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REVIEW ARTICLE

Synthetic strategy of 2-thioxo-4-thiazolidinone with core chemistry and biological importance

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ABSTRACT

Due to the vast range of biological actions that rhodanine and its derivatives exhibit, they are recognized as privileged structures in pharmacological research. However, the rhodanine skeleton synthesis process has certain limitations. However, the rhodanine ring's reactivity enabled the creation of various arylidenes at position 5 and carboxylic acids at position 3, respectively. The principal pathways of heterocycle alteration are determined by the most reactive sites in 4-thiazolidinone, which are 3 and 5. In a review paper, the chemistry of 4-thiazolidinones was discussed, in particular the rhodanine ring and several methods for its reactions, including ring modification. The study deals with thioureas and thioglycolic acid react in a single step, catalyzed by protic acid, resulting in the direct preparation of N-aryl rhodanines as well as the rhodanine skeleton, offering a novel method for the synthesis of rhodanine and its derivatives. The presented approach is simple, effective, atom-efficient, and practical in high yields.

KEY WORDS: 4-Thiazolidinones, Heterocycle, Methylene carbon, Rhodanine, SN2 type, Synthesis, Thiazolidone, Thioglycolic acid, Thiourea

INTRODUCTION

The potential of 4-thiazolidinones as medications has been taken into consideration by pharmaceutical experts since the turn of the 20th century.[1] As a result, rhodanines, thiazolidine-2,4-diones, and thiazol-4(5H)-ones, which include sulfur and nitrogen, became intriguing target structures for therapeutic development and discovery.[2] The N-3 and C-5 positions of the nucleus can be substituted in a variety of ways by the rhodanine core. Researchers from all over the world have worked tirelessly to show that the presence of arylidene substituents at the C-5 position and carboxyalkyl (acetic, propionic, butyric, and pentanoic) acid fragments at the N-3 position demonstrated higher biological activity.[3] The antidiabetic,[4] anti-HIV,[5,6] anti-infective,[7]anti-Alzheimer,[8]anticancer,[9-12]antibacterial,[13] anti-tubercular,[14] antifungal,[15] anti-anxiety,[16] anti-inflammatory,[17] anti-depressant,[18] and anti-HSV microbicides[19] actions of the synthesised compounds have been investigated. In addition, the mechanistic analysis has shown that rhodanine-based ligands may interact with a range of pharmacological targets. The medicine epalrestat, which is intended to halt the progression of diabetic neuropathy, is a notable example of a well-advertised medication.[20] Rhodanine structural scaffolds have also reportedly been used in the production of certain highly effective solar material polymers. They may also be employed as a reagent for the detection of metal ions and have coordination abilities. Rhodanine and its derivatives hence have a wide range of uses in analytical, photo, and coordination chemistry in addition to playing a significant part in pharmaceutical and biochemistry chemistry.[21-23] The excellent biological activities that rhodanine analogues have demonstrated in the life sciences and pharmaceuticals have made them the primary structural component of novel medications and desirable synthetic targets.

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CHEMISTRY OF RHODANINE

The ability of rhodanine to control and change electrochemical and spectral properties is an intriguing argument for why it is utilized in solar cells and colors.[24] Rhodanine is a five-membered heterocycle with amino and thioether groups at positions 1 and 3, respectively. It shares structural similarities with the compounds thiazolidine-2,4-dione and 2-iminothiazolidine-4-one, which have an oxo or imino group at position 2 instead of a thioxo group. In addition, it has a connection to 4-thioxothiazolidin-2-one, which has oxo and thioxo groups in positions opposite to those in rhodanine.[25] Rhodanine modification is the next step in the synthesis of rhodanine derivatives. There are several MCRs in this set of transformations as well as straightforward reactions. The synthesis of several thiazolidinone-based chemicals uses radonine and its derivatives as efficient building blocks. The Knoevenagel reaction, which involves condensing rhodanine and an oxo compound, is one of the most used methods for fundamental core alteration.[26] The target compounds can be produced by attacking an electrophilic center because to the nucleophilic activity of the carbon atom of methylene at the C5 position. For various 5-ene-rhodanines synthesis (5-aryl (alkyl) idene-, 5-heterylidene-, and 5-enamine-addition to the synthesis of 5-ene-rhodanines), the Knoevenagel condensation and related methods are straightforward and effective instruments. It is important to pay attention to the structural variations between 5-substituted derivatives with single and double bonds. Planar conjugated systems are created via the C5 exocyclic double bond of 5-ene-4-thiazolidinones. This double bond may be easily reduced to create corresponding unconjugated structures. Due to the greater ease of enolization at the 5-position under physiological circumstances, it is challenging to retain stereochemistry at this location in these types of non-conjugated complexes. Marketed drug and basic SAR study is incorporated on it[1] [Figure 1].

METHODS FOR THE SYNTHESIS OF RHODANINE CORE

Various methods are available in the literature describing the synthesis of rhodanine skeletal from different starting

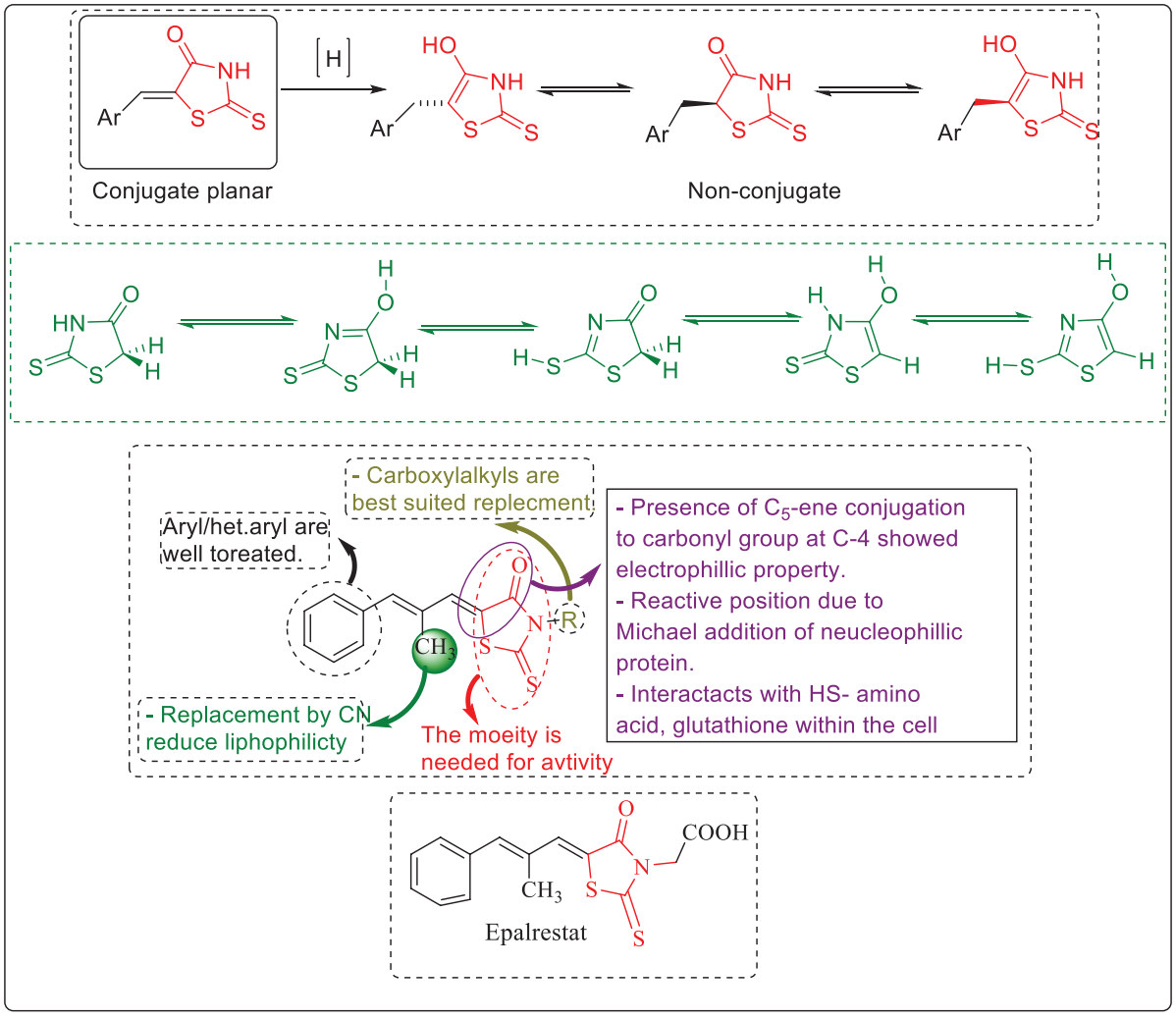

Figure 1: Conjugation and stereochemistry of rhodanine core with basic SAR study and marketed drug Epalrestat.

materials utilizing different reaction conditions. We have concise some of the schemes 1–8 in [Figure 2]. In synthetic scheme 1, alkaline solution of appropriate amine **(1)** was reacted with carbon disulphide **(2)** then treated with an aqueous solution of sodium chloroacetate **(3)** followed by the acidification and refluxed to afford the desired product **(4).**[27] Scheme 2 reports the preparation of *N*-substituted rhodanine **(4)** by reacting amines **(1)** with trithiocarbonyl diglycolic acid **(5)** in the company of 1,1'-carbonyldiimidazole in THF at 0°C **(6)**.[28] Scheme 3 reports a rapid and convenient method for producing substituted rhodanines **(4)** using the "Holmberg method" under microwave-assisted conditions. The process parameters were tweaked to perfection and best results for the preparation were formed by utilizing dimethoxyethane (DME) as a solvent and adding 1 equivalent of trimethylamine **(1)**. Using the optimized protocol, reaction of bis (carboxymethyl)-trithiocarbonate **(5)** with diverse amines in DME under microwave irradiation at 90°C for 10 min in the presence of trimethylamine as a base afforded corresponding *N*-functionalized rhodanines in moderate to excellent yield.[29] In scheme 4 and 5, Nitsche and Klein reported the microwave-assisted, one-pot, three-step methodology for the synthesis of N-substituted rhodanines quickly and efficiently **(4)**. The protocol involves the reaction of amines **(1)** majorly alkyl- and benzylamines with carbon disulfide **(2)** in ethanol under basic environment in a microwave reactor meant for 5 min by 100°C. Then after, chloroacetic acid is added. **(7)** and a second reaction for 5 min at 100°C. The reaction mixture was acidified using excess of aqueous hydrochloric acid and heated at 120°C meant for 30 min to afford the product. Ethanol found to be more appropriate solvent than water in case of benzylamines and long reaction period in the third

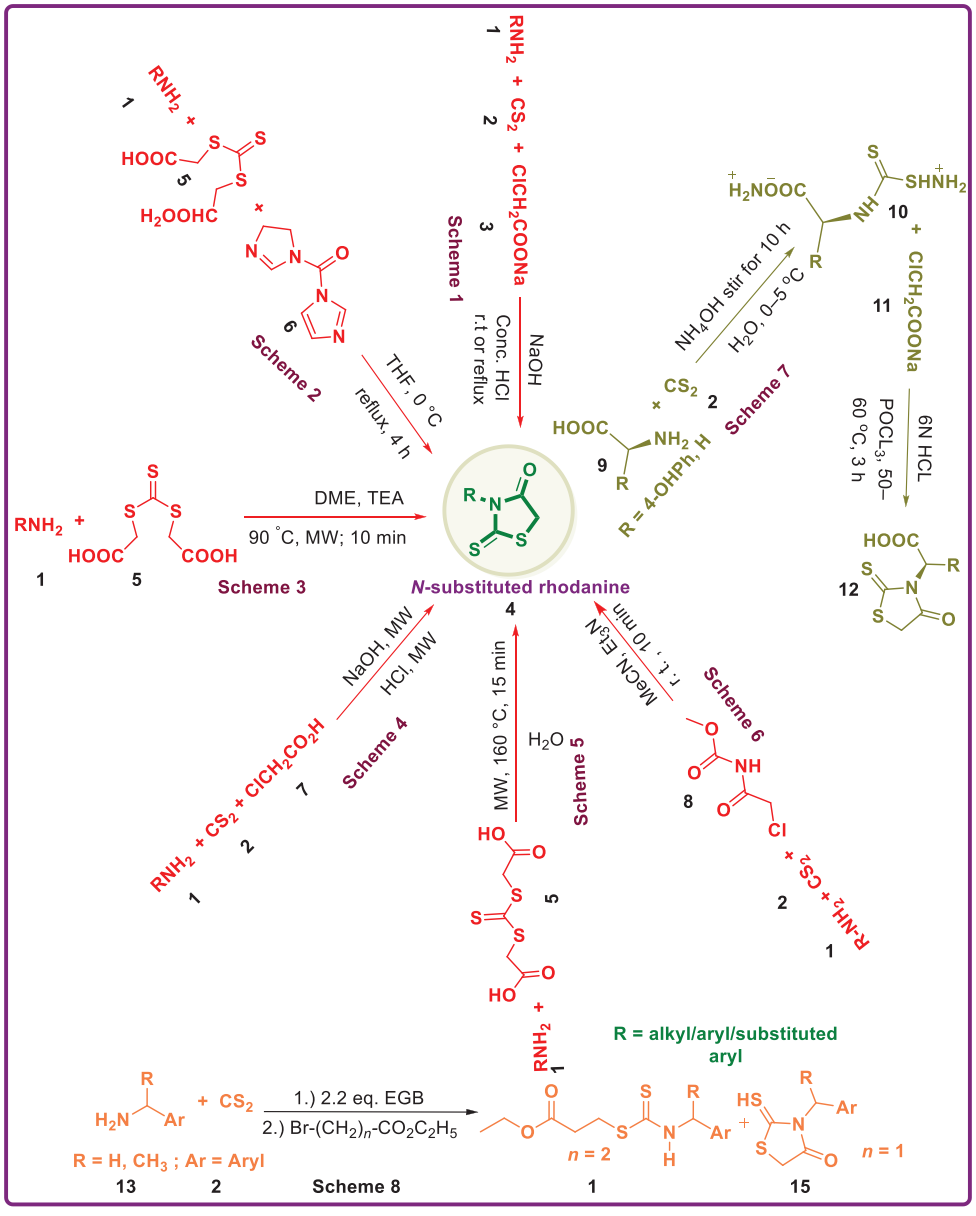

Figure 2: Various synthetic routes for 2-Thioxo-4-thiazolidinone.

phase led to high products. The authors also demonstrated an alternative, microwave-assisted one-pot, and one-step protocol for the synthesis of *N*-arylrhodanines **(4)** using bis (carboxymethyl) trithiocarbonate **(5)** reagent in water for arylamine substrate **(1)**. The developed protocol allows the preparations of a numerous *N*-substituted rhodanines **(4).**[30] In scheme 6, Liang *et al*. constructed the multi-component reaction of primary amine **(1)**, carbon disulphide **(2)** and 4-methoxyphenyl (2-chloroacetyl) carbamate **(8)** to gain 5-unsubstituted rhodanines **(4)**. The proposed reaction mechanism for this process is depicted in [Figure 3].[31] In scheme 7, Kumar *et al*. demonstrated an effective and stereospecific procedure for the conversion of free amino group **(9)** to the equivalent (±)-2-thioxo-thiazolidine-4-ones. The synthetic strategy involves the conversion of amino acid to ammonium salt which, in turn, reacts with carbon disulfide **(2)** to form dithiocarbomates **(10)**. The intermediate dithiocarbamates on reaction with sodium

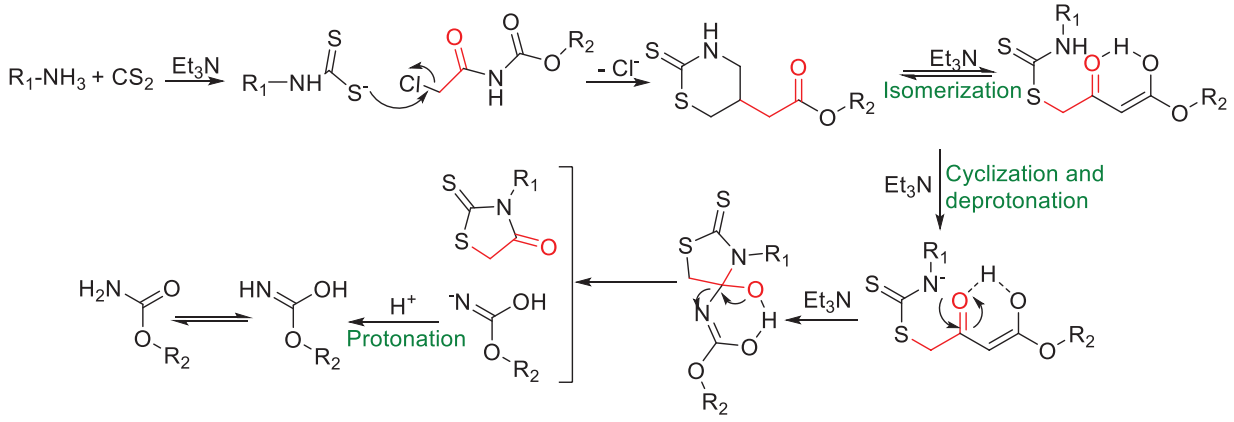

Figure 3: Mechanism for the synthesis of Rhodanine from carbamate.

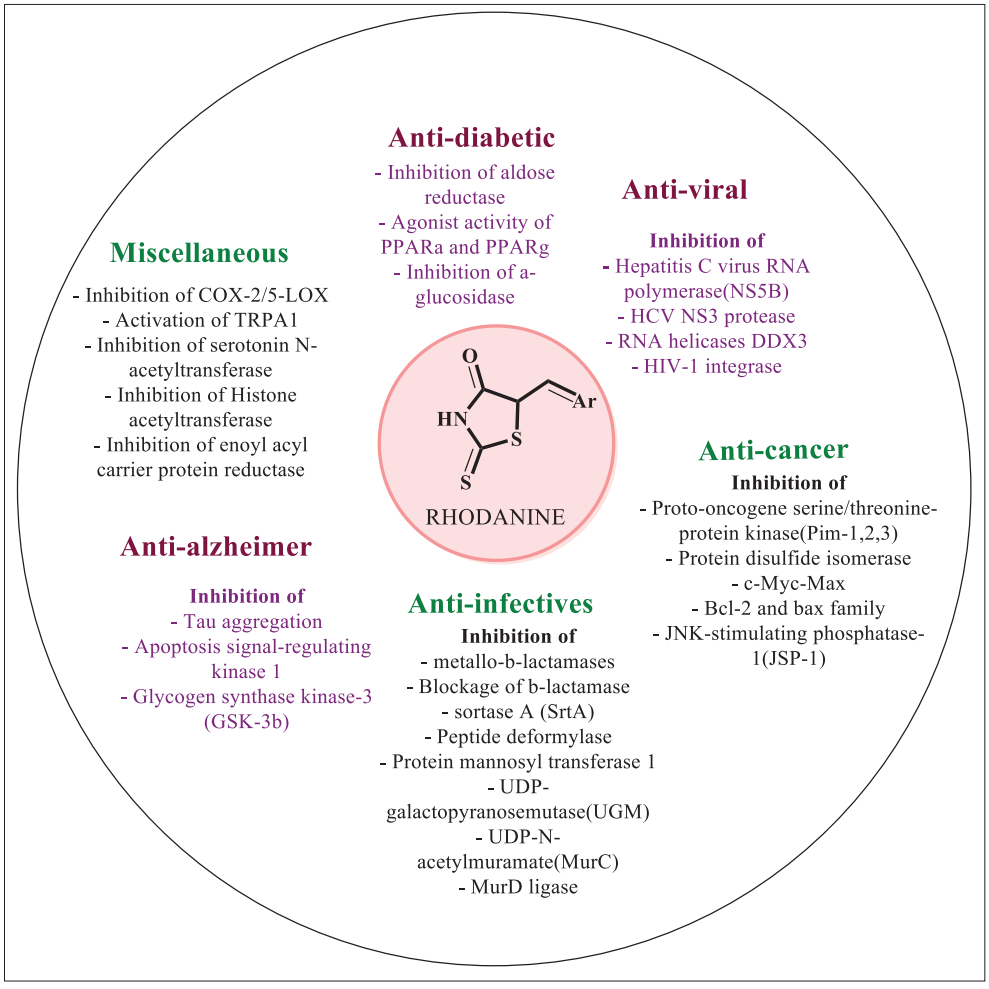

Figure 4: Various biological importance of rhodanine.

chloroacetate **(11)** followed by cyclisation under acidic environment in the company of phosphorous oxychloride yielded 2-thioxo-thiazolidine-4-ones **(12).**[4] Scheme 8 reports the electrogenerated base (EGB)-promoted preparation of *N*-benzylic 2-thioxo-thiazolidine-4-ones and carbamodithioate derivatives as of several benzylic amines **(13)**, carbon disulfide and alkyl acid ester. The protocol involves the generation of required amount of base (cyanomethyl and aminocrotonitrile species) by electrolysis of dry acetonitrile under galvanostatic conditions at −20°C with magnesium as terminal anode electrode and stainless steel as cathode electrode under an inactive nitrogen atmosphere. Then, amine and carbon disulfide were added followed by the addition of bromoalkyl acid ester to afford benzylic carbamodithioates **(14)** along with ring closure benzylic rhodanine **(15)** product in good yields.[32]

BIOLOGICAL IMPORTANCE

For more than 50 years, rhodanines have been the subject of extensive research, and they have been shown to be hits and lead against a broad variety of drug development targets in many therapeutic domains, as well as being useful as beginning points for medicinal chemistry.[33] Rhodanine basically inhibits various cancer targets such as, Proto-oncogene serine/threonine-protein kinase (Pim-1,2,3),[34] Protein disulfide isomerase, c-Myc-Max, Bcl-2 and bax family, and JNK-stimulating phosphatase-1. Similarly, it inhibits viral targets such as Hepatitis C virus RNA polymerase (NS5B),[35] HCV NS3 protease, and RNA helicases DDX3 HIV-1 integrase.[36] Moreover, for antimicrobial, antidiabetic, antialzhemier targets such as inhibition of metallo-b-lactamases, Blockage of Beta-lactamase, sortase A (SrtA).[37] Peptide deformylase, Protein mannosyl transferase 1,[38] UDP-galactopyranosemutase (UGM), and UDP-N-acetylmuramate (MurC) MurD ligase. Furthermore, inhibition of Tau aggregation, apoptosis signal-regulating kinase 1, glycogen synthase kinase-3b, inhibition of COX-2/5-LOX, activation of TRPA1 (1), inhibition of serotonin N-acetyltransferase,[39] inhibition of histone acetyltransferase, and inhibition of enoyl acyl carrier protein reductase[40] [Figure 4].

CONCLUSION

We offered a novel approach to the synthesis of rhodanine and its derivatives. The synthesis process is simple, effective, atom-efficient, and practical in appropriate to excellent yields. An adaptable nucleus, thiazolidione, and its derivatives are particularly fascinating substances that have played a significant role in medicine and pharmacy. Ongoing study is being done on this subject wherein, the researchers' ability to create novel rhodanine derivatives with the necessary therapeutic efficacy for various disease management and eradication will be greatly aided by the detailed biological activity used by the rhodanine motif and its chemistry discussed in this study.

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