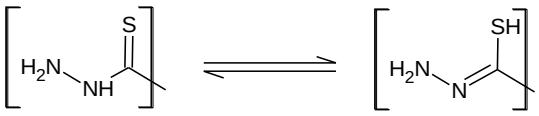
Abstract: In this work we studied the reaction of carbohydrazides with some reagents having electrophilic centers such as arylmethylenemalononitrile, aromatic aldehydes, bis(methylthio)methylenemalononitrile, dimethyl acetylene-dicarboxylate and cyanoguanidine. The resulting products are five-membered heterocyclic rings such as thiadiazoles, thiazoles, triazoles; and six-membered heterocyclic rings such as triazines.

Keywords: Carbothiohydrazide – Thiosemicarbazide – Thiocarbohydrazide – Triazole – Cyanoguanidine.

1 Introduction

Carbothiohydrazides are compounds that possessing both hydrazino and thione groups. They exist in two tautomeric forms (**Fig. 1**). They are active and interesting arrangement structures for many scientists [1,2]. The C(=S)-NH group and -NH-NH- hydrazide fragment play a very important role in pharmaceutic chemistry due to their potentially high anti-fungal, anti-bacterial [3], anti-viral (HIV-1) and anti-malarial activities [4].



I **II**

Fig. 1: Tautomeric forms of carbothiohydrazides

Carbothiohydrazides also exist in many synthetic reagents such as; alkyl hydrazinecarbodithioate **1** [5,6], thiosemicarbazide **2** [7], thiocarbohydrazide **3** [8] and *N*-arylhydrazinecarbothioamide **4** [9] (**Fig. 2**). Their derivatives are more widely used in heterocyclic synthesis than thiourea derivatives [10].

1,3,4-Thiadiazoles have a wide range of pharmacological activities such as; anti-bacterial [11], anti-malarial, anti-microbial, anti-oxidant [12], anti-convulsant [13], anti-parasitic [14], anti-tuberculosis [15], anti-leishmanial [16], anti-inflammatory [17] and anti-cancer agents [18]. Also, 4-thiazolidinones exhibit distinct biological activities such as; anti-inflammatory [19], anti-microbial [20], anti-diabetic [21], anti-tuberculosis [22] and anti-cancer [23].

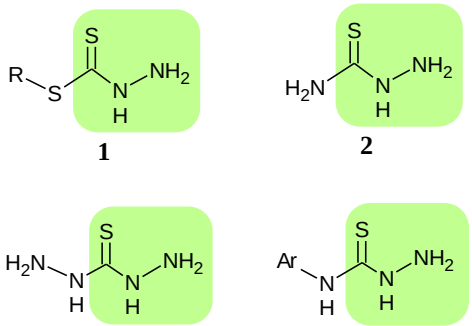


Fig. 2: Reagents containing carbothiohydrazides

On the other hand, heterocyclic compounds with five-membered rings containing three nitrogen atoms such as 1,2,4-triazoles play an important critical role in the structural elucidation of various natural products [24] and they are able to form hydrogen bonds with suitable targets leading to improve pharmacokinetics, pharmacological, and toxicological properties [25]. They are also associated with different pharmaceutical activities such as anti-cancer [26], anti-bacterial [27], anti-tubercular [28], anti-fungal [29] and

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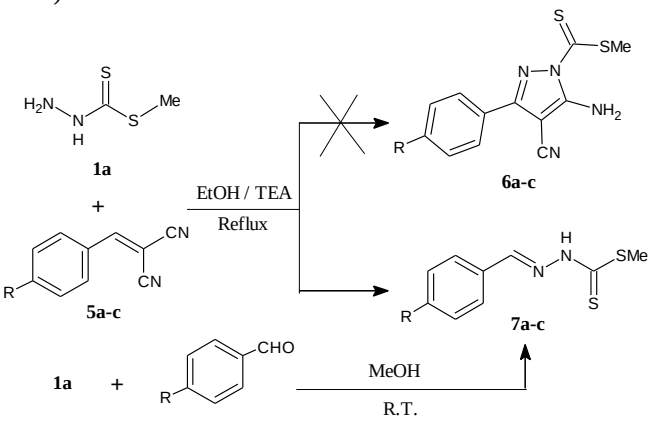
anti-inflammatory [30]. Also, heterocyclic compounds with six-membered rings containing three nitrogen atoms such as 1,3,5-triazines show a wide spectrum of effects on biological systems [31,32].

In the light of the foregoing data, in this work we aimed to use various nucleophilic carbothiohydrazides as starting materials to react with divers reagents containing electrophilic centers such as; arylmethylenemalononitrile, *bis*(methylthio)methylenemalononitrile, dimethyl acetylene-dicarboxylate DMAD and cyanoguanidine to produce new five- and six-membered heterocyclic rings

2 Results and Discussion

Herein, we interest to introduce new reactions for carboyhiohydrazide derivatives. Thus, attempts for preparation of methyl 5-amino-3-aryl-4-cyano-1*H*-pyrazole-1-carbodithioates **6a-c** from the reaction of methyl hydrazinecarbodithioate **1a** with arylmethylene-malononitrile **5a-c** in refluxing ethanol in the presence of triethylamine (TEA) were failed, while their reactions gave unexpected methyl 2-arylidenehydrazinecarbodithioates **7a-c** (**Scheme 1**). These products are identical with authentic samples, which prepared according to the reported procedure [33] *via Schiff base* condensation between **1a** with various aromatic aldehydes namely; benzaldehyde, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, respectively, (**Scheme 1**). The chemical structures of all newly synthesized compounds were confirmed based on their spectral analyses; FT-IR, ^{1}H, ^{13}C NMR, Mass Spectra as well as their elemental analysis data (*see* **Experimental Part**).

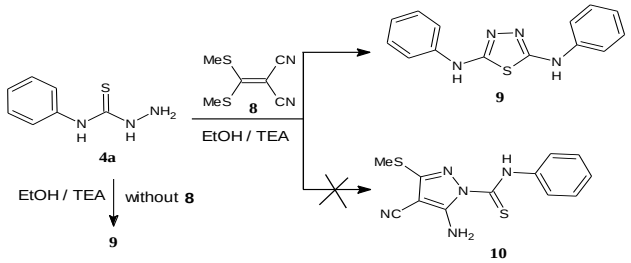


5, 6, 7: R = H **(a)**, Cl **(b)**, OMe **(c)**

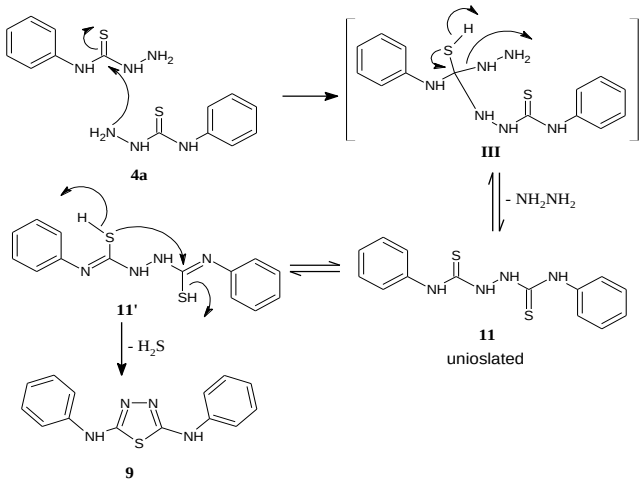
Scheme 1: Reaction of carbothiohydrazide **1a** with arylmethylenemalononitrile and/or aromatic aldehydes

Treatment of starting material *N*-phenyl hydrazinecarbothioamide **4a** [34] with *bis*(methylthio)methylenemalononitrile **8** in refluxing ethanol and in the presence of TEA as catalyst gave the unexpected *N*,*N*'-diphenyl-1,3,4-thiadiazole-2,5-diamine (**9**) [35], instead of the expected product of 5-amino-4-cyano-3-(methylthio)-*N*-phenyl-1*H*-pyrazole-1-carbothioamide (**10**). The same product thiadiazole **9** was also prepared *via* refluxing of **4a** alone in EtOH/TEA, **Scheme 2**.

The reaction mechanism for the formation of thiadiazole **9** was postulated, *via* nucleophilic addition of terminal amino group at thione carbon of another molecule to form intermediate **III**, followed by elimination of hydrazine to afford unisolated intermediate *bis*(*N*-phenylthiourea) BPTU **11**, which exists in tautomeric form **11'**. The later intermediate undergoes intramolecular cyclization through nucleophilic attack of sulfur lone pair at C=N give the target thiadiazole **9** with elimination of hydrogen sulfide, **Scheme 3**.

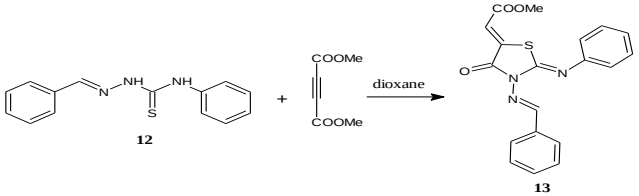


Scheme 2: Reaction of carbothioamide **4a** with/without *S*,*S*-dimethylacetal **8** in EtOH/TEA



Scheme 3: The suggested reaction mechanism for the formation of thiadiazole **9**

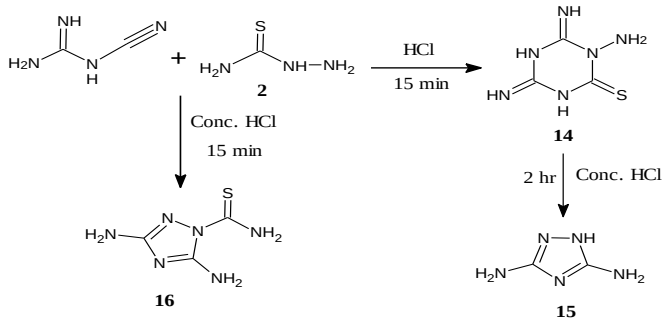
On the other hand, reaction of 2-benzylidene-*N*-phenylhydrazinecarbothioamide **12** [5] with dimethyl acetylene-dicarboxylate DMAD in dry dioxane gave the corresponding methyl 2-{4-oxo-2-(phenylimino)-3-[(phenyl-methylene)amino]-1,3-thiazolidin-5-ylid-ene}-acetate (**13**), **Scheme 4**.



Scheme 4: Reaction of benzylidene–carbothioamide **12** with DMAD in dioxane.

The IR spectrum of 4-thiazolidinone **13** showed the disappearance of characteristic absorption bands for N–H groups, while it showed the appearance of new characteristic absorption bands at 1695 and 1717 cm^{-1} for carbonyl groups in both thiazolidine ring and ester group, respectively. Its ^{1}H NMR spectrum showed three singlet signals at δ 3.85, 6.84 and 8.48 ppm characteristic for OCH_3, C<u>H</u>–COOMe and CH=N groups, respectively; and multiplet signals at δ 7.50–7.82 ppm due to protons of two phenyl groups. Its ^{13}C NMR spectrum showed thirteen signals at δ 115.6, 128.5, 128.6, 129.4, 129.6, 131.9, 134.0, 134.6, 142.0, 160.5, 161.3, 164.6, 166.5 and 168.3 ppm, which are assigned to aromatic sp^2–carbons and carbonyl groups; while carbon of methoxy group was presented as a singlet signal in aliphatic region at δ 53.0 ppm.

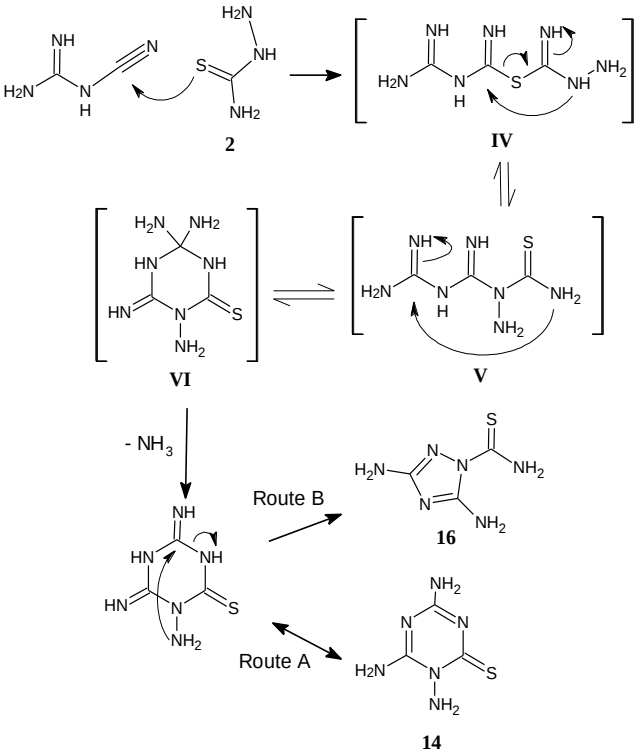
In 1976, *Joshua & Rajan* [36] reported that reaction of thiosemicarbazide **2** with cyanoguanidine CG in an acidic medium (concentrated hydrochloric acid) at boiling water bath yielded 1-amino-4,6-diiminohexahydro-1,3,5-triazine-2-thione (**14**). Also, 3,5-diamino-1,2,4-triazole **15** was separated as salt by acid hydrolysis of **14** with losing of thiocyanic acid, **Scheme 5**. While, recently in 2006 *Chernyshev et al.* reported that reaction of thiosemicarbazide **2** with CG in the same condition gave 3,5-diamino-1-thiocarbamoyl-1,2,4-triazole (**16**) instead of *s*-triazine **14** [37]. From these facts, here we studied the reaction of thiosemicarbazide **2** with **CG** in different conditions. Thus, using concentrated hydrochloric acid (5 N) gave 1,2,4-triazole **16**. While, their reaction by refluxing in diluted hydrochloric acid (0.15 N) for 1.5 hr gave 1-amino-4,6-diiminohexahydro-1,3,5-triazine-2-thione (**14**), **Scheme 5**.



Scheme 5: Reaction of thiosemicarbazide **2** with CG in HCl.

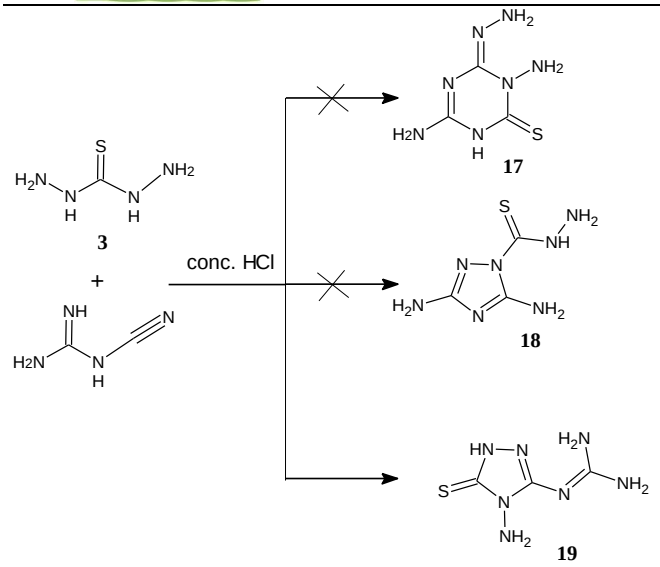
The reaction mechanism for the formation of triazine **14** and triazole **16** was postulated as shown in **Scheme 6**. The mechanism is initiated by nucleophilic addition of thiosemicarbazide's sulfur atom at cyanoguanidine cyano group to form intermediate **IV**. The intermediate **IV** undergoes rearrangement and cyclization to afford intermediates **V** and **VI**, which followed to produce the target product triazine **14** *via* elimination of ammonia (Route **A**). In concentrated HCl, the triazine ring undergoes ring opening and recyclization to give the second target product of triazole **16**, (Route **B**), **Scheme 6**.

On the other hand, in 1976 *Joshua & Rajan* reported that reaction of thiocarbohydrazide **3** with CG in concentrated hydrochloric acid in boiling water bath for 15 mins yielded only 1,4-diamino-6-hydrazonohexahydro-1,3,5-triazine-2-thione (**17**), which cannot convert into triazoles [36]. While, by repeating the reaction using the same condition (concentrated hydrochloric acid, 5 N), but for extra time (30 mins), it gave 2-(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)guanidine (**19**), instead of triazine **17** [36] and triazole **18** [37], **Scheme 7**.

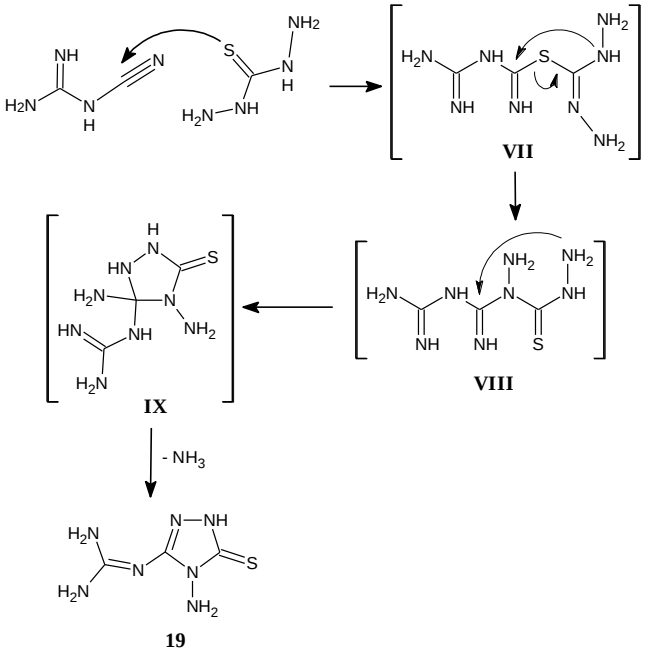


Scheme 6: The suggested reaction mechanism for the formation of triazine **14** and triazole **16.**

The reaction mechanism for the formation of triazole **19** was postulated *via* nucleophilic addition of thiocarbohydrazide's sulfur atom on cyanoguanine cyano group to form intermediate **VII**, which undergoes rearrangement and cyclization to afford intermediates **VIII** and **IX**. The intermediate **IX** was subjected to eliminate ammonia molecule, **Scheme 8**.



Scheme 7: Reaction of thiocarbohydrazide **3** with CG in concentrated HCl

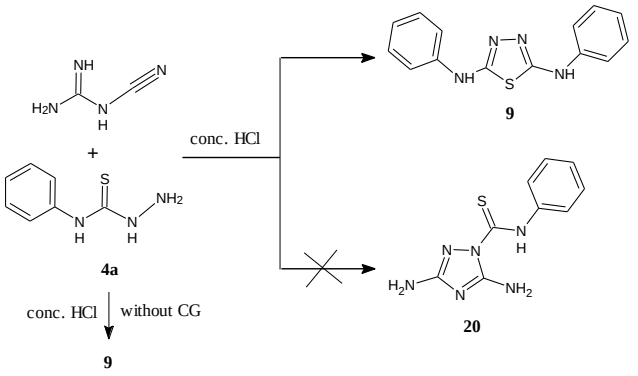


Scheme 8: The suggested reaction mechanism for the formation of triazole **19**

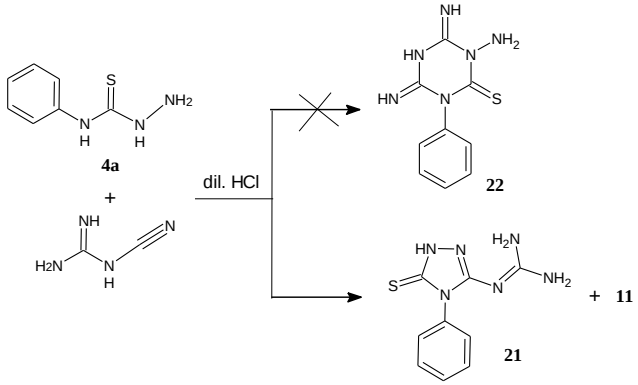
IR spectrum of triazole **19** showed characteristic absorption bands at 3168, 3212, 3298, 3413 cm^{-1} for ($3NH_2$ and NH); 1654 cm^{-1} for (C=N); and 1156 cm^{-1} for (C=S). Its ^1H NMR spectrum showed the presence of two singlet signals at δ 5.18 and 6.45 ppm characteristic of N-NH_2 and C-$(NH_2)_2$ protons, respectively; while proton of NH group was appeared as broad singlet signal in down field at δ 12.42 ppm. All signals were disappeared by D_2O. Its ^{13}C NMR spectrum showed three signals at δ 153.3, 158.1, 161.0 ppm which are assigned to aromatic carbons and (C=S) group.

In the same manner, reaction of *N*-phenyl thiosemicarbazide (**4a**) with cyanoguanidine was studied. Thus, their reaction in concentrated hydrochloric acid (5 N) and heating in water bath for 6 hrs gave thiadiazole **9**, which is identical with that previously prepared [35], instead of triazole **20**, (*see* **Scheme 2 & 9**). The same product **9** was also formed *via* reaction of **4a** in the same condition in absence of CG**.**

While, their reaction in diluted hydrochloric acid (0.15 N) and heating under reflux for 1.5 hrs gave a mixture of BPTU **11** [38] and 2-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)guanidine (**21**), instead of triazine **22**, **Scheme 10**.



Scheme 9: Reaction of *N*-phenyl thiosemicarbazide **4a** with CG in concentrated HCl



Scheme 10: Reaction of *N*-phenyl thiosemicarbazide **4a** with CG in diluted HCl

IR spectrum of 1,2,4-triazolyl guanidine **21** showed characteristic absorption bands at 3291, 3328, 3443, 3467 cm^{-1} for amino and imino groups; 3092 cm^{-1} for aromatic C–H; 1610, 1648 cm^{-1} for C=N; and 1254 cm^{-1} due to C=S. Its ^1H NMR spectrum showed the presence of singlet signal at δ 6.47 ppm for two symmetrical NH_2 protons; douplet signal at δ 7.28, 7.30 ppm with coupling constant J = 7.8 Hz for two aromatic protons; two triplet signals at δ 7.38–7.49 ppm with coupling constant J = 7.3 and 7.5 Hz for three aromatic protons; while proton of NH adjacent to C=S appeared at δ 12.91 ppm as singlet signal. All protons of NH and NH_2 groups disappeared by D_2O. Its ^{13}C NMR spectrum

showed seven signals at δ 128.5, 128.9, 129.4, 135.2, 155.5, 158.3 and 164.3 ppm, which are assigned to sp^2–aromatic carbons.

3 Experimental

General Information

All commercially available reagents were purchased from Merck, Aldrich and Fluka and were used without further purification. All reactions were monitored by thin layer chromatography (TLC) using precoated plates of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F254) using UV light (254 nm/365 nm) for visualization. Melting points were detected with a Kofler melting points apparatus and uncorrected. Infrared spectra were recorded with a FT-IR-ALPHBROKER-Platinum-ATR spectrometer and are given as cm^{-1} using the attenuated total reflection (ATR) method. ^{1}H NMR and ^{13}C NMR spectra for all compounds were recorded in DMSO-d_6 on a Bruker Bio Spin AG spectrometer at 400 MHz and 100 MHz, respectively. For ^{1}H NMR, chemical shifts (δ) were given in parts per million (ppm) with reference to tetramethylsilane (TMS) as an internal standard (δ=0); coupling constants (J) were given in hertz (Hz) and data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t= triplet, m=multiplet, dd=doublet of doublets). For ^{13}C NMR, TMS (δ=0) or DMSO (δ=39.51) was used as internal standard and spectra were obtained with complete proton decoupling. Elemental analyses were obtained on a Perkin-Elmer CHN-analyzer model.

Synthesis of methyl hydrazinecarbodithioate (1a)

To a cooled solution of potassium hydroxide (purity 90 %, 6.2 g, 0.1 mol) in a mixture of distilled water (7 mL) and 2-propanol (7 mL), hydrazine hydrate 80 % (6.1 mL, 0.1 mol) was added with stirring. Ice-cooled carbon disulfide (9.1 mL, 0.15 mol) was added drop wise to the above stirred solution that was maintained below 10 ºC above 1.5 hrs. The obtained bright yellow mixture was further stirred for 1 hr, and then, ice-cooled methyl iodide (9.3 mL, 0.15 mol) was added drop wise over a period of 2 hrs. The reaction mixture was stirred for an additional 1.5 hrs to obtain a white precipitate. The formed precipitate was then filtered, washed with ice-cooled water, dried and recrystallized from dichloromethane. Yield: 46 %; m.p. 80-82 ºC: [lit. [5] m.p.: 90-92 ºC].

Synthesis of methyl 2-arylidenehydrazinecarbodithioate derivatives 7a-c

Method A [33]**:**

To a solution of methyl hydrazinecarbodithioate **(1a)** (0.12 g, 1.0 mmol) in MeOH (30 mL), selected aromatic aldehydes (1.0 mmol) namely; benzaldehyde, 4-chlorobenzaldehyde and/or 4-methoxy-benzaldehyde was added. The reaction mixture was then stirred at room temperature for 30 mins, the formed precipitate was filtered and treated with MeOH (10 mL).

Method B:

A mixture of methyl hydrazinecarbodithioate **(1a)** (0.12 g, 1.0 mmol), an appropriate arylmethylenemalononitrile **5a-c** (1.0 mmol) and three drops of triethylamine in ethanol (10 mL) was refluxed for 2 hrs (monitored with TLC). After cooling, the formed precipitate was then filtered and recrystallized from methanol.

Methyl 2-(4-chlorobenzylidene)hydrazinecarbodithioate (7b):

Yield (***Method A*** : 89 %; ***Method B***: 77 %); white solid; m.p.: 192-194 °C. IR (ATR) ν_{max} 3120 (NH), 3098, 3007 ($CH_{aromatic}$), 2959 ($CH_{aliphatic}$), 1593 (C=N) cm^{-1}; ^{1}H NMR δ (ppm): 2.54 (s, 3H, SCH_3), 7.53, 7.55 (d, J = 8.5 Hz, 2H, $CH_{arom.}$), 7.74, 7.76 (d, J = 8.5 Hz, 2H, $CH_{arom.}$), 8.25 (s, 1H, N=CH), 13.31 (s, 1H, NH).

Methyl 2-(4-methoxybenzylidene)hydrazinecarbodithioate (7c):

Yield (***Method A***: 90 %, ***Method B***: 82 %); white solid; m.p.: 163-165 °C. IR (ATR) ν_{max} 3112 (NH), 3046 ($CH_{aromatic}$), 2961 ($CH_{aliphatic}$), 1601 (C=N) cm^{-1}; ^{1}H NMR δ (ppm): 2.54 (s, 3H, SCH_3), 3.82 (s, 3H, OCH_3), 7.02, 7.04 (d, J = 8.3 Hz, 2H, $CH_{arom.}$), 7.66, 7.68 (d, J = 8.3 Hz, 2H, $CH_{arom.}$), 8.21 (s, 1H, N=CH), 13.08 (br. s, 1H, NH).

Synthesis of *N,N'*-diphenyl-1,3,4-thiadiazole-2,5-diamine (9)

Method A:

A solution of *N*-phenyl hydrazinecarbothioamide **(4a)** (0.17 g, 1.0 mmol) with/without *bis*(methylthio) methylene-malononitrile **(8)** (0.34 g, 2 mmol) in ethanol (10 mL) was refluxed in the presence of TEA (3 drops) for 8 hrs (monitored by TLC). After cooling, the formed precipitate was collected by filtration and recrystallized from ethanol.

Method B:

A solution of *N*-phenyl hydrazinecarbothioamide **(4a)** (0.17 g, 1.0 mmol) with/without cyanoguanidine (0.08g, 1.0 mmol) in concentrated hydrochloric acid (10 mL, 5 N) was heated in water bath for 6 hrs. After complement of the reaction, the reaction mixture was then cooled to room temperature, then added distilled water (15 mL) and neutralized by ammonium hydroxide. The formed precipitate was collected by filtration, washed by distilled water, dried and recrystallized from ethanol.

Yield (***Method A***: 78 %, ***Method B***: 68 %); m.p.: 240 °C (lit. [35] m.p.: 239-240 ºC). IR (ATR) ν_{max} 3182 (N-H), 3026 ($CH_{aromatic}$), 1595 (C=N); ^{1}H NMR δ (ppm): 6.93-6.96 (t, J = 7.3 Hz, 2H, $CH_{arom.}$), 7.29-7.33 (t, J = 7.8 Hz, 4H, $CH_{arom.}$), 7.55, 7.57 (d, J = 8.1 Hz, 4H, $CH_{arom.}$), 9.76 (s, 2H, 2NH); ^{13}C NMR δ (ppm): 117.3, 121.5, 129.3, 141.8, 156.3.

Synthesize of methyl 3-[benzylideneamino]-4-oxo-2-(phenylimino)-1,3-thiazolidin-5-ylidene]acetate (13):

An equimolar amount of 2-benzylidene-*N*-phenylhydrazine-carbothioamide **(12)** (0.25 g, 1 mmol) and dimethyl acetylene-dicarboxylate DMAD (0.12 g, 1 mmol)

in dioxane (10 mL) was stirred at room temperature for 30 mins, followed by refluxing for 2 hrs. After cooling, the formed precipitate was filtrated off and recrystallized from ethanol. Yield 73 %; m.p.: 218-220 °C. IR (ATR) ν_{max} 3065 ($CH_{aromatic}$), 2957, 2852 ($CH_{aliphatic}$), 1717 (C=O_{ester}), 1694 (C=$O_{thiazolidine}$) cm^{-1}; ^{1}H NMR δ (ppm): 3.85 (s, 3H, OCH_3), 6.84 (s, 1H, CHCOOMe), 7.50-7.59 (m, 8H, $CH_{arom.}$), 7.80-7.82 (m, 2H, $CH_{arom.}$), 8.48 (s, 1H, CH=N). ^{13}C NMR δ (ppm): 53.0, 115.6, 128.5, 128.6, 129.4, 129.6, 131.9, 134.0, 134.6, 142.0, 160.5, 161.3, 164.6, 166.5, 171.3. Elemental Analysis Calcd. (%) for $C_{19}H_{15}N_3O_3S$ (365.41): C, 62.45; H, 4.14; N, 11.50; S, 8.78. Found: C, 62.34; H, 4.53; N, 11.62; S, 8.89.

Synthesis of 1,4,6-triamino-1,3,5-triazine-2(1*H*)-thione (14)

A mixture of thiosemicarbazide (**2**) (0.46 g, 5 mmol) and cyanoguanidine (0.42 g, 5 mmol) in diluted hydrochloric acid (30 mL, 0.15 N) was refluxed for 1.5 hrs. After cooling, the reaction mixture was neutralized by ammonium hydroxide and the formed precipitate was collected by filtration, washed with water, dried and used without further purification. Yield 85 %; m.p.: > 300 ºC. IR (ATR) ν_{max} 3154, 3341, 3425 ($3NH_2$), 1641 (C=N), 1240 (C=S) cm^{-1}; ^{1}H NMR δ (ppm): 5.64 (s, 2H, NH_2), 6.43 (s, 2H, NH_2), 7.36 (br. s, 2H, NH_2); All disappeared by D_2O; ^{13}C NMR δ (ppm): 150.0, 162.7, 165.9. Elemental Analysis Calcd. (%) for $C_3H_6N_6S$ (158.18): C, 22.78; H, 3.82; N, 53.13; S, 20.27. Found: C, 22.64; H, 3.86; N, 53.22; S, 20.34. Mass spectrum: molecular ion *m*/*z* (rel. intensity %): 159 $[MH]^+$ (100).

Synthesize of 3,5-diamino-1-thiocarbamoyl-1,2,4-triazole (16)

A mixture of thiosemicarbazide (**2**) (0.46 g, 5 mmol) and cyanoguanidine (0.42 g, 5 mmol) in concentrated hydrochloric acid (20 mL, 5 N) was heated on a water bath for 15 mins. The mixture was then diluted with water (30 mL) and neutralized by ammonium hydroxide into pH~8. The obtained precipitate was collected by filtration, washed with water, dried and crystallized from ethanol. Yield 92 %; m.p.: 178-180 °C. IR (ATR) ν_{max} 3139, 3190, 3251, 3349, 3403 ($3NH_2$), 1631 (C=N), 1117 (C=S) cm^{-1}; ^{1}H NMR δ (ppm): 5.55 (s, 2H, exchangeable NH_2-C3), 8.13 (s, 2H, exchangeable NH_2-C5), 8.19 (s, 1H, exchangeable $NH_{thioamide}$), 9.07 (s, 1H, exchangeable $NH_{thioamide}$); ^{13}C NMR δ (ppm): 157.6, 160.2, 174.7. Elemental Analysis Calcd. (%) for $C_3H_6N_6S$ (158.18): C, 22.78; H, 3.82; N, 53.13; S, 20.27. Found: C, 22.84; H, 3.68; N, 53.29; S, 20.17. Mass spectrum: molecular ion *m*/*z* (rel. intensity %): 159 $[MH]^+$ (100).

Synthesis of 2-(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)guanidine (19)

A mixture of thiocarbohydrazide (**3**) (0.53 g, 5 mmol) and cyanoguanidine (0.42 g, 5 mmol) in concentrated hydrochloric acid (20 mL, 5 N) was heated on a water bath for 30 mins. The mixture was then diluted with water (30 mL) and neutralized by ammonium hydroxide into pH~8. The formed precipitate was collected by filtration, washed with water, dried and crystallized from ethanol. Yield 85 %; m.p.: > 300. IR (ATR) ν_{max} 3168, 3212, 3298, 3413 ($3NH_2$ and NH), 1654 (C=N), 1156 (C=S) cm^{-1}; ^{1}H NMR δ (ppm): 5.18 (s, 2H, exchangeable N-NH_2), 6.45 (s, 4H, exchangeable C-$(NH_2)_2$), 12.42 (br. s, 1H, NH); ^{13}C NMR δ (ppm): 153.3, 158.1, 161.0. Elemental Analysis Calcd. (%) for $C_3H_7N_7S$ (173.19): C, 20.80; H, 4.07; N, 56.61; S, 18.51. Found: C, 20.71; H, 4.22; N, 56.57; S, 18.45.

Reaction of *N*-phenyl thiosemicarbazide (4a) with cyanoguanidine in diluted hydrochloric acid

A mixture of *N*-phenyl thiosemicarbazide **(4a**) (0.85 g, 5 mmol) and cyanoguanidine (0.42 g, 5 mmol) in diluted hydrochloric acid (20 mL, 0.15 N) was refluxed for 1.5 hrs (monitored with TLC). The formed precipitate was filtered on hot and neutralized by ammonium hydroxide solution to give BPTU **11**. The filtrate was neutralized by ammonium hydroxide solution and the formed precipitate was then collected by filtration, dried and crystallized from ethanol to give compound **21**.

***Bis*(*N*-phenylthiourea) BPTU (11)**

M.p.: 180-182 °C (lit. [38] m.p.: 178-179 ºC). IR (ATR) ν_{max} 3204 (NH), 3100 ($CH_{aromatic}$), 1183 (C=S) cm^{-1}; ^{1}H NMR δ (ppm): 7.14-7.18 (t, *J* = 7.2 Hz, 2H, $CH_{arom.}$), 7.32-7.36 (t, *J* = 7.8 Hz, 4H, $CH_{arom.}$), 7.55, 7.57 (d, *J* = 7.8 Hz, 4H, $CH_{arom.}$), 9.66 (s, 2H, 2NH, disappeared by D_2O), 9.85 (s, 2H, 2NH, disappeared by D_2O).

2-(4-Phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)guanidine (21)

M.p.: 270 °C. IR (ATR) ν_{max} 3291, 3328, 3443, 3467 ($2NH_2$, NH), 3092 ($CH_{aromatic}$), 1610, 1648 (C=N), 1254 (C=S) cm^{-1}; ^{1}H NMR δ (ppm): 6.47 (s, 4H, $2NH_2$, disappeared by D_2O), 7.28, 7.30 (d, *J* = 7.8 Hz, 2H, $CH_{arom.}$), 7.38-7.42 (t, *J* = 7.7 Hz, 1H, $CH_{arom.}$), 7.46-7.49 (t, *J* = 7.5 Hz, 2H, $CH_{arom.}$), 12.91 (s, 1H, NH, disappeared by D_2O); ^{13}C NMR δ (ppm): 128.5, 128.9, 129.4, 135.2, 155.5, 158.3, 164.3. Elemental Analysis Calcd. (%) for $C_9H_{10}N_6S$ (234.28): C, 46.14; H, 4.30; N, 35.87; S, 13.69. Found: C, 46.35; H, 4.25; N, 35.78; S, 13.78.

Conclusion

In this work, we have successfully synthesized 1,3,4-thiadiazole-2,5-diamines **9**, 4-thiazolidinone **13**, *s*-triazine-2-thione **14**, 1,2,4-triazole **16** and **19** from diverse carbothiohydrazides using different reagents having electrophilic centers such as *bis*(methylthio)methylene-malononitrile, DMAD and cyanoguanidine.

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