



IJEMS

The International Journal for Engineering and Modern Science

Journal homepage: <https://modernacademy-journal.syncege.net>



Article

Synthetic Procedures and Chemical Reactions for Thiocarbohydrazide: An Overview

Marwa M. Fouad * 

Basic Science Department, Modern Academy for Engineering and Technology, Cairo, Egypt.

ARTICLE INFO.

Article history:

Received 21 May 2026

Revised 6 July 2026

Accepted 3 August 2026

Available online 10 September 2026

Keywords:

Thiocarbohydrazide
isatin, pyrazolotriazole
diacetyl, benzil
phenylglyoxal hydrate

ABSTRACT

This study reviews the synthesis and chemical reactivity of thiocarbohydrazide (**1**) from 2005 to the present. Various preparation methods using hydrazine hydrate and carbon disulfide in water or methanol were investigated, with methanol providing a high yield of **96% based on hydrazine**. The versatile reactivity of thiocarbohydrazide (**1**) in the synthesis of sulfur-containing heterocycles was also examined. Its reactions with aldehydes produced different products depending on the aldehyde stoichiometry, while reaction with acetylacetone (**6**) afforded the 3,5-dimethylpyrazole derivative **7**. Treatment with substituted isatin derivatives (**11a–d**) yielded bis-isatin derivatives (**12a–d**). Heating **1** with ethyl cyanoacetate afforded the amino-pyrazolotriazole derivative **16** through elimination of ethanol and water. Reactions with carboxylic acids (**19**) produced substituted 3-mercapto-1,2,4-triazoles (**20**) using either microwave heating in **dimethylformamide (DMF)** or thermal reflux in ethanol. Although reflux required a longer reaction time, it generally provided higher yields. Reactions of **1** with diacetyl, phenylglyoxal hydrate, and benzil afforded monohydrazone **22** and 5-hydroxytriazine-3-thione derivatives **26a,b**. Further reactions with malononitriles, quinoxalines, carbonyl cyanides, coumarin derivatives, and oxazinones are also reviewed.



1. Introduction

Studying thiocarbohydrazide and its derivatives is a fascinating endeavor, as they are widely utilized and possess valuable reactions. The carbonic and thiocarbonic acid derivatives of hydrazine are known as carbohydrazide and thiocarbohydrazide, respectively. These compounds contain the functional group RNHCSNHR, which is crucial for the production of various organic heterocyclic ring systems. As a result, thiocarbohydrazides are commonly used in heterocyclic synthesis.

Based on their many applications and advantageous interactions, thiocarbohydrazide (**1**) and its derived products are extensively sought after for additional study. Apart from their therapeutic significance, they are also useful in a number of other applications, like assessing three-dimensional ultrastructure testing techniques for interphase nuclei and tissues. These substances, which are often called "foggy agents," are classified as safe, storable, cool-burning pyrotechnic smoke-dispersing ingredients. Chemical warfare agents have also employed them. Conversely, thiocarbohydrazides [1-4] are used as complexing agents in solvent extraction separation procedures and as very efficient adsorbents for heavy metal ions [5].

Furthermore, higher homologues of the well-known thiosemicarbazones and their metal complexes are called thiocarbohydrazones. The additional hydrazine moiety offers structural variety, ligands with different metal binding mechanisms, and potential biological consequences. Few examples of asymmetric ligands have been published, and the intriguing coordination chemistry of thiocarbohydrazide has mostly concentrated on symmetric derivatives, which are comparatively easy to synthesize [6].

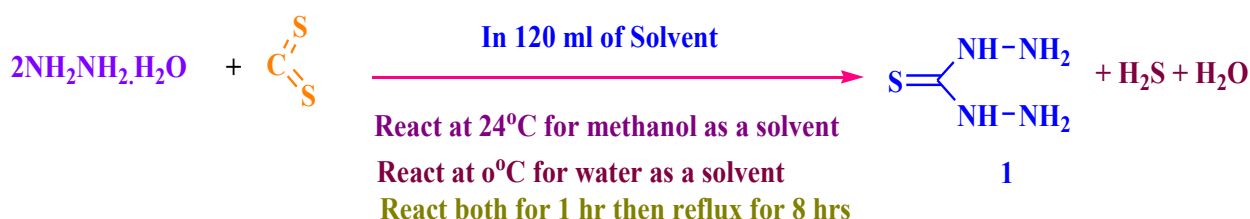
In addition, the first antiviral substances known to have broad-spectrum antiviral activity against a variety of DNA and RNA viruses were thiosemicarbazones [7]. Previous investigations have shown that isatin- β -thiosemicarbazone and isatin- β -semicarbohydrazone exhibit antiviral efficacy against several viral strains [8,9]. However, the biological activities of isatin- β -thiocarbohydrazone and isatin- β -carbohydrazone against DNA and RNA viruses have not been tested.

After carefully considering these facts and building upon my previous research [10-14], this study aims to investigate various methods for synthesizing thiocarbohydrazide and explore its potential as a reactive agent in the production of diverse sulfur-containing heterocycles.

2. Synthesized Methodologies

2.1. From carbon disulphide and hydrazine

The scaling up method for synthesizing thiocarbohydrazide **1** was investigated [5] using CS₂ and hydrazine hydrate as starting materials and 2-chloroethanol as a catalyst. Based on the data, the optimal reaction conditions were determined to be a ratio of CS₂ to hydrazine hydrate of 1:3.1-3.2 mol, a temperature of 80°C, a reaction time of 10-11 hours, and a catalyst consumption of 0.15 mol per CS₂ mol. The use of a turbine agitator was found to be the most effective option, resulting in a thiocarbohydrazide yield of over 90%. This reaction involved the reaction of N₂H₄ and CS₂ in the presence of H₂O to produce thiocarbohydrazide **1**, which was then heated to eliminate H₂S.

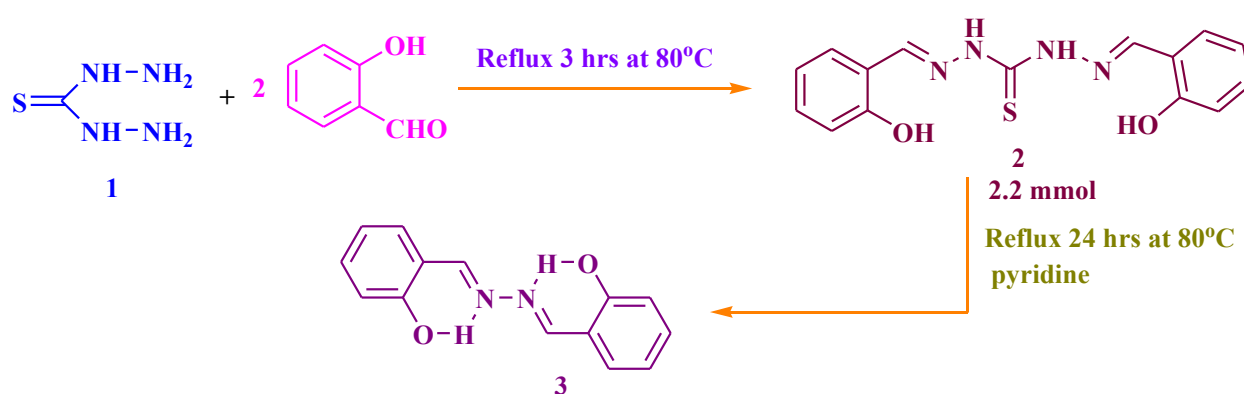


Scheme 1

An alternative method [15] was used for synthesis: 0.4 moles of 85% hydrazine hydrate were added to a 500 mL round-bottomed flask with two necks, connected to a reflux device. The mixture was stirred at 24°C using a magnetic stirrer. After 60 minutes, 0.08 moles of carbon disulfide were gradually added and the hydrazine solution was vigorously stirred. Then, 120 milliliters of methanol were added and the reaction solution was refluxed for eight hours at 60°C. The resulting precipitate, thiocarbohydrazide, was separated by filtering after allowing the solution to settle at room temperature. The precipitate was then washed with methanol and dried. To purify the crude product, it was dissolved in water at 40°C, allowed to settle at room temperature, and refrigerated for 12 hours at 0°C. The resulting white needle crystals were vacuum-dried and washed with methanol (Scheme 1). The actual yield was 0.38 moles (96%). So, changing the reaction mixture from water to methanol results in a high yield of thiocarbohydrazide (96% based on [hydrazine]). This technique reduces the comparatively costly loss of carbon disulfide.

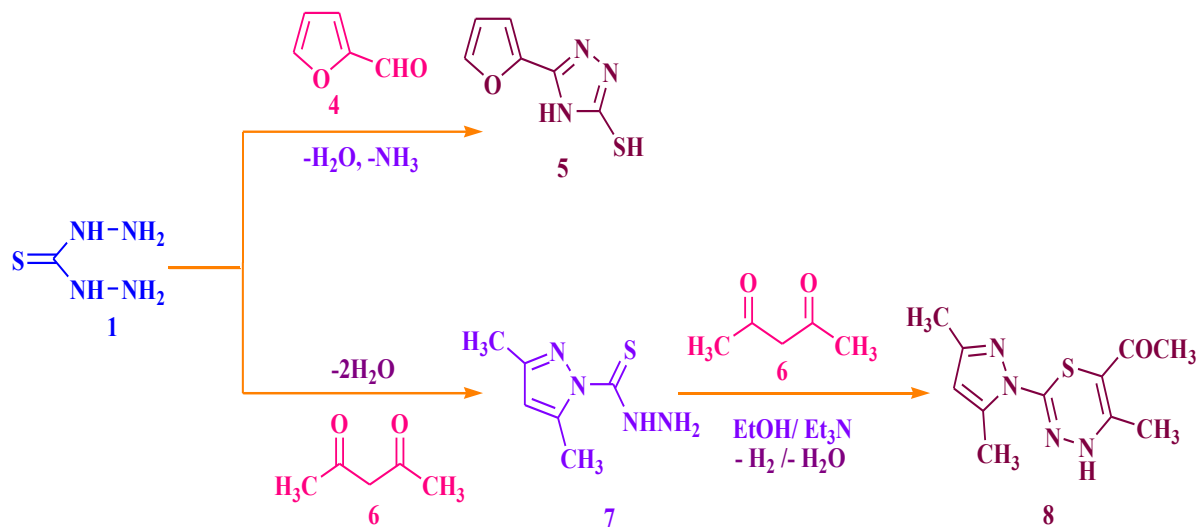
3. Chemical reactions

3.1. Reaction of thiocarbohydrazide 1 with aldehydes and ketones



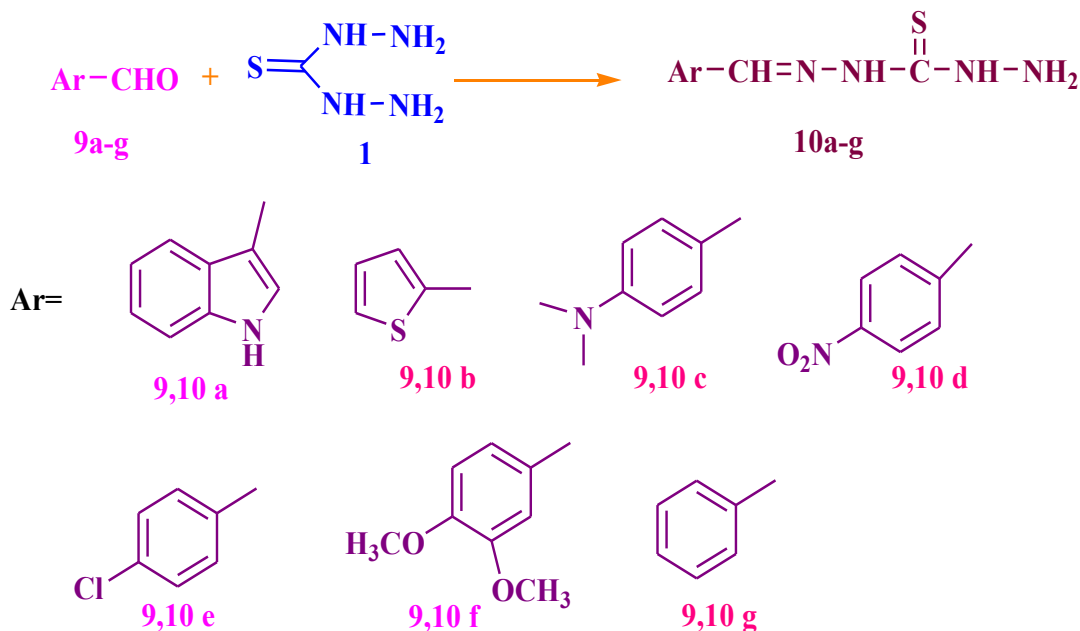
Scheme 2

The product obtained from the reaction between thiocarbohydrazide and aldehyde is dependent on the amount of aldehyde used. For instance, when 2.2 mmol of thiocarbohydrazide is reacted with 4.4 mmol of salicylaldehyde, 1,5-Bis(2-hydroxybenzaldehyde)- dithiocarbohydrazone (2) is formed. This compound then undergoes decomposition and rearrangement [15] to yield salicylaldehyde azine 3 upon refluxing in pyridine at 80°C, as shown in Scheme 2. However, when the reaction is carried out at a higher temperature of 130°C, thiocarbohydrazide (1) is reacted with an equivalent amount of either furan-2-carbaldehyde (4) or pentane-2,4-dione (acetyl acetone) (6). This results in the formation of a single, distinguishable product [16] in each case: either (furan-2-yl)triazole compound 5 or 3,5-dimethylpyrazole derivative 7. This product is then treated with another molecule of acetyl acetone [17] in ethanol in the presence of a catalytic amount of triethylamine to yield the relevant 3,5-dimethyl-pyrazolyl-thiadiazine compound 8, as disclosed in Scheme 3.

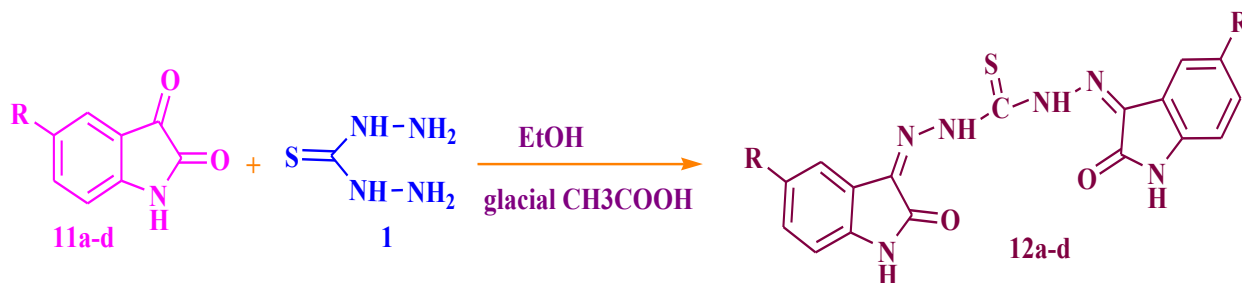


Scheme 3

Additionally, thiocarbonylhydrazide **1** (0.01 mol), substituted aldehyde **9a-g** (0.01 mol), and a few drops of glacial acetic acid were combined equimolarly [18] in 30 ml of ethanol for one hour, to afford monothiocarbonylhydrazones **10a-g** (Scheme 4). Likewise, when 0.01 mol of thiocarbonylhydrazide and 0.02 mol of suitable substituted isatin derivatives **11a-d** were combined in a 1:1 mixture of ethanol and acetic acid, bis-isatin derivatives **12a-d** were produced, Scheme 5 [18].



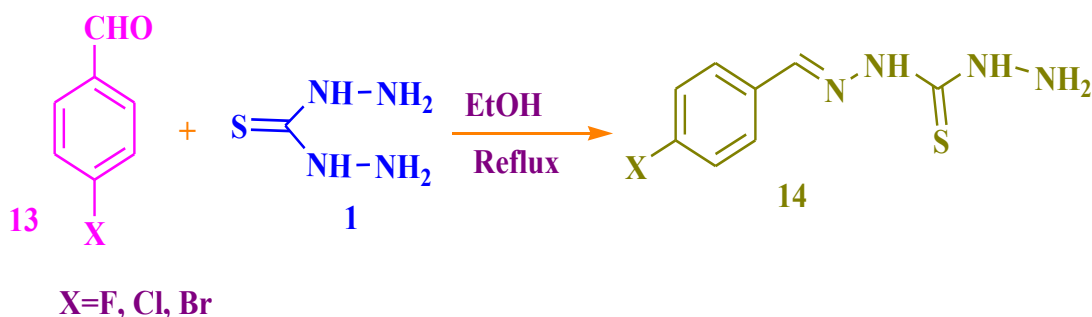
Scheme 4



11,12 a, R=H; 11,12 b, R=Cl; 11,12 c, R=CH₃, 11,12d, R=NO₂

Scheme 5

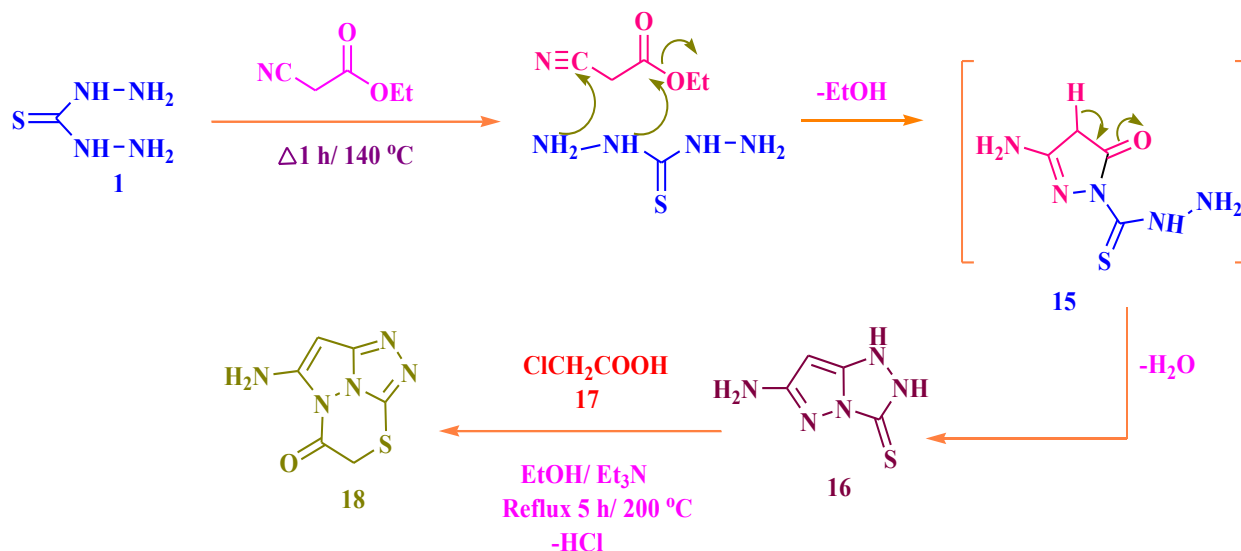
Furthermore, after dissolving the thiocarbohydrazide **1** in heated alcohol, the appropriate aldehyde **13** (*p*-chlorobenzaldehyde / *p*-fluoro benzaldehyde / *p*-bromo benzaldehyde) is added in a 1:1 molar ratio. The reaction is catalyzed by a small amount of glacial acetic acid and proceeds smoothly to produce the Schiff bases of thiocarbohydrazide **14**, as implied in Scheme 6 [19].



Scheme 6

3.2. Reaction of thiocarbohydrazide 1 with ethyl cyanoacetate

By heating thiocarbohydrazide (**1**) and ethyl cyanoacetate [11] at a temperature range of 140-150 °C, an addition reaction occurred between the carbonyl and nitrile groups of ethyl cyanoacetate and thiocarbohydrazide (**1**). This resulted in the formation of intermediate **15** by removing an ethanol molecule. The elimination of water then led to the production of the amino-pyrazolotriazole derivative **16** (Scheme 7). To synthesize compound **18**, 1-amino-5-thia-2a¹,3,4,7a-tetraazacyclopenta[cd]inden-7(6*H*)-one, a catalytic amount of triethylamine was added to compound **16** and a similar amount of chloroacetic acid **17** in ethanol under reflux conditions (Scheme 7).



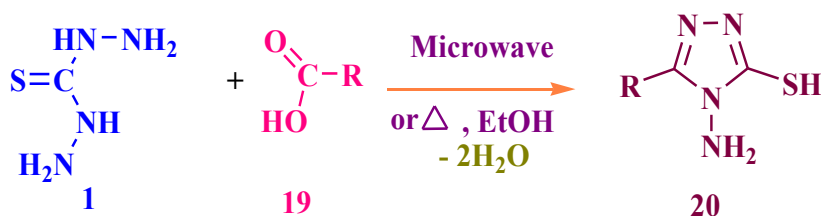
Scheme 7

3.3. Reaction of thiocarbohydrazide **1** with carboxylic acids

Thiocarbohydrazide (**1**) was reacted with carboxylic acid **19** using two different methods as follows:

First Method [20]: 20 milliliters of DMF were added to a round-bottom flask containing thiocarbohydrazide (0.015 mol) and substituted aromatic acids (0.01 mol). The mixture was then microwave-heated for 8–10 minutes at Power level 6 (420 Watt) to produce the appropriate substituted 3-mercapto-1,2,4-triazoles **20**. While this method is fast, the yield percentage is only moderate (Scheme 8).

Second Method [16]: (5 mmol) of thiocarbohydrazide (**1**) was dissolved in 20 milliliters of ethanol, and then the appropriate organic acid was added. This could be a fatty acid, such as stearic acid (5 mmol), or an aromatic carboxylic acid, such as gallic acid (5 mmol) or 4-hydrobenzoic acid (5 mmol). The triazole products **20** were produced after seven hours of refluxing (Scheme 8). Although this procedure takes longer than the previous one, it results in a higher yield.



By Microwave method, $\text{R} =$ 4-OHph, 4-OCH₃Ph, 4-CH₃Ph, 3,4,5-triOHPh, 4-NH₂Ph, 2-OHPh, 4-pyridyl, 4-Clph, 4-NO₂Ph, 2-Clph,

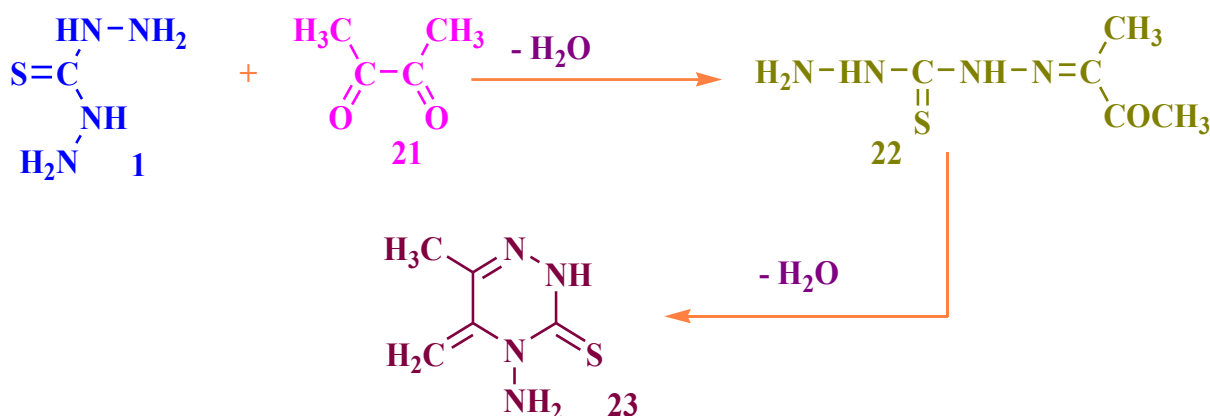
By thermal heating, $\text{R} =$ C₁₇H₃₅, 3,4,5-triOHPh, 4-OHph

Scheme 8

3.4. Reaction of thiocarbohydrazide 1 with 1,2-dicarbonyl compounds

Thiocarbohydrazide was reacted with diacetyl, phenylglyoxal hydrate, and benzil [21].

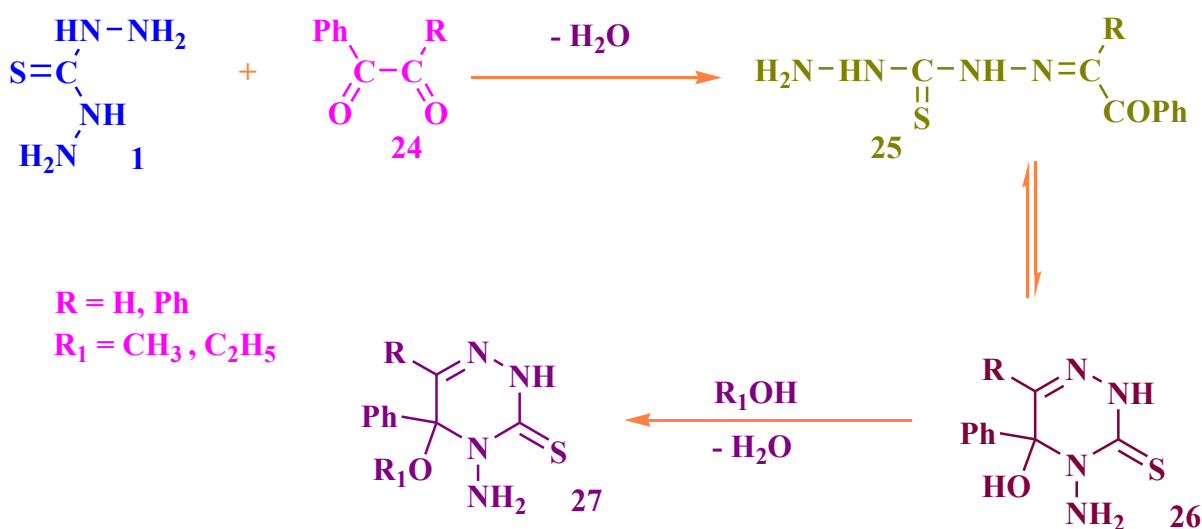
When diacetyl and thiocarbohydrazide are reacted in a mild manner (using a 1:1 molar ratio of reagents, methanol, and chilling in ice), a mixture is produced. According to ^1H NMR spectroscopy, this mixture contains approximately 30% of monohydrazone **22** and 70% of 5-methylene-triazine-3-thione **23** (Scheme 9). The latter was then extracted using hexane to isolate it in its pure form, and its properties were further characterized using ^1H and ^{13}C NMR spectroscopy.



Scheme 9

5-Hydroxy-triazine-3-thione **26a** was produced when phenylglyoxal hydrate and thiocarbohydrazide reacted in water and benzene (molar ratio 1:1). This was inferred from ^1H and ^{13}C NMR spectra as well as mass-spectrometric data (m/z 222 $[\text{M}]^+$), as displayed in Scheme 10.

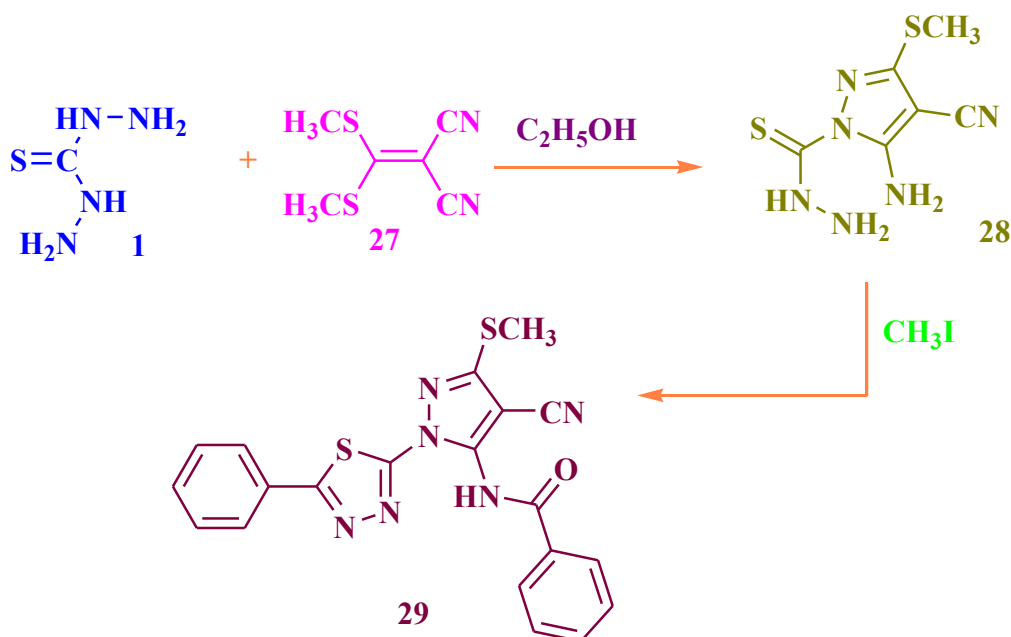
Benzil reacts with thiocarbohydrazide in benzene to produce compound **26b**, which shares many structural characteristics with compounds formed by reacting with phenylglyoxal hydrate (Scheme 10). However, due to the formation of an oligomeric precipitate in the benzene solution, the reaction between thiocarbohydrazide and benzil is challenging. This compound only exhibits aromatic proton signals in the ^1H NMR spectrum and has low solubility in various solvents.



Scheme 10

3.5. Reaction of thiocarbohydrazide 1 with Malononitrile Compounds

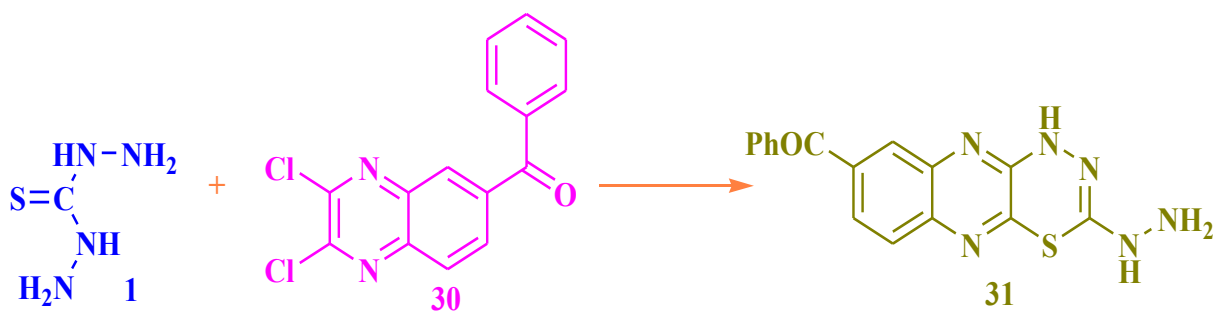
Thiocarbohydrazide (**1**) was reacted with 2-(bis(methylthio)methylene) malononitrile (**27**) in ethanol, resulting in [5] the production of carbothiohydrazide derivative **28**. This compound was then treated with PhCOOH and POCl₃ to yield (thiadiazol-2-yl) pyrazole-4-carbonitrile analogues **29**, as explained in Scheme 11.



Scheme 11

3.6. Reaction of thiocarbohydrazide 1 with Quinoxaline Analogues

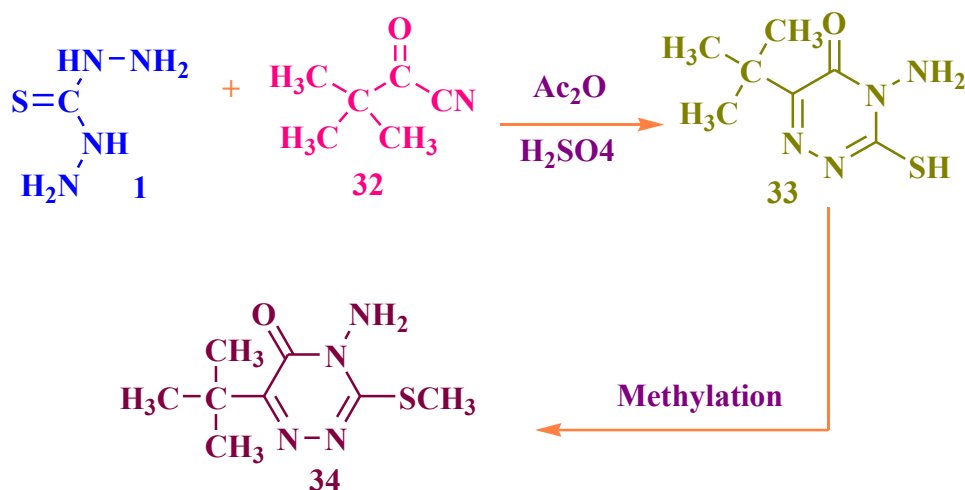
(3-Hydrazineyl-1H-[1,3,4]thiadiazino[5,6-*b*]quinoxalin-8-yl)(phenyl)methanone (**31**) was synthesized by condensing 6-benzoyl-2,3-dichloroquinoxaline (**30**) with thiocarbohydrazide **1**, as demonstrated in Scheme 12 [5].



Scheme 12

3.7. Reaction of thiocarbohydrazide 1 carbonyl cyanide derivative

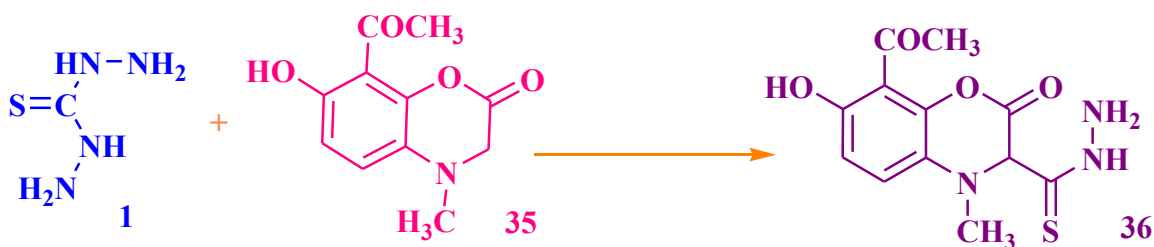
4-Amino-6-(tert-butyl)-3-mercapto-1,2,4-triazin-5(4*H*)-one (**33**) was produced by cyclocondensation of thiocarbohydrazide **1** water solution with a combination of sulfuric acid, acetic anhydride (Ac₂O), and tert-butylcarbonyl cyanide (pivaloyl cyanide, **32**) while stirring. Triazinone **33** was methylated to produce the 4-amino-6-(tert-butyl)-3-(methylthio)-1,2,4-triazin-5(4*H*)-one (**34**), as explained in Scheme 13 [5].



Scheme 13

3.8. Reaction of thiocarbohydrazide 1 with coumarin Derivatives

N-4-methyl-7-hydroxy-8-acetocoumarinylthiocarbohydrazide (**36**), which is regarded as a ligand in nature, was produced when thiocarbohydrazide **1** interacted with *N*-4-methyl-7-hydroxy-8-acetocoumarin (**35**), as disclosed in Scheme 14 [5].

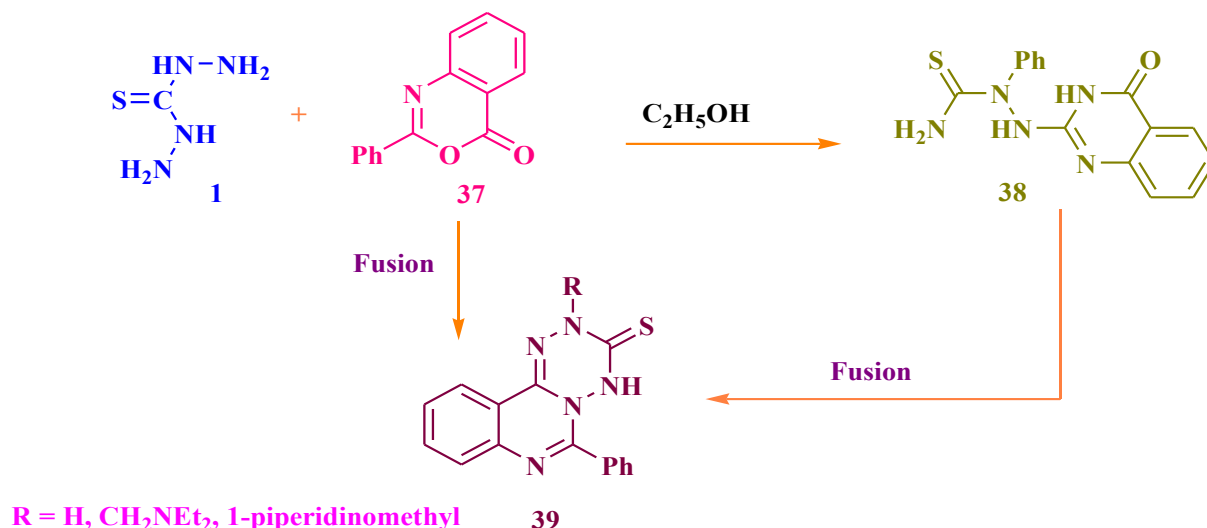


Scheme 14

3.9. Reaction of thiocarbohydrazide 1 Oxazinone Derivatives

In the refluxing ethanol reaction [5], 2-phenyl-benzoxazinone **37** reacts with thiocarbohydrazide **1** to produce 2-phenyl-3-thiosemicarbazido-quinazolinone **38**. However, when the reaction blend is heated at 160 degrees Celsius in an oil bath, thioxo-tetrazinoquinazoline **39** (R = H) is produced in a 79% isolated

yield. This same compound is also produced when **38** is heated at 170 degrees Celsius in an oil bath. Furthermore, compound **39** (R = H) can be converted to **39** (R = CH₂NEt₂, 1-piperidinomethyl) by reacting with paraformaldehyde and secondary amines, as shown in Scheme 15.



Scheme 15

4. Conclusion

The current research explored various methods used over the past 20 years for thiocarbohydrazide (**1**) production and reactions. The amount of aldehyde utilized in the reaction between thiocarbohydrazide (**1**) and aldehyde (furan-2-carbaldehyde or salicylaldehyde) determines the result.

Additionally, 3,5-dimethylpyrazole derivative **7** is produced by reacting thiocarbohydrazide (**1**) with an equivalent quantity of pentane-2,4-dione (acetylacetone) (**6**).

Furthermore, monothiocarbohydrazones **10a-g**, bis-isatin derivatives **12a-d**, and the Schiff bases of thiocarbohydrazide **14** were obtained by equimolarly combining thiocarbohydrazide and substituted aromatic or heteroaromatic aldehyde **9a-g**, substituted isatin compounds **11a-d**, or *p*-halogen aldehyde **13** in the presence of glacial acetic acid and ethanol. Thiocarbohydrazide (**1**) and ethyl cyanoacetate are heated to produce the amino-pyrazolotriazole derivative **16**, which eliminates ethanol and water molecules. Thiocarbohydrazide (**1**) and carboxylic acids **19** can react utilizing microwave or thermal reflux heating techniques when DMF is used as a solvent, producing substituted 3-mercapto-1,2,4-triazoles **20**. Though it takes longer than the microwave approach, thermal reflux heating yields a greater result.

Moreover, thiocarbohydrazide was employed as an adaptable antecedent for the production of several sulfur heterocyclic compounds. such as, 5-methylene-triazine-3-thione, 5-hydroxy-triazine-3-thiones, (thiadiazol-2-yl)pyrazole-4-carbonitrile analogues, thiadiazino[5,6-*b*]quinoxaline, 4-amino-6-(tert-butyl)-3-mercapto-1,2,4-triazin-one, 4-amino-6-(tert-butyl)-3-(methylthio)-1,2,4-triazinone derivatives, acetocoumarinylthiocarbohydrazide and 3-thiosemicarbazido-quinazolinone analogues.

ORCID iDs

Marwa M. Fouad  <https://orcid.org/0000-0002-1586-6910>

Funding: There was no external funding for this study.

Data Availability Statement: This published article contains all the data created or examined during this study.

Conflicts of Interest: No potential conflicts of interest were disclosed by the author.

References

- [1] Çavuş, M. S.; Yakan, H.; Özorak, C.; Muglu, H.; Bakir, T. K. New N,N'-bis(thioamido)thiocarbohydrazones and carbohydrazones: synthesis, structure characterization, antioxidant activity, corrosion inhibitors and DFT studies. *Research on Chemical Intermediates* **2022**, 48, 1593–1613. <https://doi.org/10.1007/s11164-022-04659-z>
- [2] Yakan, H.; Omer, H. H. S.; Buruk, O.; Cakmak, S.; Marah, S.; Veyisoglu, A.; Muglu, H.; Ozen, T.; Kutuk, H. Synthesis, structure elucidation, biological activity, enzyme inhibition and molecular docking studies of new Schiff bases based on 5-nitroisatin-thiocarbo-hydrazone. *Journal of Molecular Structure* **2023**, 1277, 134799. <https://doi.org/10.1016/j.molstruc.2022.134799>
- [3] Yakan, H.; Çakmak, Ş.; Buruk, O.; Veyisoglu, A.; Muglu, H.; Karakullukcu, N. T. New 5-methylisatin including thiocarbohydrazones: preparation, structure elucidation and antimicrobial activity. *Research on Chemical Intermediates* **2022**, 48, 4331–4345. <https://doi.org/10.1007/s11164-022-04799-2>
- [4] Çavuş, M. S.; Yakan, H.; Başkan, C.; Erdogan, M.; Muglu, H. Thio/carbohydrazone derivatives from iso(thio)/cyanates: preparation, structure elucidation, DFT studies, antimicrobial activity and DNA interactions. *Research on Chemical Intermediates* **2023**, 49, 2639–2667. <https://doi.org/10.1007/s11164-023-05014-6>
- [5] Metwally, M. A.; Khalifa, M. E.; Koketsu, M. Thiocarbohydrazides: synthesis and reactions. *American Journal of Chemistry* **2012**, 2(2), 38-51. <https://doi.org/10.5923/j.chemistry.20120202.09>
- [6] Bonaccorso, C.; Marzo, T.; La Mendola, D. Biological applications of thiocarbohydrazones and their metal complexes: a perspective review. *Pharmaceuticals* **2020**, 13(1), 4. <https://doi.org/10.3390/ph13010004>
- [7] Castro, E. F.; Fabian, L. E.; Caputto, M. E.; Gagey, D.; Finkielsztejn, L. M.; Moltrasio, G. Y.; Moglioni, A. G.; Campos, R. H.; Cavallaro, L. V. Inhibition of bovine viral diarrhea virus RNA synthesis by thiosemicarbazone derived from 5,6-dimethoxy-1-indanone. *Journal of Virology* **2011**, 85(11), 5436–5445. <https://doi.org/10.1128/JVI.00859-10>
- [8] Quenelle, D. C.; Keith, K. A.; Kern, E. R. In vitro and in vivo evaluation of isatin-beta-thiosemicarbazone and marboran against vaccinia and cowpox virus infections. *Antiviral Research* **2006**, 71(1), 24–30. <https://doi.org/10.1016/j.antiviral.2006.02.010>
- [9] Pandeya, S. N.; Smitha, S.; Jyoti, M.; Sridhar, S. K. Biological activities of isatin and its derivatives. *Acta Pharm* **2005**, 55(1), 27–46. PMID: 15907222. <https://pubmed.ncbi.nlm.nih.gov/15907222/>
- [10] Fouad, M. M.; Ali, K. A.; Mahmoud, K.; Ragab, E. A. Synthesis and antitumor evaluation of innovative naphthalene-based heterocycles against MCF7 breast cancer cells. *Egyptian Journal of Chemistry* **2025**, 68(6), 463–475. <https://doi.org/10.21608/ejchem.2025.373699.11560>

- [11] Fouad, M. M.; Fouad, A. M.; Fouad, A. M. Synthesizing unique triazolo[3,4-b][1,3,4]thiadiazines as effective anti-alzheimer's medications: an in vitro study. *Chemistry & Biodiversity* **2025**, 22(8), e202500260. <https://doi.org/10.1002/cbdv.202500260>
- [12] Fouad, M. M.; Farag, A. M.; Ragab, E. A. Synthesis and Reactions of 2-[(methylsulfanyl)(phenylamino) and 2-[(methylsulfanyl)(N-methylphenylamino) methyldene]-1,3-diphenylpropane-1,3-dione. *The International Journal for Engineering and Modern science* **2024**, 3(1), 24005. <https://modernacademy-journal.syncege.net/index.php/journal/article/view/49>
- [13] Fouad, M. M.; Farag, A. M.; Elgemeie, G. H.; Shaker, N. O.; Alian, N. A. Synthesis of novel thiazole-based heterocycles as new anti-bacterial and anti-fungal agents. *Egyptian Journal of Chemistry* **2023**, 66(13), 733-743. <https://doi.org/10.21608/ejchem.2023.180589.7326>
- [14] Othman, H. S.; AbdEl-Zaher, K.; Fouad, M. M.; Nawwar, G. A. M. Facile synthesis of functional heterocycles utilizing activated Benzylidene- acetones. *Egyptian Journal of Chemistry* **2023**, 66(13), 861-867. <https://doi.org/10.21608/ejchem.2023.189232.7501>
- [15] Lugasi, S. O. New synthetic pathways for thiocarbohydrazide and salicylaldehyde azine compounds. *Asian Journal of Chemical Sciences* **2017**, 3(1), 1-8. <https://doi.org/10.9734/AJOCS/2017/35504>
- [16] Fouad, M. M.; Fouad, A. M. Use of thiocarbohydrazide in the production of new sulphur-containing heterocycles as antimicrobial ingredients. *Moroccan Journal of Chemistry* **2025** 13(1), 286-311. <https://doi.org/10.48317/IMIST.PRSM/morjchem-v13i1.50387>
- [17] Fouad, M. M.; Elaasser, M. M. Convenient one-pot synthesis and biological evaluation of new 3,5-dimethyl-1H-pyrazole-1-carbothiohydrazide derivatives as anti-tumor agents. *ChemistrySelect* **2024**, 9(11), e202400225. <https://doi.org/10.1002/slct.202400225>
- [18] Gangarapu, K.; Manda, S.; Jallapally, A.; Thota, S.; Karki, S. S.; Balzarini, J.; De Clercq, E.; Tokuda, H. Synthesis of thiocarbohydrazide and carbohydrazide derivatives as possible biologically active agents. *Medicinal Chemistry Research* **2014**, 23(2), 1046-1056. <https://doi.org/10.1007/s00044-013-0684-3>
- [19] Nalawade, A. M.; Nalawade, R. A.; Shejwal, R. V. Synthesis, characterisation and biological activities of some aromatic thiocarbohydrazones. *Bioscience Discovery* **2017**, 8(2), 274-279. <http://biosciencediscovery.com>
- [20] Dadlani, V. G.; Chhabhaiya, H.; Somani, R. R.; Tripathi, P. K. Synthesis, molecular docking, and biological evaluation of novel 1,2,4-triazole-isatin derivatives as potential mycobacterium tuberculosis shikimate kinase inhibitors. *Chemical Biology & Drug Design* **2022**, 100(2), 230–244. <https://doi.org/10.1111/cbdd.14060>
- [21] Alekseyev, V. V.; Lagoda, I. V.; Yakimovich, S. I.; Yegorova, M. B. 1,2,4-Triazines – products of reaction of thiocarbohydrazide and its alkyl(aryl)-substituted derivatives with 1,2-dicarbonyl compounds. *Chemistry of Heterocyclic Compounds* **2010**, 46, 971–982. <https://doi.org/10.1007/s10593-010-0610-2>