Thiocarbohydrazides: Synthesis and Reactions

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Abstract  Thiocarbohydrazides are an important class of compounds which possess applications in many fields. The chemistry of thiocarbohydrazides has gained increased interest in both synthetic organic chemistry and biological fields and has considerable value in many useful applications such as the assessment process of the three-dimensional ultrastructural examination techniques of interphase nuclei and tissues, besides their therapeutic importance. They are also described for use as fogging agents and are considered as safe, storable, and cool-burning pyrotechnic compounds for dissemination of smoke, chemical warfare agents. On the other hand, thiocarbohydrazides are used in performing a highly selective heavy metal ion adsorbent and as complexing agents for the solvent extraction separation methods. The present review covers the literature up to date for the synthesis, reactions and applications of such compounds.

Keywords  Thiocarbohydrazides, TCH-Method, Ion Determination, Complex Formation, Thiohydrazide

1. Introduction

Study of thiocarbohydrazide and its derivatives is of great interest due to the wide use of these compounds and their valuable reactions. J. P. Thiery (1967) invented a technique for staining of cells involved in the assessment process of the ultrastructural cytochemical reactivity by scanning electron microscopy. This technique depends on periodic acid-thiocarbohydrazide-silver proteinate compound (TCH), where coating biological specimens of soft tissues with thiocarbohydrazide technique, the individual cells are clearly defined, surface contours are uniformly coated, intercellular borders are visible, cell-surface shape is outlined, and area contours are suitable for planimetry at higher magnification⁵, the carbohydrate content of atrial-specific granules of muscle⁶, intracellular glycoproteins⁷, ultrathin sections of Araldite-embedded atriums and ventricles were also stained in the assessment process of the ultra-structural cytochemical reactivity, renin activity, and cathepsin D activity of atriums and ventricles of the bullfrog⁸.⁹. The above technique was especially useful in the study of the roundish bodies and in the compositional and structural comparison of the siphon wall with the wound wall. Also this method was applied for vicinal glycol group detection to the study of gastric mucosa endocrine cells e.g: cat, rabbit and mouse gastric mucosa endocrine cells⁸ and the surface membrane of mouse myocardioid cells⁸. Polysaccharides associated with the cellular surface of a Gregarine (parasitic protozoan) were studied by periodic acid-thiocarbohydrazide-Ag proteinate cytochemical characterization and biochemical analysis of an isolated ghost fraction⁹. Conjugation of thiocarbohydrazide with a 40,000 Dalton dextran gave thiocarboxydrazyl-dextran, which is stable for a long time and suitable for electron microscopic demonstration of lectin receptors¹⁰. An ultrastructural analysis of Malus pumila was performed by examination of the adaxial leaf cuticle by electron microscopy to determine the transcuticular movement of foliarly applied chemicals, where an aqueous solution of uranyl acetate, AgNO₃, and PhHgOAc was applied to the cuticle surface of leaf segments floated on solutions of phosphate salts or thiocarbohydrazide (TCH) which reacted within the cuticle to form insoluble electron-opaque deposits indicative of their pathways of transcuticular movement¹¹. Also, ultrastructural cytochemistry of complex carbohydrates in lysosomal granules of human neutrophils, rabbit heterophils, rabbit and human eosinophils and basophils, and human monocytes was performed¹². The carbohydrate content of human auricular specific granules was assessed by means of the periodic acid-thiocarboxydrazide-silver proteinate technique¹³. Methods for visualization of complex carbohydrates ultra-structurally were employed to study specific organelles of the rat bone marrow and peripheral blood monocyte and alveolar and peritoneal macrophages¹⁴ ¹⁶. A thiocarboxyhydrazide-Ag-proteinate (TCH-SP) sequence was applied to thin sections of specimens that had been reacted with the high Fe diamine (HID) method for ultra-structural localization of sulfated complex carbohydrates¹⁷. Ultra-structural antibody localization of α-macroglobulin in mem-
brane-limited vesicles in cultured cells was performed by using post-sectioning staining with the osmium/thiocarbohydrazide/osmium and uranyl acetate/lead citrate procedures18. Staining the outer hair cells of the guinea pig sections with the HIO4-thiocarbohydrazide-OsO4 (PATCO) to study the effects of fixation and processing upon the morphological appearance of glycogen within these cells resulted in the appearance of distinct, coarse granules in the cytoplasm of the outer hair cells19. Ultra-structure of the cell wall of Candida albicans blastospores was studied, where thin sections of C. albicans blastospores were treated by the periodic acid-thiocarbohydrazide-silver proteinate method and the electron microscopic observations were correlated with literature data on the polysaccharide composition of C. albicans cell walls to give a model of the wall20. The HIO4/PA /thiocarbohydrazide (TCH) /Ag proteinate (SP) staining method for electron microscopy of plant materials produced an intensified, finely-granular product over starch grains, walls, dictyosomes, and their secretion products21. Occurrence and biosynthesis of very long chain fatty acids and alkane in plasmalemma enriched fractions from Sacccharomyces cerevisiae was studied, where electron microscopic identification of plasmalemma is best achieved with a periodic acid/thiocarbohydrazide/Ag proteinate stain22. The ligand Os binding technique with thiocarbohydrazide is a successful alternative to evaporation or sputter coating of botanical specimens23. Studies of the chemistry of the positive contrast reaction of glycogen in Epon-thin sections with tungstophosphoric acid (TPA) treated with thiocarbohydrazide were performed24. The glycogen of megakaryocytes and blood platelets was investigated in glutaraldehyde and OsO4-fixed tissues by the HIO4-thiocarbohydrazide-Ag proteinate method (PA-TCH-SP)25. Enzymic activity and galactomannan mobilization in germinating seeds of fenugreek (Trigonella foenum-graecum L. Leguminosae) was studied by electron microscopy using periodate-thiocarbohydrazide-silver proteinate technique26. Mature and differentiating sieve tubes were examined cytchemically in Robinia pseudoacacia, Acer pseudoplatanus, and Dianthus caryophyllus by the thiocarbohydrazide-silver proteinate method27. The organization of the growing cell wall of Parenchyma, sieve cells, and collenchyma28 and the filamentous structures of sieve elements of Mypmophides peltata petioles contained no polysaccharide components were demonstrated by this technique29. Demonstration of cholinesterases by the formation of osmium blacks at the sites of Hatchett's brown (Cu3Fe(CN)6.7H2O), which deposited at the sites of cholinesterase activity in tissues by the procedure of M. J. Karnovsky and L. Roots (1964), could be enhanced by bridging to Os through thiocarbohydrazide (TCH)30. Reaction of thiocarbohydrazide with aromatic isothiocyanates afforded thiocarbobis(thiosemicarbazides). These compounds and their Cu and Ni chelates were found to have active biological effect upon plant protection against fungi31. Thiocarbohydrazide as aldehyde blocking agent, block transformation of human peripheral lymphocytes by galactose oxidase32,33. NaBH4 was shown to be an effective blocking reagent of aldehyde produced by HIO4 oxidation of polysaccharides in thin sections of glutaraldehyde-Os fixed epoxy-embedded tissue prepared for thiocarbohydrazide-Ag proteinate staining in electron microscopy studies34. Aldehyde reagents in the presence of heat caused rapid degradation of apurinic acid to soluble fragments. The histochemical demonstration was carried out in case of stabilizing of apurinic by reaction with thiocarbohydrazide, where thiocarbohydrazide derivatives of apurinic acid were resistant to depolymerization during incubation in both Gomez’s methenamine Ag solution and Protargol and were visualized with Ag solution35.

The thiocarbohydrazones RR'C:NNHC(S)NHNC:R'R3 (R, R1, R2 and R3 = H, alkyl or aryl) are fungicidies for textile fabrics, where prevented the growth of Aspergillus niger and Chaetomium globsum on cotton36. Thiocarbohydrazide (TCH) besides the other sulfur-containing hydrazides such as methylthiocarbazinate (MDTC), and thiosemicarbazide (TSC) have convulsant action, where the 3 drugs inhibited pyridoxal phosphokinase in vitro. Long-latency convulsions after MDTC are comparable to those seen after TSC37.

In the endothelial cells lining the rat splenic blood vessels, neutral carbohydrates were studied by means of combined periodic acid-thiocarbohydrazide-silver protein (PA-TCH-SP) and α-amylase digestion methods38. A variety of sialic acids contained in the rat epididymis were histochemically examined, where hydrated sections were subjected either to the lectin methods using biotinylated Limax flavus, Sambucus nigra, Sambucus sieboldiana or Maackia amurensis lectins or to the selective periodate oxidn.- phenylhydrazine-thiocarbohydrazide-silver protein-physical development technique with or without sapon39. Epipendymides from male Sprague-Dawley rats on post-natal days 14, 21, 30, 39, 49, 56 and 70 were fixed in Bouin's fluid and embedded routinely in paraffin wax and the hydrated sections were subjected to the selective periodate oxidn.- phenylhydrazine-thiocarbohydrazide-silver protein-physical development technique with or without sapon40. Thiocarbohydrazide showed structural reinforcement effect in the preparation of rabbit knee articular cartilage for the scanning electron microscope by enhancing the binding of osmium tetroxide to it, possibly along with that of other soluble tissue constituents41. The ontogeny of pepsinogen C-producing cells in rat fundic glands was studied, where the maturation stages of the chief cells could be traced by electron microscopy along the longitudinal axis of the rat fundic gland by double-staining with anti-pepsinogen C antibody and HIO4-thiocarbohydrazide-Ag proteinate. The ontogeny of sulfated glycoconjugate-producing cells in the rat fundic gland has been also studied using HID-thiocarbohydrazide (TCH)-silver proteinate (SP)-physical development (PD) technique under electron microscopy42. Sequential secretory changes in granular tubule cells caused by the secretagogue cyclocytidine were studied at the ultrastructural level using the periodic acid-thiocarbohydrazide-silver proteinate technique (PA-TCH-SP)43. An electron microscopic analysis with specific histochemical stainings for acidic glycocon-
jugates was carried out to examine the endothelium lining blood vessels of the rat spleen using high or low iron diamine-thiocarbohydrazide-silver protein-physical development (HID or LID-TCH-SP-PD) method, with or without prior digestion with acidic glycoconjugate-degrading enzymes, such as heparinase, testicular hyaluronidase, chondroitinase B and neuraminidase. Micro-heterogeneity of pectins and calcium distribution in the epidermal and cortical parenchyma cell walls of flax hypocotyls was determined using a combination of subtractive treatment and PATAg (periodic acid-thiocarbohydrazide-silver proteinate) staining method. Detection of acidic glycoconjugates in a variety of mammalian connective tissues by means of a physical development procedure into high or low iron diamine-thiocarbohydrazide-silver protein (HID or LID- TCH-SP) methods. The cellulose synthesized in the mannan medium by Acetobacter xylina in the presence of acetyl glucosmannan was stained heavily by the periodic acid-thiocarbohydrazide-silver proteinate (PA-TAG) method for X-ray diffractometry and FT-IR spectroscopy determination of its crystal structure. The presence and localization of storage polysaccharides and of polysaccharides as cell structure constituents of Paracoccidioides brasiliensis yeast-like cells and protoplasts were studied using the same technique. Identification of two glycosylated components of Mycoplasma penetrans using transmission electron microscopy was performed by staining with periodic acid-thiocarbohydrazide silver proteinate. Lysozyme-expressing cells in human labial salivary glands were electron-lucent and exhibited reactivity for mucus staining by the periodic acid-thiocarbohydrazide-silver proteinate (PA-TCH-SP) technique.

Barley chromosomes were prepared for high-resolution scanning electron microscopy SEM using a combination of enzyme maceration, treatment in acetic acid and osmium impregnation using thiocarbohydrazide. Using this technique, the three-dimensional ultrastructure of interphase nuclei and mitotic chromosomes was examined. Pollen grains made conductive for SEM by coating in a series of osmium and thiocarbohydrazide solutions (OTOTO) show charging artifacts when nonconductive detritus (sand grains, plant fragments, etc.) is present in the immediate sample area of the SEM scanning probe. Transmission light microscopy of structurally colored semithin cartilage sections using silver proteinate by thiocarbohydrazones staining method and cytochemical investigations on tunic morphogenesis in the sea peach Halocynthia papillosa (Tunicata, Ascidiacea) demonstrated by the same method. Keratan sulfate glycosaminoglycans in murine eosinophil-specific granules were examined using high iron diamine-thiocarbohydrazide-silver proteinate physical development method (HID-TCH-SP-PD) for staining. On the other hand, thiocarbohydrazide derivatives; iasatin-thiocarbohydrazone (IsTCH) and N-ethylisatin-β-thiocarbohydrazone (N-Et-IsTCH) showed antiproliferative action towards healthy human peripheral blood mononuclear cells (PBMC) and on two neoplastic cell lines.

A highly selective heavy metal ion adsorbent could be obtained when coconut shell activated carbon is soaked in acidic aqueous thiocarbohydrazide and contacted with an aqueous heavy metal ion, e.g. Hg (II), which is effective at a lower pH without leakage of thiocarbohydrazide. Also, the S-containing triazine resin used to adsorb metals from wastewaters is prepared by reacting cyanuric chloride with thiocarbohydrazide and polyether diamine or an aminosulfonylic acid or its salt in a polar nonprotic solvent which is inert to the polar solvent. Thiocarbohydrazide was used as a complexing agent for the solvent extraction separation of some bivalent metal such as Cd from Co, Cu, and Pb and of Pb from Ni and Pd and Cu from Zn and Hg and of Pb from Zn and Cd using various masking agents. Bis(5-sulfo-phenylthiocarbohydrazide (disodium salt, Na₂H₂L) was used as metallochromic indicator for determination of Zn by complexometric titration.

Thiocarbohydrazides, thiosemicarbazides and their hydrazones are described for use as fogging agents for the fogging development of unfogged direct-positive Ag halide emulsions. The formation process of photographic images is described by processing the photographic material in the presence of thiocarbohydrazide compounds of the type R₁R₂NNHCsNHR₃R₄ (I; R¹, R₂ = H or R, satuFurther research on the methylene group may together form a carbocyclic or heterocyclic ring; R³ + R⁴ may form a methylene group or an alkyl, aryl, or heterocyclic substituted methylene group and the substituents on the methylene group may altogether form a carboxylic or heterocyclic ring; R⁵ = H or R⁴ with R⁵ or R⁴ may comprise the necessary atoms to form a 5- or 6-membered heterocyclic ring) in the emulsion layer as stabilizers. Thus, Thiocarbohydrazides with aliphatic, aromatic or heterocyclic substituents have an antifogging effect during the 1st, and exert a fogging effect during the 2nd color development of reversal materials so that an overall exposure or chemical fogging is unnecessary.

Weatherability improvers for jet-printing ink compositions and inks contain water-soluble dyes, wetting agents, water, and discoloration inhibitors selected from thioureas, thiosemicarbazides, and thiocarbohydrazides. The sheet especially useful in ink-jet recording with a coating of a porous ink-receptive layer containing selected derivatives from thiourea, thiosemicarbazide, and thiocarbohydrazide shows good ink absorption and dye fixability and provides high-quality images showing no discoloration upon storage. Receptor sheets with good ink absorptivity and color-fixing ability for the nonimpact printing comprise a porous ink-receiving layer containing iodine or iodides as quenching agents and of thiourea, thiosemicarbazide, and thiocarbohydrazide derivatives as antifading agents.

Thiocarbohydrazide, thiosemicarbazide, ethylenebis(thiosemicarbazide) and dithiobiurea are considered as safe, storable, and cool-burning pyrotechnic compounds for dissemination of smoke, chemical warfare agents, etc.

2. Synthesis
2.1. From Hydrazine and Carbon Disulphide

The scale-up technology for synthesis of thiocarbamoylhydrazine (TCH) 1 was studied, using 2-chloroethanol as catalyst, CS₂ and hydrazine hydrate as starting materials. The results showed that the optimized reaction conditions were CS₂/hydrazine hydrate 1:3.1- 3.2 mol, time 10-11 h, temperature 80°C, and the consumption of catalyst 0.15 mol/CS₂ mol. It was found the turbine agitator was preferable, and the total yield of TCH was >90%76. Therefore, thiocarbamoylhydrazine 1 was prepared by reaction of N₂H₄ with CS₂ in the presence of H₂O with subsequent heating to remove H₂S77,78.

The products present due to the decomposition of the formed intermediate hydrazine dithiocarbazinate H₂N₃HCS₃H₂N₂H₂ were determined by potentiometric titration with 0.1M AgNO₃ of a 0.2-0.3-g sample solution treated with 5 mL 25% NH₄OH solution and 50 mL H₂O using S²⁻ selective electrode versus calomel or Ag/AgCl electrode79,80.

\[ \text{NH}_2\text{NH}_2\text{H}_2\text{O} + \text{CS}_2 \xrightarrow{\text{H}_2\text{O}} \text{H}_2\text{N}_3\text{S}\text{NH}_2 \]

3. Reactions

3.1. Cyclocondensation with Cyanide Derivatives

3.1.1. Reaction with Carbonyl Cyanide Derivatives

Cyclocondensation of thiocarbamoylhydrazine 1 solution in water with a mixture of acetic anhydride, sulfuric acid and tert-butylcarbonyl cyanide with stirring, afforded triazine compound 2. Methylation of triazine compound 2 gave herbicide metribuzin 381.

\[ \text{H}_2\text{N}_3\text{S}\text{NH}_2 + (\text{CH}_3)_2\text{COCN} \xrightarrow{\text{Ac}_2\text{O}} \text{H}_2\text{N}_3\text{S}\text{SH}_2\text{O}_2 \]

\[ \text{Methylation} \]

3.1.2. Reaction with Dicyandiamide

Reaction of thiocarbohydrazide 1 with dicyandiamide RNHC(=NH)CN (R = H, Ph, p-MeC₆H₄, p-ClC₆H₄) gave 1-amino - 4-imino(or arylimino) - 6 - hydrazonohexahydro-1,3,5-triazine-2-thiones 4, which were converted into 8-amino (or arylimino) - 6 - hydrazono - 3 - phenyl - 4H,6H - [1,3,5]triazino-[2,1-b][1,3,4]thiadiazines 5 upon treatment with PhCOCH₂Br.

3.1.3. Reaction with Malononitrile Derivatives

Reaction of thiocarbamoylhydrazide 1 with 2-(bis(methylthio)methylene)malononitrile in ethanol gave 1-(5-amino-4-cyan-3-methylthiopyrazol-1-yl)carbothiohydrazide 9, which on treatment with PhCO₂H and POCl₃ gave 5-benzoylamino-3-methylthio-1-(5-phenyl-1,3,4-thiadiazol-2-yl)pyrazole-4-carbonitrile 1083.

3.1.4. Reaction with Isothiocyanate Derivatives

Cyclization of thiocarbamoylhydrazide 1 with isothiocyanate derivatives (R = alkyl, alkenyl, cycloalkyl, aryl) gave
1-(3-Mercapto-4-substituted-1,2,4-triazol-5-yl)-3-thiosemicarbazide \[11^{84}\].

![Chemical structure 1](image1)

3.1.5. Reaction with Diisocyanate

The polyaddition of thiocarbohydrazide and diisocyanate derivatives in boiling xylene-DMF mixture gave insoluble, low molecular weight thiocarbohydrazide polyurea copolymer which has good dielectric properties, but low mechanical strength and relatively low heat resistance\[85\].

3.2. Reaction with Amides

Cyclocondensation of thiocarbohydrazide 1 with tert-butyl-2-(1-methylcyclopropyl)-2-oxoacetamide, followed by methylation with MeI gave 1,2,4-triazin-5-one derivative \[12\]. At 250 g/ha pre-emergent \[12\] gave 100% control of various weeds, e.g., Stellaria media. The product showed herbicidal activity\[86, 87\].

![Chemical structure 12](image2)

3.3. Cyclocondensation with S-Methylated Compounds

Cyclocondensation of thiocarbohydrazide 1 with S-methylated compounds in PhMe in pyridine gave \[13^{88}\].

![Chemical structure 13](image3)

3.4. Reaction with Acetyl Chloride Derivatives

Thiadiazines \[14, R = 3,4-(HO)_{2}C_{6}H_{5}, 2,5-(HO)_{2}C_{6}H_{3}, 2,3,4-(HO)_{2}C_{6}H_{2}\] were obtained by treatment of RCOCH_{2}Cl with thiocarbohydrazide \[18^{90}\].

![Chemical structure 14](image4)

3.5. Complex Formation Reactions

3.5.1. Complexation with Metal Ions

Lanthanum(III) and praseodymium(III) complexes of thiocarbohydrazide were synthesized in the form of \([M(L_{1})Cl_{2}], [M(L_{2})Cl], [M(L_{3})Cl] \), and \([M(L_{4})]\)]\[81\]. Coordination polymers of Cu\[2+\], Ni\[2+\] and Zn\[2+\] containing Schiff bases derived from thiocarbohydrazide were synthesized and characterized by elemental analysis, IR, reflectance spectra, magnetic, DSC, TGA, x-ray diffraction and fluorescence studies\[82\]. Cu(I), Zn(II), Fe(II) complexes of 1,5-bis(acetophenone)thiocarbohydrazone were synthesized by the electrochemical oxidation of anodic metal in nonaqueous solution\[83\]. Complexes of tin(IV) and organotin(IV) chlorides with Schiff bases derived from thiocarbohydrazide as Cl\[3\]SnL, PhClSnL and R\[2\]SnL (\(R = Ph, Bu, PhCH_{2}, p-MeC_{6}H_{4}, C_{6}H_{11}L = \text{dianion of 15}, R^{1} = H, Me\)) were prepared by the reaction of the Schiff bases with the Sn(IV) or organo-Sn(IV) chlorides\[84\].

![Chemical structure 15](image5)
cm$^{-1}$, respectively. The IR and Raman spectra (30-4000 cm$^{-1}$) of thio-carboxyhydradize and deuterated thio-carboxyhydradize were measured. Vibrational assignments were discussed by referring to characteristic group frequencies of related molecules and force constant calculations. Also, Raman and IR spectra (30-4000 cm$^{-1}$) of dichloro-bis(thio-carboxyhydradize)cadmium(II) 16 was measured where, the vibrational spectra of the Cd complex of thio-carboxyhydradize were discussed in relation to that of the free ligand.

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\text{ML}_2X_2 (L = \text{thio-carboxyhydradize, } M = \text{Zn, Cd, Pb, Hg; } X = \text{ClO}_4^-, \text{NO}_3^-), \text{CrL}_2(\text{NO}_3)_3, \text{PbL} (\text{NO}_3)_2, [\text{MnL}_2]X_2, \text{VOQ} \text{SO}_4 (Q = L \text{ and semicarboxadize), and VOZ} (\text{ClO}_4)_2 (Z = \text{thio-}\text{semicarboxadize}) \text{ were prepared and characterized by magnetic properties, IR and x-ray spectra. Thio-carboxyhydradize is bidentate and coordinates through the S atom and 1 amino group. [NiL]_2(\text{ClO}_4)_2 (L = \text{thiosemicarboxadize}) \text{ and } [\text{MQ}]_2X_2 (M = \text{Cu, Ni, } X = \text{ClO}_4^-, \text{NO}_3^-, Q = \text{thio-carboxyhydradize; } M = \text{Co, } X = \text{ClO}_4^-, \text{NO}_3^-), \text{Cl}) \text{ were prepared by the reaction of the ligand with the appropriate metal salt. The diamagnetic Co(III) complexes and paramagnetic Ni(II) complexes have pseudoctahedral symmetry; the paramagnetic Cu(II) complexes have the tetragonal-distorted octahedral configuration. The ligands L and Q are bound to the metal through the S atom and N atom of the amino group. The electronic spectrum of } [\text{CrL}_2]\text{Cl [HL = 4-(o-hydroxybenzamido)thiosemicarboxadize] gave 4 bands at 13600, 17420, 27400, and 34500 cm}^{-1} \text{ from which Raeh interelectronic repulsion parameters B35 and B55 were calculated, which yielded a covalency parameter 0.89. Several mono- and bis-carbene- and thio-carboxononydradize ligands and metal complexes of Cu(II), Fe(II), and Zn(II) salts were tested in vitro against Gram positive and Gram negative bacteria, yeasts and moulds. In general, the bisthio-carboxononydradizeznos possess the best antimicrobial properties and Gram positive bacteria are the most sensitive microorganisms. Cobalt(II) chloride forms a 1:1 complex with Schiff base derived from salicyaldehyde and thio-carboxononydradize. Kinetic parameters like apparent activation energy, frequency factor, activation entropy and apparent order of reaction of complex have been determined employing Freeman- Carroll, Fuoss et al., Coats-Redfern, Karkhanawala-Dharwadker and Doyle methods as modified by Zsako using non-isothermal TG curves. The complex decomposes regularly without any distinguishable rest with random nucleation mechanism. The complexes of tin(IV) chloride with tetradentate Schiff bases H$_2$L derived from the 1:2 condensation of thio-carboxononydradize with benzoin, were prepared in alcoholic medium. Sn(II) and Sn(IV) complexes of dibenzaldehyde thio-carboxononydradize, diacetophenone thio-carboxononydradize, dicyclohexanone thio-carboxononydradize, disalicyaldehyde thio-carboxononydradize, dicinnamaldehyde thio-carboxononydradize and di-o- hydroxyacetophenone thio-carboxononydradize were prepared as chloro and iodo heteroleptic complexes. The Cu(II), Ni(II) and Zn(II) metal complexes of Schiff bases derived from thio-carboxononydradize and salicyaldehyde, o-vanillin, 2,4-dihydroxybenzaldehyde or 2-hydroxy-1-naphthaldehyde were showed fluorescence, antibacterial and pigmentation properties. The ligand 1,5-bis(p-aminoacetophenone) thio-carboxononydradize was synthesized by condensation reaction of thio-carboxononydradize with 4'-aminoacetophenone in ethanol in the presence of acetic acid by refluxing for 4 hours. Its complexes with Cu(I), Zn(II), Fe(II), Sn(II), and Pb(II) were synthesized by electrochemical oxidation of anodic metal method with Cu, Zn, Fe, Sn, or Pb as anodes in the ligand/nonaqueous solution.

3.5.2. Determination of Metal ions

Online separation and sequential determination of trace amounts of heavy metals in biological materials by flow injection inductively coupled plasma atomic emission spectrometry were conducted based on the complexation of the metal ions with 1,5-bis(di-2-pyridyl)methylene thio-carboxononydradize.

3.5.3. Zinc Determination

A simple and rapid method is described for the preconcentration and determination of zinc in water using column packed with silica gel functionalized with 1,5-bis(di-2-pyridyl)methylene thio-carboxononydradize (DPTH-gel).

3.5.4. Copper Determination

Cu (1.8-15.0 µg) was determined spectrophotometrically at 455 nm (molar absorptivity was 2.06 × 104) after complexation at pH 2.5 with 1,5-diphenylthio-carboxononydradize and extraction of the complex into BuOAc. Beer’s law was obeyed for 0.18-1.5 ppm Cu. Ag present in atms. equivalent to Cu interfered. The method was used to determine 0.735 ppm Cu in a 100-g mushroom sample.

3.5.5. Bismuth Determination

Reaction of di(p-sulfophenyl)thio-carboxononydradize with bismuth ions at pH 1.15, where Bi$^{3+}$ replaces 1 proton from each of 3 molecules of the diion of di(p - sulfo phenyl)thio-carboxononydradize to form a red complex, with maximum absorbance at 510 nm, and a formation const. of (3.4 ± 1.2) × 10$^{-22}$. This reagent is a satisfactory metal indicator for use in the EDTA titration of Bi$^{3+}$.

3.5.6. Cadmium Determination

An FI-ICP-AES method for the determination of trace levels of cadmium in biological samples is described based on the complexation of the metal ion with 1,5 - bis(di - 2-pyridyl)methylene thio-carboxononydradize (DPTH) and its
subsequent online extraction into iso-Bu Me ketone (IBMK)\textsuperscript{113}.

3.5.7. Cobalt Determination

Determination of cobalt in biological samples by electrothermal atomic absorption spectrometry after extraction of the metal into Me iso-Bu ketone (MIBK) containing 1,5-bis(di-2-pyridylmethylene) thiocarbohydrazide\textsuperscript{114}.

3.5.8. Palladium Determination

The use of thiocarbohydrazide as a masking agent provides rapid masking at room temperature, enabling an EDTA titration to give an indirect determination of palladium\textsuperscript{115}.

3.5.9. Mercury Determination

Automated online separation-preconcentration system for inductively coupled plasma atomic emission spectrometry and its application to mercury determination, where the preconcentration step is performed on a chelating resin microcolumn [silica gel functionalized with 1,5-bis(di-2-pyridyl)methylene thiocarbohydrazide] placed in the injection valve of a simple flow manifold\textsuperscript{116}.

3.6. Reaction with Organic Acids

Cyclocondensation of thiocarbohydrazide 1 with organic acids RCOOH and condensation of the resulting aminotriazolothiones with ketones R'-COR\textsuperscript{2}, the (methyleneamino) triazolothiones 17 \( [R = \text{Me, Et, MeCH}_2\text{CH}_2; \ R' = 2\text{-furanyl, 2-pyridinyl, } \text{H, Me}] \) were obtained\textsuperscript{117}.

\[
\begin{align*}
\text{HN} & \quad \text{N} & \quad \text{N} & \quad \text{R} & \quad \text{R}' & \quad \text{R}^2 \\
\end{align*}
\]

The reaction of thiocarbohydrazide 1 with carboxylic acids RCOOH \( [R = \text{PhCH}_2, \text{Me, 4-MeC}_6\text{H}_4, \text{Ph, Ph(CH)}_2\text{H2, Ph(CH)}_2\text{3, Me2CHCH2}] \) at the melting temperature allowed an improved preparation of the 5-substituted aminomercapto-1,2,4-triazoles 18, which reacted easily with carboxylic acids or carboxylic acid chlorides to afford the 1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles 19 \( (R_1 = \text{Et, Me2CHCH2, Ph, Me}) \)\textsuperscript{118}. These compounds did not show any significant activity\textsuperscript{119}.

The product of thiocarbohydrazides, organic acids, and the macrocyclic compounds produced by condensation of benzil and thiocarbohydrazide, showed corrosion inhibition action, their inhibiting action on corrosion inhibition of mild steel was investigated by weight loss and potentiodynamic polarization methods\textsuperscript{120,121}.

3.6.1. Reaction with Valeric Acid

Cyclization of EtCHMeCOCO\textsubscript{2}H or Me(CH\textsubscript{2})\textsubscript{3}C(Z)CO\textsubscript{2}H \( (Z = \text{O, S}) \) with 1 followed by treatment with Mel to give 6-sec-butyl-1,2,4-triazin-5(4H)-ones 20 was useful as herbicides\textsuperscript{122}.

3.6.2. Reaction with Aldonic Acids

Three Schiff base ligands, bis(o-formylphenoxy)acetic acid thiocarbohydrazide, mono(o-formylphenoxy)acetic acid thiocarbohydrazide, and bis(o-formylphenoxy)acetic acid hydrazone, were prepared by condensation of (o-formylphenoxy)acetic acid with thiocarbohydrazide 1 and hydrazine hydrate\textsuperscript{125}.

3.6.3. Reaction with (o-formylphenoxy)Acetic Acid

Reaction of thiocarbohydrazide with aldonic acids gave 3-(alditol-1-yl)-4-aminomercapto-1,2,4-triazoles. Their reactions with phenacyl bromide afforded the corresponding acyclo-nucleoside analogs 3-(alditol-1-yl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines. Triazoles and their fused heterocyclic analogs possess significant biological activities\textsuperscript{124}.

3.6.4. Reaction with 3-Nitrobenzenecarboxylic Acid

Reaction of thiocarbohydrazide 1 with R'CO\textsubscript{2}H and 3-nitrobenzenecarboxylic acid in the presence of an organic solvent to give 87.4% of 22 \( (R' = \text{Me(CH)}_2\text{3, SO}_2\text{(CH)}_2\text{3}) \)\textsuperscript{126}.

3.6.5. Reaction with Arylpyruvic Acids
Condensation of thiocarbohydrazide 1 with arylpyruvic acids \( RC_6H_4CH_2COCO_2H \) (\( R = H, 4-Cl, 3,4-OCH_3 \)) in aqueous ethanol gave 4-amino-6-aryl methyl-3-mercapto-1,2,4-triazin-5(4H)-ones 23 (\( R^1 = H \)). In a modified method 23 have also been prepared by direct condensation of the intermediate azalactones 24 with thiocarbohydrazide 1. Compound 23 (\( R^1 = H \)) on condensation with substituted benzaldehydes ArCHO (\( Ar = 4-MeC_6H_4, 2-HOC_6H_4, 5-Br-2-HOC_6H_4, \) etc.) afford the corresponding Schiff bases 23 (\( R^1 = \text{CHAr} \)). Some of them are screened for their antifungal activities.

3.6.7. Reaction with Dicarboxylic Acid

Bis(mercaptotriazolyl)alkanes 25 (\( R = H, NH_2; \ n = 1-4 \)) were prepared in one-step from thiocarbohydrazide derivatves and dicarboxylic acid e.g., \( \text{HO}_2C(CH_2)_n\text{COOH} \).

3.6.8. Reaction with Substituted Oxobutanoic Acid

Reaction of thiocarbohydrazide 1 with 3,3-dimethyl-2-oxobutanoic acid and/or 2,2-dibromo-3,3-dimethylbutanoic acid in \( H_2O-MeOH \) at reflux afforded 4-amino-6-tert-butyl-3-mercapto-1,2,4-triazin-5-one 26.

While, reaction of thiosemicarbazide 1 with alkali metal salts of 3,3-dimethyl-2-oxobutyrlic acid, e.g. \( \text{Me}_2\text{CCO}_{2}\text{Na}^- \) formed by treating of pinacolone with \( \text{SCl}_2 \) followed by \( \text{Me}_2\text{NH} \) and hydrolysis, gave 6-tert-butyl-3-mercapto-4-amino-1,2,4-triazin-5(4H)-one 27.

3.6.9. Reaction with Glycine Derivatives

Condensation of thiocarbohydrazide 1 and glycine afforded N-(dihydrazinomethylene)glycine 28 which was assayed for reduction of hyperglycemia and obesity in mice.

3.7. Reaction with Esters

Condensation of \( \text{NH}_2\text{HNC(SMe):NNH}_2\text{HCl} \) with the RCOCH_2Et, the pyrazolotriazoles 29 (\( R = \text{Ph, 4-}, 3\text{-ONC}_6\text{H}_4, R^1 = \text{SMe} \) were obtained. Treatment of 29 (\( R = \text{Me, } R^1 = \text{Ph} \) with 4-diethy lamino-2-methylaniline, gave a range of azamethine dyes.

3.8. Reaction with Quinoxaline Derivatives

Condensation of thiocarbohydrazide 1 with 6-benzoyl-2,3-dichloroquinoxaline yielded triazole derivative.

3.9. Reaction with Coumarin Derivatives

The interaction of thiocarbohydrazide 1 with N-4-methyl-7-hydroxy-8-acetocoumarin yielded N-4-methyl-7-hydroxy-8-acetocoumarinylthiocarbohydrazide (MHACTC) 32 which is considered as ligand in nature.

3.10. Oxidation

Thiocarbohydrazide 1, in addition to thiosemicarbazide and thiourea underwent Cu²⁺ mediated oxidation in DMF in the presence of 2,2'-bipyridine (bpy) to produce cis-[Cu(bpy)(H_2O)_2SO_4] which crystallized in space group triclinic P.hivin.1.

3.11. Reaction with Bisasatin

By improved Sandmeyer procedure 2,6-diaminotoluene...
was converted into the bisisatin. Refluxing bisisatin with thiocarbohydrazide 1 in acetic acid afforded the corresponding bis-Schiff bases 33 \([Z = \text{NNHC(S)NH}H_2]\), which underwent refluxing with acetic anhydride to give N-acetylated bis-1,3,4-thiadiazole compound 34 in 73% yield\(^{137}\).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{NH}_2 \\
& \quad \text{H} \\
\text{O} & \quad \text{O} \\
& \quad \text{O} \\
& \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

3.12. Reaction with Oxazinone Derivative

Reaction of 2-phenyl-4H-3,1-benzoxazin-4-one with thiocarbohydrazide 1 in refluxing ethanol affords 2-phenyl-3-thiosemicarbazido - 4 (3H) - quinazolinone 35. However, thiaoxo-tetraoxoquinazoline 36 \((R = H)\) is obtained in 79% isolated yield when the reaction mixture is fused in an oil bath at 160°C and also obtained when 35 is heated in an oil bath at 170°C. Compound 36 \((R = H)\) reacted with paraformaldehyde and secondary amines to afford 36 \((R = \text{CH}_3\text{NEt}_2, 1\text{-piperidinomethyl})\)\(^{138}\).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{NH}_2 \\
& \quad \text{H} \\
\text{O} & \quad \text{O} \\
& \quad \text{O} \\
& \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

3.13. Reaction with Lactones

Reaction of D-glucono- or D-galactono-1,5-lactones and D-glycero-D-guloheptonic-1,4-lactone with thiocarbohydrazide 1 afforded the seco C-nucleosides 4-amino-3-(D-gluc- or D-galacto-pentitol-1-yl)-5-mercapto-1,2,4 - triazoles and 4-amino-3-(D-glycero-D-gulo-hexitol- 1-yl)-5-mercapto-1,2,4-triazole, e.g.; reaction of di-Et galactrate with thiocarboxyhydrazide 1 gave 1,4-bis (4-amino-5- mercapto-1,2,4-triazol-3-yl)-galacto-tetritol, which upon reaction with acetic anhydride gave 1,4-bis(6-methyl-1,2,4-triazololo[3,4-b] 1,3,4-thiadiazol-3-yl)- 1,2,3,4-tetra-O- acetyl-galacto-tetritol. When the tetra-O-acetylgalactaric acid was used instead of di-Et galactrate, the attack of thiocarboxyhydrazide had taken place on the ester group rather than the carboxylic group\(^{139}\). The synthesis of 4-amino-3-(D-gluco- or D-galacto- pentitol-1-yl)-5-mercapto-1,2,4- triazoles and their conversion to the resp. 6-methyl-3 - (1,2,3,4,5 - penta-O-acetyl- pentitol-1-yl)1,2,4-triazololo[3,4-b]1,3,4-thiadiazoles, e.g. 37, have been achieved. The vicinal coupling constituents were used to deduce the favoured conformations\(^{140}\).

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{S} \\
& \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

3.14. Reaction with Aldehydes and Ketones

3.14.1. Reaction with Benzaldehyde Derivatives

1,5-Bis(2-chloro-4-(piperazin-1-yl)benzylidene)thiocarbohydrazide 38, useful as anthelmintics, was obtained by reaction of 2-chloro-4-(1-piperazinyl)benzaldehyde with thiocarbohydrazide 1\(^{141}\).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{NH}_2 \\
& \quad \text{H} \\
\text{O} & \quad \text{O} \\
& \quad \text{O} \\
& \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

3.14.2. Reaction with Dialdehydes

Cyclocondensation of thiocarbohydrazide 1 with dialdehydes \((n = 1, 2)\) in the presence of Al or Ga ions afforded macroheterocycles containing thiocarbohydrazone fragments 39 \((n = 1, 2)\)\(^{142}\).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{NH}_2 \\
& \quad \text{H} \\
\text{O} & \quad \text{O} \\
& \quad \text{O} \\
& \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

3.14.3. Reaction with Hydroxybenzaldehyde

Reaction of thiocarbohydrazide 1 with 2-hydroxybenzaldehyde gave 1,5 -bis(2-hydroxybenzaldehyde) dithiocarboxyhydrazone 40\(^{143}\).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{NH}_2 \\
& \quad \text{H} \\
\text{O} & \quad \text{O} \\
& \quad \text{O} \\
& \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

3.14.4. Reaction with Ketones
3.15. Reaction with Dialkene Derivatives

Condensation of thiocarboxyhydrazide 1 and di(2- formylphenoxo)ethylene 2-OHCC6H4OCH2CH2OC6H4 - 2 CHO afforded (2:2) macrocyclic thiocarboxyhydrazone 46. 47

3.16. Reaction with Amines and Amides

The ion exchange resins with increased selectivity for copper are prepared by reaction of thiocarboxyhydrazide or hydrazothiocarbamide with epichlorohydrin and polyethylenepolyamines. Reaction of 3,3-diethyl-2-oxybutanamide with thiocarboxyhydrazide 1 and MeI gave amino (methylthio)triazinones 47 (R = 1-methycyclopropyl, Me2C). 149

3.17. Reaction with Hydrazones

Reaction of thiocarboxyhydrazide 1 with PhC(OEt)-NH.HCl gave the thiocarboxyhydrazide derivative PhC(OEt):NH.HCl : NNHCCH2NNH2 48, which cyclised to give tetrazenethione 49. Heating 49 in (2N) HCl gave triazolethione 50 (R = NH2). 150

Using thiocarboxyhydrazide and thiosemicarbazides, 3-amino-2-alkyl/arylimino-5-carbethoxy-thiazolidin-4-ones 51, 4,5-dihydro-5-carbethoxy-4H,6H-1,3,4-thiadiazin-5-one 52, 5,7-disubstituted-4H-pyrazol[5,4-e]1,3,4-thiadiazines 53 and 2-hydropo1,7-phenyl-4H-isoxazol[5,4-e]-1,3,4-thiadiazine 54 derivatives have been synthesized. 151

Synthesis of fused pyrimido[4,5-e]thiadiazines and novel
spiro compounds such as 55, 56, and 57 and their precursors were reported.\(^{152}\)

4. Conclusions

The review covers recent literature regarding the synthesis and chemical reactions of thiocarbohydrazides. Thiocarbohydrazides are easily synthesized and are useful in the synthesis of highly functionalized heterocyclic compounds and used in the design of novel highly effective pharmaceuticals with a broad spectrum, besides their applications in several methods for metal ions determination and structural determination of cells and tissues.

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