CHEMICAL AND BIOLOGICAL POTENTIAL OF 1,2,4-OXADIAZOLE PROPIONIC THIOSEMICARBAZIDES IN THE SYNTHESIS OF HETEROCYCLIC MOLECULES

José Maurício dos Santos Filho[1]; Luan C. G. Ramos[2]; Savio M. Pinheiro[2]

[1]*Laboratório de Planejamento e Síntese Aplicados à Química Medicinal (**SintMed**®)-Departamento de Engenharia Química-UFPE-PE;* [2]*Laboratório de Síntese Orgânica e Biocatálise-UFPB-PB.*

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Introduction

The field of organic synthesis has made significant progress in recent years, focusing on developing efficient and versatile methodologies for constructing heterocyclic compounds. Due to their diverse biological activities and unique properties, heterocycles are of great interest in a wide range of fields, including pharmaceuticals, medicinal chemistry, natural products, agrochemicals, and materials science. Efficient synthesis of heterocyclic structures is crucial for their widespread applications. Therefore, developing new and efficient methods for rapidly synthesizing heterocyclic architectures is becoming increasingly important [Javahershebas *et al.* 2024]. Under this perspective, the thiosemicarbazide scaffold is one of the most versatile substrates for building heterocyclic compounds.

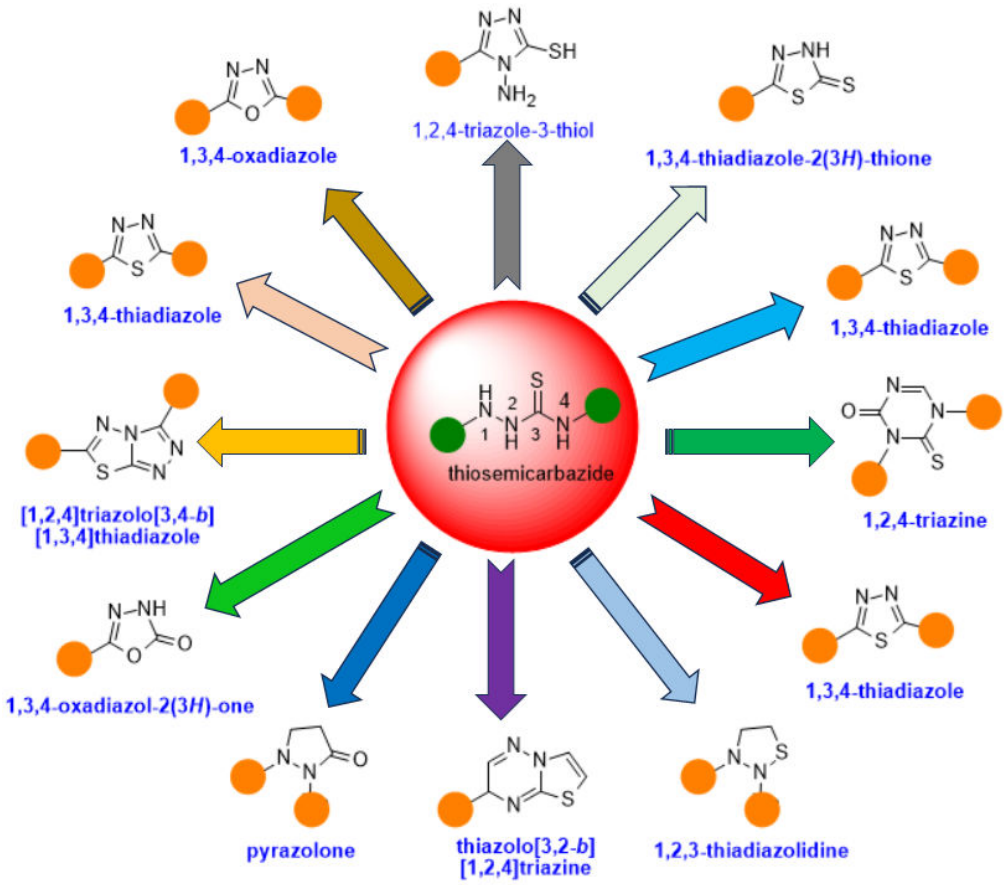


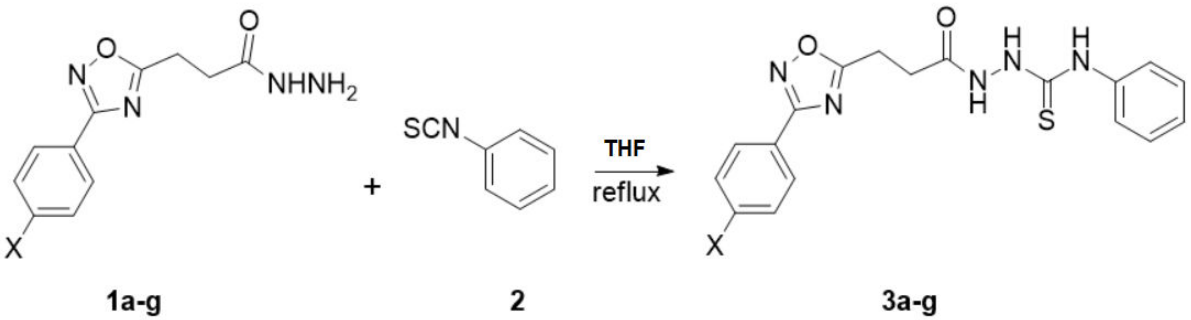
Figure 1. Heterocompounds from thiosemicarbazides.

Thiosemicarbazide moiety (-NH_2-NH-CSNH2-) has attracted great interest for many years as a reactant for synthetic organic chemistry. The chemical behavior of thiosemicarbazide is similar to its correspondent semicarbazide, however, the former is of superior chemical adaptability of the thione group compared to that of the keto group and is liable for more diverse chemical transformations. Due to the presence of several reactive centers, these compounds are widely used in the synthesis of nitrogen- and sulfur-containing heterocyclic compounds, *e.g.*, thiazoles, pyrazoles, thiadiazoles, triazoles, thiadiazines, triazines, pyrimidines, including fused compounds, such as thiazolotriazines, pyrazolotriazines, and so on [Acharya *et al.* 2021], as seen in Figure 1. The diversity of heterocycles generated from thiosemicarbazides is associated primarily with the fact that these compounds can exhibit properties of N(1),N(2)-, N(1),N(4)-, N(2),N(4)-, N(1),S-, N(2),S- and N(4),S-dinucleophiles. During the past few decades, interest has been rapidly growing in attaining insight into the chemistry of thiosemicarbazide derivatives due to their noticeable biological activities and synthetic applicability. Among the accumulative number of nitrogen and sulfur comprising derivatives, thiosemicarbazides are also considered by many scientists as interesting targets for drug design as standard substrates for heterocyclic chemistry [Metwally *et al.* 2011].

Beyond their synthetic importance, thiosemicarbazides occupy a central place in medicinal chemistry. Thiosemicarbazides display interesting biological activities, including anticancer, antimicrobial, anti-HIV, antiviral, insecticidal, antisclerotic, anti-oxidant, and antiparasitic activities. They also play an important role in the regulation of plant growth. These sulfur and nitrogen donor ligands can build coordination complexes, which are reported for their biological responses [Asifa *et al.* 2021]. Besides, hybrids of heterocyclic compounds bearing thiosemicarbazide are of special importance for the bioactive response, as well as for the design of two or more heterocycles in one molecule. In a previous work of our group, a series of 1,2,4-oxadiazole thiosemicarbazides was reported, providing anti-inflammatory compounds, including the synthesis of 1,2,4- and 1,3,4-oxadiazole rings linked together [dos Santos Filho *et al.* 2009]. This strategy was retaken in this work, envisaging the structural planning of novel heterocyclic hybrids with potential biological activity.

Material and Methods

The key intermediates 1,2,4-oxadiazole propionic acyl hydrazides **1a-g** were prepared in two steps according to a previous methodology used at ***SintMed***® [dos Santos Filho *et al.* 2009], based on a cyclocondensation reaction between amidoximes and ethyl 4-chloro-4-oxobutyrate in the presence of a base in dry tetrahydrofuran (THF) [Maingot *et al.* 2010], followed by refluxing of the intermediate products in ethanol with hydrazine hydrate. Isolated hydrazides **1a-g** were then refluxed in THF in the presence of phenyl isothiocyanate **2** to afford the 1,2,4-oxadiazole propionic thiosemicarbazides **3a-g** (Scheme 1), according to the general procedure below.



X = H (a), CH_3 (b), F (c), Cl (d), Br (e), NO_2 (f), OCH_3 (g)

Scheme 1. Synthetic route for 1,2,4-oxadiazole propionic thiosemicarbazides **3a-g.**

Preparation of 1,2,4-oxadiazole propionic thiosemicarbazides **3a-g**. A solution of appropriate hydrazides **1a-g** (1 eq.) in THF was mixed with phenyl isothiocyanate **2** (1 eq.) and refluxed for 5 h until the reaction's completion was observed by thin layer chromatography (TLC). After cooling, the solvent was removed under vacuum, and the crude products were recrystallized from ethanol to afford the products as white solids, whose yields, melting points, and infrared (IV) data are given in Table 1. Melting points were determined on a Gallenkamp capillary apparatus and were uncorrected. Infrared spectra were recorded using KBr discs on a Perkin-Elmer Paragon 500 FT-IR spectrometer.

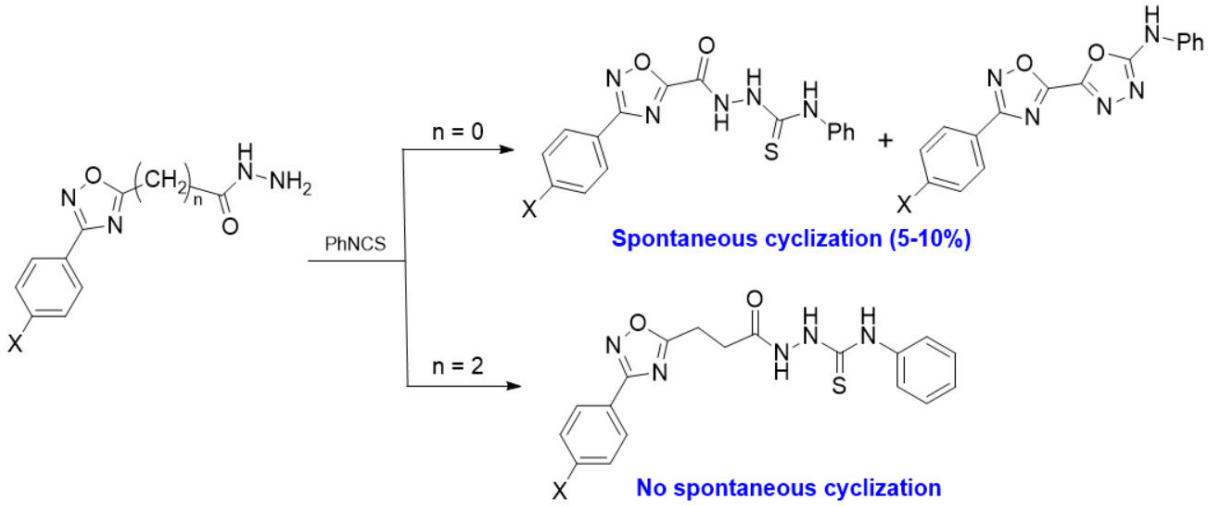
Results and Discussion

The synthesis of compounds 1,2,4-oxadiazole propionic thiosemicarbazides **3a-g** was successfully carried out according to the proposed methodology in good yields. The targeted products were isolated as pure solids after recrystallization from EtOH and characterized through their TLC analyses, melting points, and infrared (IR) spectroscopic data as observed in Table 1. Characteristic bands for NH (3370-3230 cm^{-1}), C=O (1680-1640 cm^{-1}), and C=S (1280-1150 cm^{-1}) were observed, indicating the structural identity of the obtained products. The general yields ranged from 72 to 84% after one recrystallization, which is an excellent outcome, avoiding tedious and expensive purification steps.

Table 1. Characterization data for the 1,2,4-oxadiazole propionic thiosemicarbazides **3a-g**

Comp.	X	Yield (%)	M.p. (°C)	IR (cm^{-1})
3a	H	72	162-165	3330, 3250 (NH), 3055 (Ar CH), 2965 (Aliphatic CH), 1681 (C=O), 1527 (C=C), 1156 (C=S)
3b	CH_3	78	173-175	3327, 3218 (NH), 3060 (Ar CH), 2990 (Aliphatic CH), 1678 (C=O), 1546 (C=C), 1173 (C=S)
3c	F	70	166-169	3276 (NH), 3134 (Ar CH), 2946 (Aliphatic CH), 1695 (C=O), 1533 (C=C), 1220 (C=S)
3d	Cl	72	174-176	3344, 3235 (NH), 3060 (Ar CH), 2954 (Aliphatic CH), 1691 (C=O), 1525 (C=C), 1217 (C=S)
3e	Br	84	185-188	3338 (NH), 3012 (Ar CH), 2952 (Aliphatic CH), 1683 (C=O), 1533 (C=C), 1271 (C=S)
3f	NO_2	76	184-185	3306 (NH), 3085 (Ar CH), 2934 (Aliphatic CH), 1687 (C=O), 1529 (C=C), 1178 (C=S)
3g	OCH_3	73	161-163	3128 (NH), 3070 (Ar CH), 2980 (Aliphatic CH), 1671 (C=O), 1538 (C=C), 1260 (C=S)

In our previous report [dos Santos Filho *et al.* 2009], it was ascertained that the synthesis of analog compounds without a spacer between the 1,2,4-oxadiazole ring and the carbonyl group underwent a spontaneous cyclization leading to a 1,3,4-oxadiazole ring, observed by TLC and ^{1}H NMR of crude products. As depicted in Scheme 2, this phenomenon doesn't occur in the case of compounds **3a-g**, which bear a -CH_2CH_2- spacer. From the synthetical point of view, this behavior is important, since it affects the purity and yields of the thiosemicarbazide products.



Scheme 2. Effect of the spacer on the chemical behavior of 1,2,4-oxadiazole thiosemicarbazides.

Conclusions

Herein, a successful strategy for synthesizing novel 1,2,4-oxadiazole propionic thiosemicarbazides **3a-g** was described and seven compounds were isolated and characterized. These compounds are expected to be excellent substrates for the synthesis of molecular hybrids bearing two heterocyclic rings linked together by a -CH_2CH_2- spacer, which allows more flexibility for the products and brings to light important structural features that can influence the chemical and biological activity of these compounds.

Acknowledgments

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