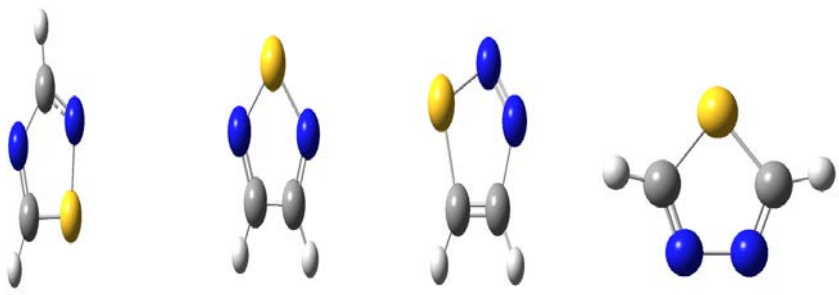
Thiadiazoles and Their Properties

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Thiadiazoles and Their Properties

Heterocyclic compounds containing structural parts specific to natural biologically active substances are being designed as a database to create new drugs over time. Thiadiazoles are biologically active five-membered aromatic heterocyclic compounds containing one sulfur and two nitrogen as heteroatoms at different positions of the ring bileşiklerdir (Boger, 1985; Jain et al., 2013; Li et al., 2013; Liu et al., 2007). The presence of these heteroatoms increases both the membrane permeability and the ability to act as versatile hydrogen bond acceptors. The inductive effect of the sulfur atom gives this structure a very weak base character with relatively high aromaticity. Thiadiazoles containing embedded sulfur atoms of vinyl groups can be considered as diazines (Meanwell, 2011; Morreira Lima & Barreira, 2005) isosteres due to their cyclic similarity, which adds to their potential to serve as fragments of bioactive structures (Aurelio et al., 2016). Thiadiazoles, which are multifunctional heterocyclic compounds, have wide applications in pharmaceutical, agricultural and materials chemistry (Haider et al., 2015; B. Hu et al., 2014). They also play an important role as versatile ligands in coordination chemistry (Frija et al., 2015). It has been widely reported that compounds bearing thiadiazole rings exhibit anticancer, anti-inflammatory, antibacterial, antifungal, antiviral, anticonvulsant and antiparasitic activities (D. Kumar et al., 2010). Thiadiazoles used as pharmacophores are useful as thiol scavengers, pesticides and corrosion inhibitors (Bentiss et al., 2004; Castro et al., 2006; Tam et al., 2005). Thiadiazoles can occur in four different regioisomeric forms such as 1,3,4- thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole and 1,2,3-thiadiazole, which enrich their structural diversity according to local polarization (Figure 1). The most widely studied thiadiazoles are the 1,2,4-thiadiazole and 1,3,4-thiadiazole isomers.

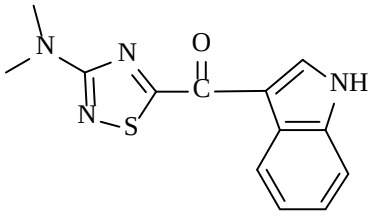


1,2,4-Thiadiazole 1,2,4-Thiadiazole 1,2,3-Thiadiazole 1,3,4-Thiadiazole

Figure 1. Regioisomer Forms of Thiadiazoles

Synthesis and Properties of 1,2,4-Thiadiazoles

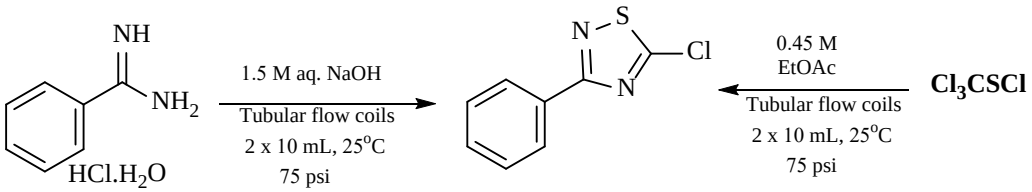
1,2,4-Thiadiazole was first described in 1821 and synthesized and characterized in 1955. Until 1980, the natural product containing the 1,2,4-thiadiazole core wasn't reported. Dendrodoin, the first natural product, is a cytotoxic product isolated from marine Tunicate Dendrodoa grass (Franz & Dhingra, 1984).



1,2,4-Thiadiazoles are generally stable due to the aromatic nature of the ring. Thiadiazoles react with acids, alkalis, oxidizing and reducing agents. Research on the reactivity of 1,2,4-thiadiazole has been done on 1,2,4-thiadiazoles with substituents in the 3- and 5-positions, which are more stable to acid, alkali, oxidizing agents and reducing agents. The 5-position in 1,2,4-thiadiazoles is the most reactive site in nucleophilic substitution reactions. The electrophilic reactions of 1,2,4-thiadiazoles are very low and limited (Kurzer, 1982).

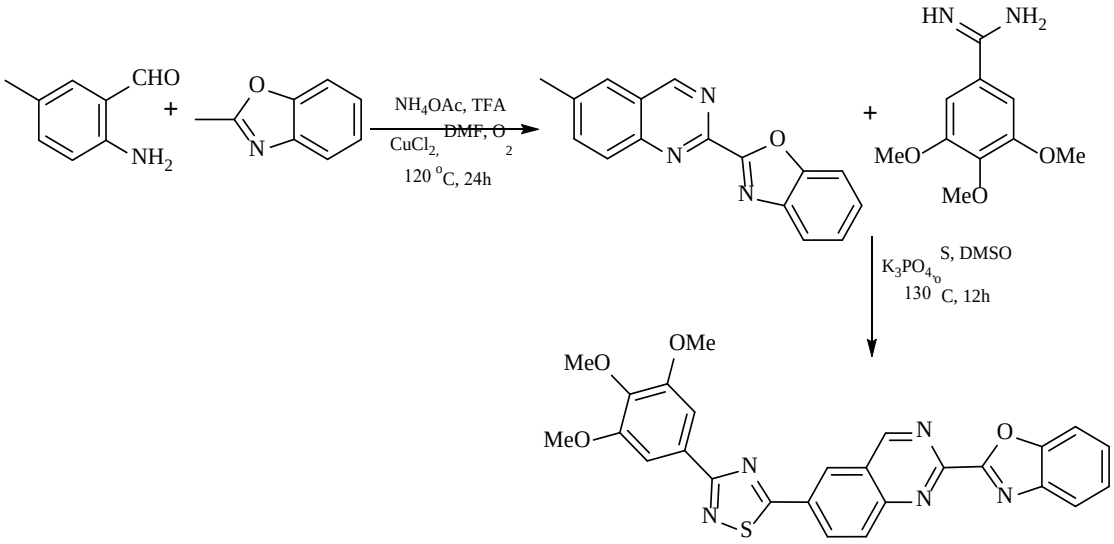
Among the thiadiazole isomers, the 1,2,4-thiadiazole structure is an important one as it resembles the ubiquitous pyrimidine moiety. 1,2,4-thiadiazole derivatives are widely used in the treatment of different pathologies, including Alzheimer's disease, in which neurodegenerative ones take an important place (Porcal et al., 2008). The synthesis of 1,2,4-thiadiazoles is achieved by various methods, including oxidative ring closure (Mariappan et al., 2016; Vanajatha & Reddy, 2016), multicomponent reactions (Xie et al., 2016) or [3+2]-cycloadditions (Aitha et al., 2016).

5-Chloro-3-phenyl-1,2,4-thiadiazole were efficiently prepared by reaction with different nitrogen, sulfur and oxygen-based nucleophiles, enabling efficient synthesis and derivatization of 1,2,4-thiadiazole heterocycles. This synthetic approach was then applied to produce a series of bromophenyl-5-chloro-1,2,4-thiadiazoles, providing a valuable introduction to further structural diversification on this important heterocyclic scaffold (Baumann & Baxendale, 2017)

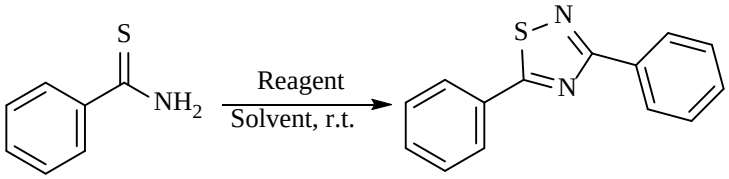


A new compound consisting of structurally modified 1,2,4-thiadiazole containing benzoxazole-quinazoline derivatives was synthesized. A series of 1,2,4-thiadiazole-containing benzoxazolequinazoline derivatives. designed and synthesized. It was

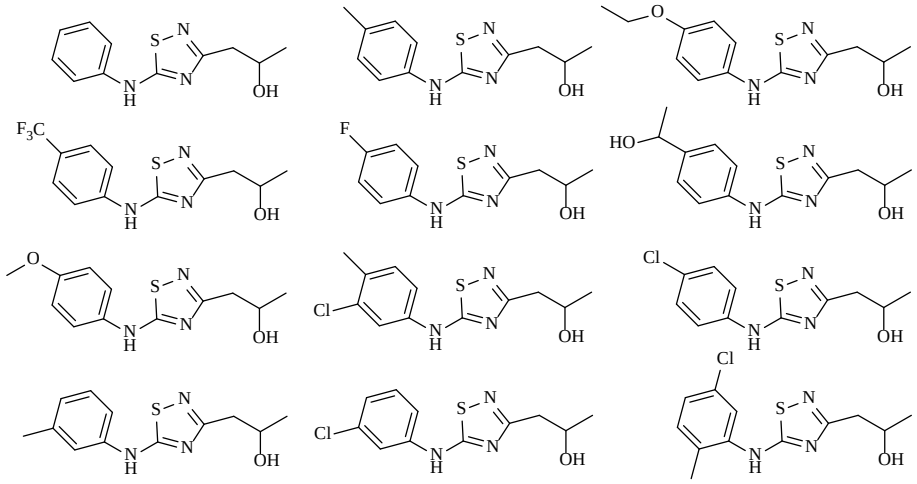
screened for its anticancer profile against human cancer cell lines, including lung cancer, breast cancer, colon cancer, and ovarian cancer, and the clinical agent as etoposide selected as positive control (Perupogu et al., 2020).



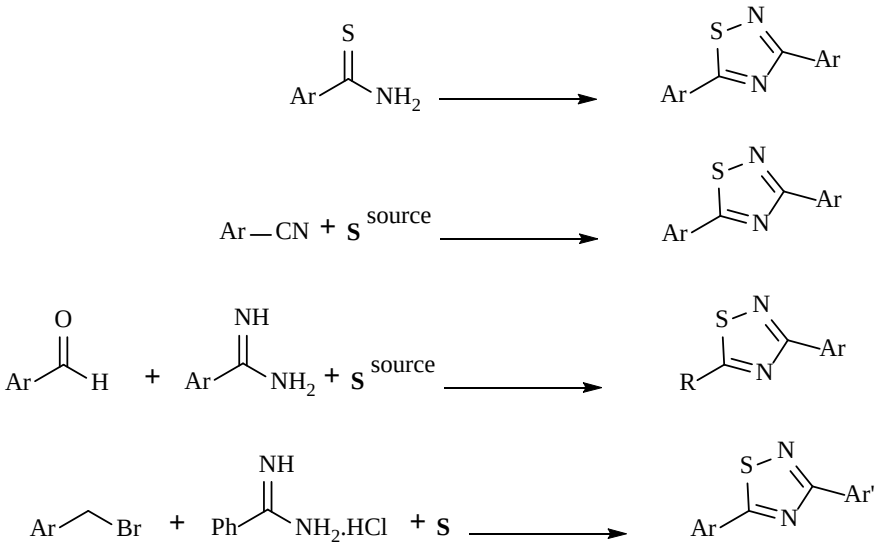
The classical methods used for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles can be expressed as intramolecular cyclization, intermolecular cyclization and oxidative dimerization of thioamides. 3,5 unsymmetrical disubstituted 1,2,4-thiadiazole was synthesized by intramolecular oxidative cyclization of amidinithioureas(Castro et al., 2006) and 1,3-dipolar cycloaddition of nitrile sulfides to nitriles (Howe & Franz, 1974). Ceric ammonium nitrate (CAN), a versatile reagent, effectively mediated the oxidative dimerization of primary thioamides in acetonitrile at room temperature, and thus the synthesis of symmetrically 3,5-disubstituted 1,2,4-thiadiazoles took place in high yield (Vanajatha & Reddy, 2016).



The effect of a structural modification on the solubility of 1,2,4-thiadiazole drug-like compounds in pharmaceutically relevant solvents n-hexane and 1-octanol and on thermodynamic aspects of solvation processes was investigated. The solubility of compounds in 1-octanol is largely independent of the nature and location of the substituent in the phenyl moiety. However, in n-hexane, the addition of any substituent to the phenyl ring of the 1,2,4-thiadiazole molecule reduces the solubility in the solvent (Surov et al., 2016)



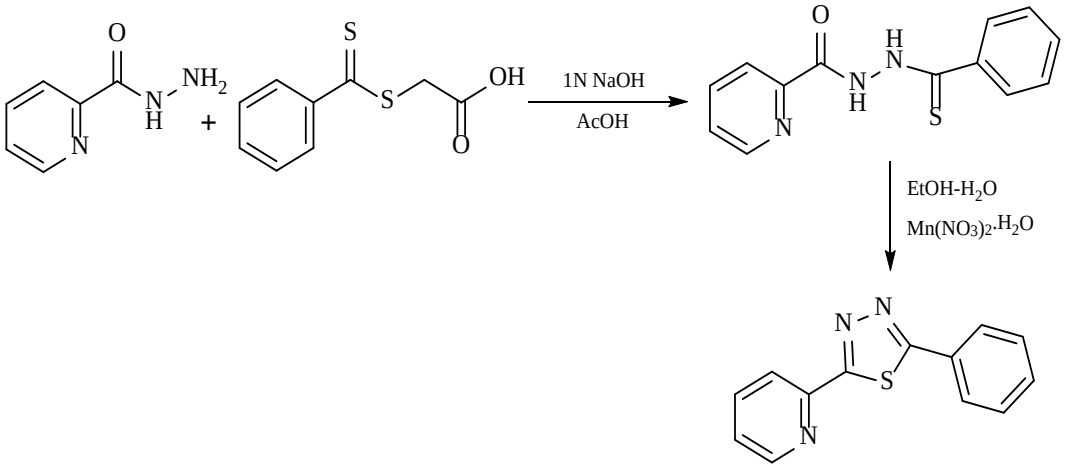
Both in terms of diversity and complexity, the development of new methods for the unsymmetrical 3,5-diaryl-1,2,4-thiadiazole or suitable substrate design has been synthesized although highly desirable but still challenging for organic chemists. Examples were not reported until Deng developed the ring between amidines, elemental sulfur and 2-methylquinolines (or aromatic aldehydes) under transition metal-free conditions (Xie et al., 2016; Zhou et al., 2017).



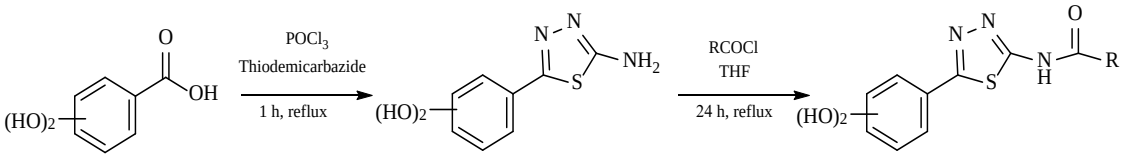
Synthesis and Properties of 1,3,4-Thiadiazoles

The synthesis of heterocyclic compounds is of great interest and various methods have been reported for their synthesis, such as oxidative cyclization of acyclic precursor such as NO-acyl hydrazine-carbodithioic acid alkyl ester (Jasinski et al., 2010; Jedlovská & Leško, 1994). It is used as a starting material in the synthesis of many chemical compounds, including 1,3,4-thiadiazoles, biocides, sulfa drugs, dyes, fungicides and chemical reaction accelerators (Jalhan et al., 2013). Thiadiazoles containing hydroxyl, amino and mercapto substituents can exist in their tautomeric form. Many industrial

applications and chemical properties such as their capacity to form complexes with metal ions have been reported (Barboiu et al., 1996). These results led to the synthesis of a new type of heterocyclic compound, assuming that the presence of phenyl and pyridine rings in the thiadiazole moiety would have much better solubility in anhydrous medium. Metal assisted cyclization of 4-phenyl-1-(2-phenylacetyl)thiosemicarbazide and N'-benzothioylpicolinohydrazide to 5-benzyl-N-phenyl-1,3,4-thiadiazol-2-amine and 2-(5-phenyl-1,3,4-thiadiazol-2-yl) pyridine attempted to prepare complexes with manganese (II) nitrate. Conversion of 5-methyl-1,3,4-thiadiazol-2-thiol to 2-(5-methyl-1,3,4-thiadiazole-2-ylthio)-5-methyl-1,3,4-thiadiazole provided using Manganeseacetate under mild conditions (Dani et al., 2013).

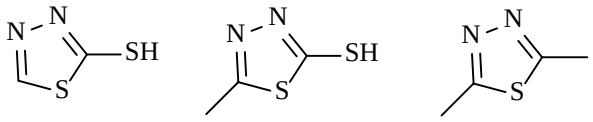


The 1,3,4-thiadiazole heterocyclic scaffold incorporated into many heterocyclic compounds with varying degrees of antiproliferative activity has the well-known pharmacophore property (Aliabadi, 2016; Haider et al., 2015). A series of 5-(2,5-dimethoxyphenyl)-1,3,4-thiadiazol-2-amino derivatives were synthesized and investigated for cytotoxic activity against HT-29 and MDA-MB-231 cancer cells. Heading molecules were synthesized in two steps (Jakovljević et al., 2017).



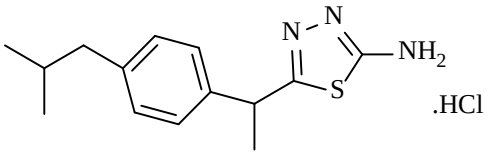
Mercapto-substituted thiadiazoles can have different tautomeric forms such as thiol or thione, which affects their reactivity. However, studies on the tautomeric stability of mercapto thiadiazoles have been reported recently(Enchev & Angelova, 2010; Esmaiel et al., 2020; Hipler et al., 2002; Ortega et al., 1996). The structural and energetic properties of heterocycles with a five-membered ring containing nitrogen and sulfur as heteroatoms can be determined to establish energy-structural correlations. These correlations are important in predicting thermochemical and thermophysical properties for other structurally related compounds. An experimental and computational thermochemical study of thiadiazoles such as 2-mercapto-1,3,4-thiadiazole, 2-mercapto-5-methyl-1,3,4-

thiadiazole and 2,5-dimethyl-1,3,4-thiadiazole has been reported (Silva et al., 2022).



1,3,4-Thiadiazoles with both electron accepting and donating groups have been reported to be potential compounds with optical, electronic, biological and chemical properties (Hu et al., 2014). Especially, 2-amino-1,3,4-thiadiazole derivatives have attracted a lot of attention due to their significant anticancer activities. 2-(4-fluorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole inhibits the proliferation of tumor cells, possibly through a mechanism that reduces cell division and decreases cell migration (Kumar et al., 2010; Remko et al., 2006).

Considering the individual pharmaceutical significance of ibuprofen and 1,3,4-thiadiazole compounds, the possibility of synthesizing chemical entities containing both ibuprofen and thiadiazole moieties was investigated. An optimized strategy was applied for a one-step acylation and cyclization reaction of the carboxylic acid group of ibuprofen with thiosemicarbazide in the presence of phosphorus oxychloride (Al-Omar et al., 2004). The target compound, 2-amino-5-ibuprofen substituted-1,3,4-thiadiazole as hydrochloride salt was synthesized and its structure was elucidated. The molecular structure and vibrational properties of the target compound are studied using experimental X-ray diffraction and spectroscopic techniques (FTIR and Raman) and complemented by quantum chemical calculations, including NBO population analysis (Channar et al., 2019).

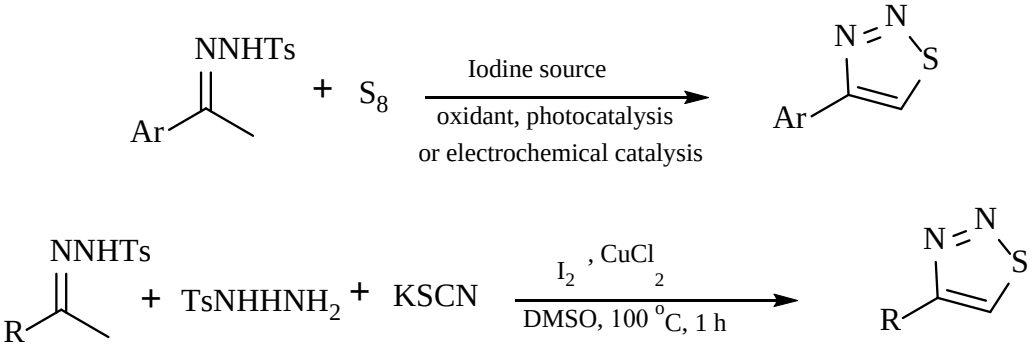


Synthesis and Properties of 1,2,3-Thiadiazoles

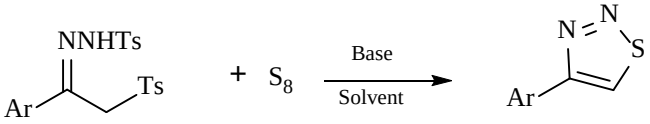
1,2,3-Thiadiazoles are widely used in pharmaceuticals, agrochemicals and organic synthesis as an important class of heterocyclic compounds. The structure of the molecular skeleton aroused great interest. Conventional methods for the synthesis of 1,2,3-thiadiazoles include Hurd-Mori synthesis (Hurd & Mori, 1955; A. Kumar et al., 2012), Wolff synthesis (Singh et al., 2013), Pechmann synthesis (May & Townsend, 1976), and the like. However, these approaches often have limitations such as diazo compounds or azides, substrates not readily available, air-sensitive sulfur sources, harsh reaction conditions, and narrow substrate coverage. Therefore, the development of a simple and effective method for accessing 1,2,3-thiadiazoles remains an active topic in organic synthesis (Feng et al., 2021).

N-tosylhydrazones are excellent agents for the synthesis of 4-aryl-1,2,3-thiadiazoles due

to their stable structure, easy availability and high reactivity. Various iodine-catalyzed cyclization reactions have been reported under the influence of oxidants, photocatalysis or electrochemical catalysis with different sulfur sources of N-tosylhydrazones (J. Chen et al., 2016; Zhang et al., 2020). $I_2/CuCl_2$ promoted one-pot three components of ketones, p-toluenesulfonyl hydrazide and KSCN have been reported to synthesize 1,2,3-thiadiazoles with aliphatic or aromatic substitutes (Feng et al., 2021; C. Wang et al., 2019).



Different derivatives of 2-(p-toluenesulfonyl)-N-tosylhydrazones were obtained with different sulfur sources. A series of 4-aryl-1,2,3-thiadiazoles and new 4-aryl-5-tosyl-1,2,3-thiadiazoles were synthesized by adjusting the reaction conditions (Feng et al., 2021).

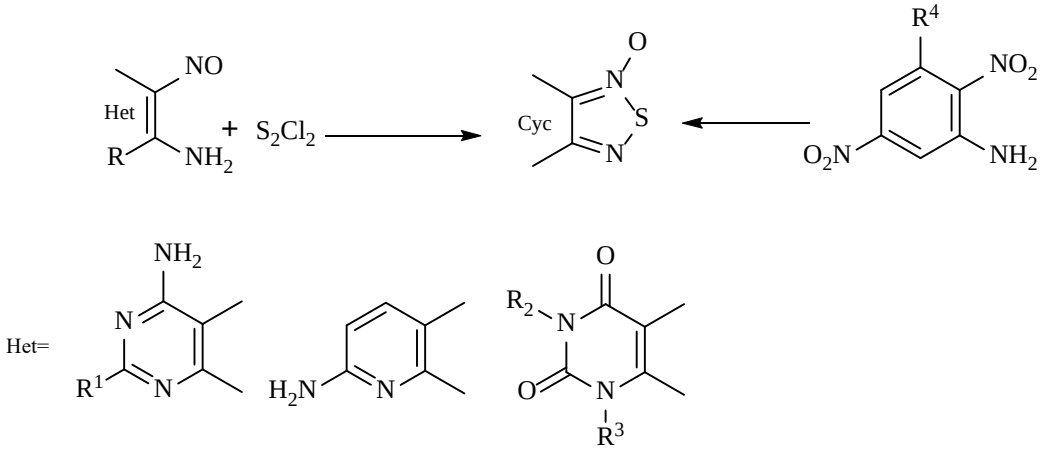


Synthesis and Properties of 1,2,5-Thiadiazoles

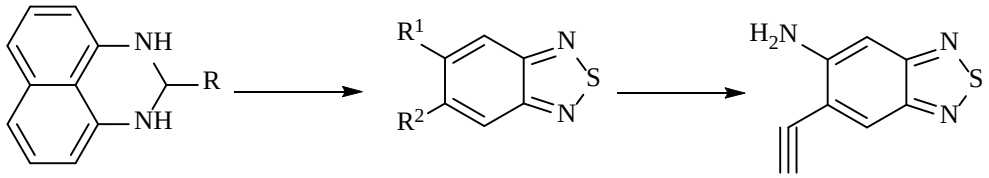
1,2,5-Thiadiazoles and their benzo-fusion derivatives have been known for many years and their synthesis, chemical and physical properties have been extensively reported (Neto et al., 2013) (Konstantinova et al., 2014). Besides their use in various branches of chemistry, medicine (Konstantinova et al., 2014), and agriculture (Gozzo, 2003) respectively. The latter is relevant when a cultivar resistant (R, they have been found to be efficient electron acceptors and used as building blocks of many real or potential molecule-based functional materials for organic electronics (Chen et al., 2014) and spintronics (Shuku et al., 2009). Recently, they have been used in the synthesis of thermally stable radical-anion salts, revealing antiferromagnetic Exchange interactions in spin systems (Gritsan & Zibarev, 2011), and also conducting charge transfer complexes with photoconductivity (Gritsan & Zibarev, 2011; Semenov et al., 2013).

Based on DFT calculations of electron affinity, N-oxides of the above-mentioned compounds, such as 1,2,5-thiadiazole 2-oxides and 2,1,3-benzothiadiazole 1-oxides, were also expected to be good precursors of stable RAs that can be isolated in salt form.

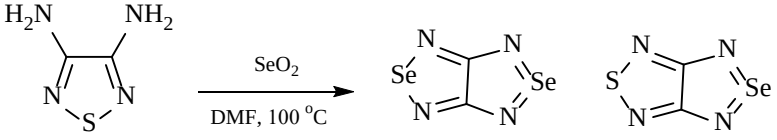
It should be emphasized that the well-studied chemistry of 1,2,5-thiadiazole, in contrast to S-oxides and S,S-oxides, including its potential applications in electrochemistry and materials science. 1,2,5-Thiadiazole 2-oxides and derivatives are rare compounds. Benzo- and heterocyclic fused derivatives were obtained in the reaction of sulfur monochloride with o-aminonitroso and o-aminonitro precursors (Konstantinova et al., 2014).



To investigate the structural diversity of 1H-2,3-dihydroperimidine derivatives, a scaffold-hopping strategy was used to replace the 1H-2,3-dihydroperimidine motif with the benzo[c][1,2,5]thiadiazole motif, designed and a series of benzo[c] [1,2,5]thiadiazole derivative was synthesized. The inhibitory activities of the synthesized compounds against protein tyrosine phosphatase 1B (PTP1B) and Src homology 2 (SH2) domain containing protein tyrosine phosphatase-2 (SHP2) were evaluated (Wang et al., 2017)



It has been reported that there are very important studies in various fields of 1,2,5-selenadiazole derived compounds, basic and applied chemistry, biomedicine and technology (Konstantinova et al., 2014). Similar to these studies, a concise and convenient synthesis of 1,2,5-thiadiazoles and fused 1,2,5-selenadiazoles from selenium dioxide has been developed (Konstantinova et al., 2015).



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