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Recent Progress in the Synthesis and Reaction of Rhodanine: A Mini-Review

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Abstract:
Rhodanine and its derivatives are very important aspect in medicinal point of view. That creates huge interest among researcher to do various research regarding rhodanine. In the present study we have studied various synthesis techniques used in the literature to synthesize rhodanine and its derivatives including various reactions. These materials have gained much interest of researchers due to its variety of applications in biomedical and pharmaceutical fields. The Rhodanine has been synthesized by various techniques having their own advantages and disadvantages. Since, the Knoevenagel condensation gives good yield and have many advantages over other techniques. This condensation helps to obtain various derivatives of Rhodanine.
Keywords: Rhodanine; Derivatives; Reaction; Synthesis; Biomedical.

Introduction:

In 1997, a study based on a database search showed that the prevalence of rhodanine-containing compounds of pharmaceutical interest is very small, despite the fact that the compounds exhibit a wide variety of bioactivities [1]. Rhodanine-3-acetic acid (RAA) was prepared by Körner [2] in 1908, and condensation products of the acid with various aldehydes were reported in the same year [3].

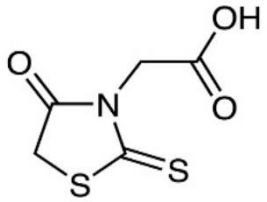


Fig. 1: Rhodanine-3-acetic acid

Since that time, many (5-arylalkylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl) alkanoic acids have been prepared and studied as potential antimycobacterial [4,5], antifungal [6-15], pesticidal [16-18], antihypertensive [19], and antineoplastic [20,21] agents. This is the reason why investigation/molecular modification and pharmacological evaluation of these molecules have attracted special attention of synthetic chemists and pharmacologists, respectively.

In recent years, a number of synthetic/pharmacological protocols based on these molecules have been emerged extensively and in witness available in the literature. These multifaceted molecules exhibit varied type of biological activities. Some recent developments in synthesis and pharmacology of these molecules are discussed in this section

Among others, derivatives of five-membered heterocyclic systems based on the core of 1,3-thiazolidine or imidazolidine

have been studied due to their broad biological activity.[22,23] Of particular interest are their derivatives containing exocyclic sulfur and oxygen atoms, such as rhodanine (2-sulfanylidene-1,3-thiazolidin-4-one)[24] or 2- thiohydantoin (2-sulfanylidene-1,3-diazolidin-4-one).[25] The presence of these double-bonded atoms with other functional groups results in particularly high density of binding sites for polar interactions and hydrogen bonds, which are responsible for their interesting biological properties.[26] A spectrum of their biological activity includes antifungal,[27,28] anticancer,[29-31] anti-diabetic,[32,33] anti-inflammatory,[34] antiviral[35,36], anticonvul-sant [37-39] and enzyme-inhibiting properties.[40,41]

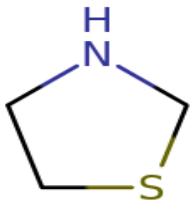


Fig.2: 1,3-thiazolidine

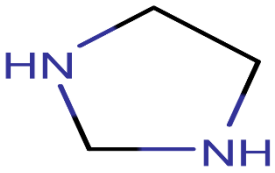
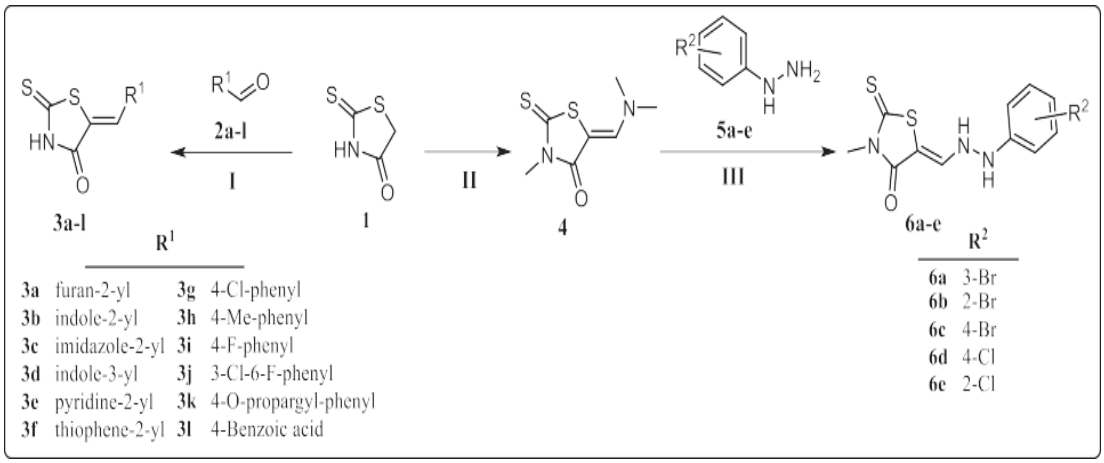


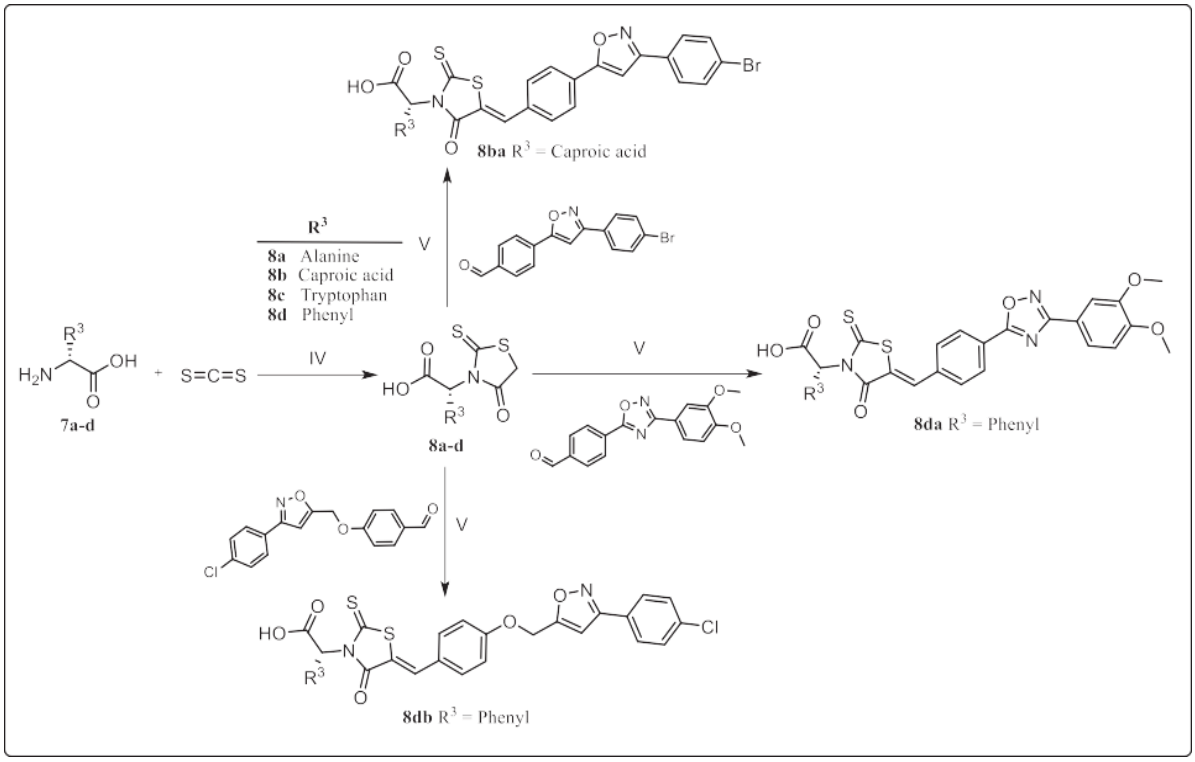
Fig.3: Imidazoline

Various methods of Synthesis of Rhodanine and its derivatives:

Rhodanine derivatives are synthesized using the synthetic routes detailed in Schemes 1 and 2. The first series of compounds were synthesized by reacting rhodanine with various aromatic and hetero-aromatic aldehydes through Knoevenagel condensation to yield different arylidene derivatives 3a–l as shown in Scheme 1.



SCHEME 1: Synthesis of rhodanine derivatives 3a–l and 6a–e: (I) Ethanol, piperidine (2 equiv.), acetic acid (2 equiv.), reflux, 12 h, 85%–97% yield; (II) DMF-DMA, THF, reflux, 4–5 h, 97% yield; (III) ethanol, reflux, 12 h, 60%–75% yield. THF, tetrahydrofuran.



SCHEME 2: Synthesis of rhodanine derivatives 8a–d and 8ba, 8da, 8db: (IV) Aq. NaOH, rt, 24 h, sodium chloroacetate, pH adjusted to 1, reflux, 12 h, 90%–95% yield; (V) ethanol, piperidine (2 equiv.), acetic acid (2 equiv.), reflux, 12 h, 75%–87% yield.

The second series of rhodanine phenyl-hydrazinyl derivatives 6a–e was prepared by reacting the key intermediate *N*, *N*-dimethyl-amino methylene derivative with various phenyl hydrazines. The key intermediate *N*, *N*-dimethyl-amino methylene derivative was obtained by treating rhodanine with dimethylformamide (DMF)-dimetylacetamide (DMA). The third series *N*-carboxylated rhodanine derivatives 8a–d were synthesized from different amino acids. Compounds 8a–d was subjected to Knoevenagel condensation with various isoxazole/1,2,4- oxadiazole containing aldehydes as shown in Scheme 2 to get the final set of compounds (8ba, 8da, and 8db).

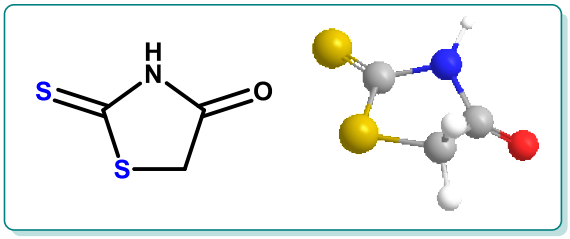
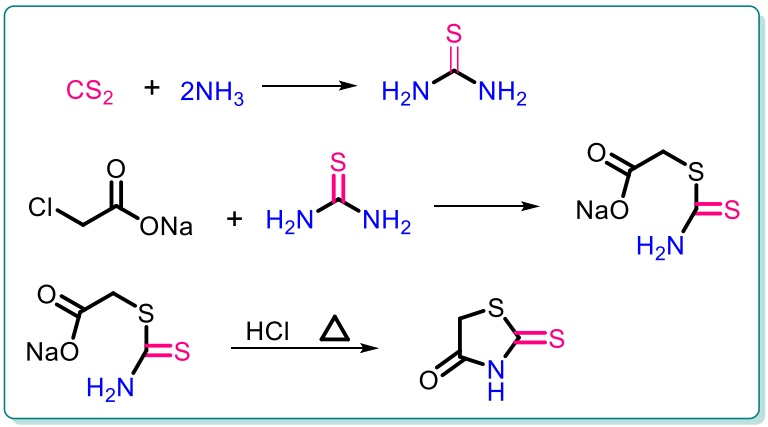


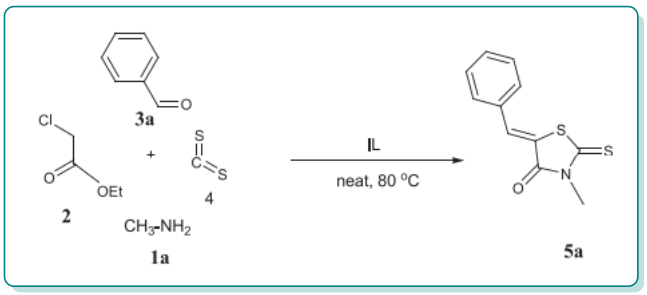
Fig.4: Rhodanine

Rhodanine is a 5-membered heterocyclic organic compound possessing thiazolidine core. It was discovered in 1877 by Marceli Nencki who named it *"Rhodaninsaure"* in reference to its synthesis from ammonium rhodanide (known as ammonium thiocyanate to modern Chemists) and chloroacetic acid in water [42]. Rhodanines can also be prepared by the reaction of carbon disulfide, ammonia, and chloroacetic acid, which proceeds *via* an intermediate dithiocarbamate [43]. Which is shown in scheme 3.



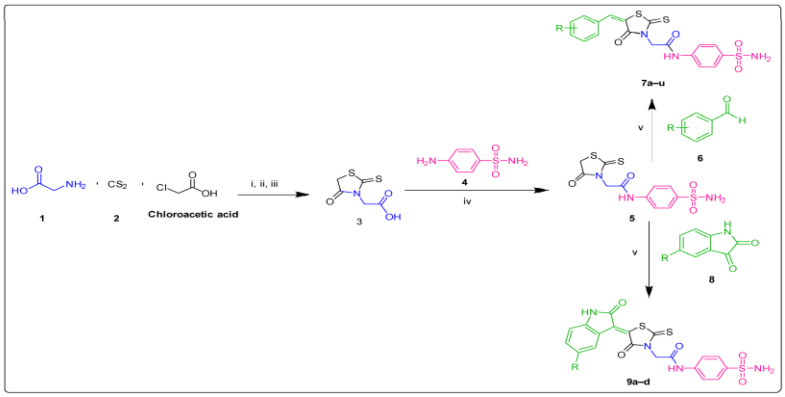
Scheme 3: Synthesis of Rhodanine

S. M. S. Chauhan et.al. [44] displayed A direct method for the synthesis of N-substituted-5-arylidene-rhodanines has been reported in high yield via [bmim] OAc-catalyzed one-pot four-component domino Knoevenagel condensation of primary amine, carbon disulfide, ethyl chloroacetate, and aromatic aldehyde under neat condition. The catalytic role of [bmim] OAc is due to the acidic nature of C-2 hydrogen of bmim cation and the basic nature of acetate anion in the noncovalent interactions. The synthetic methodology is simple and offers a wide scope for the synthesis of N-substituted-5-arylidene-rhodanines. Which is shown in scheme 4.



Scheme 4: Ionic liquid mediated synthesis of Rhodanine

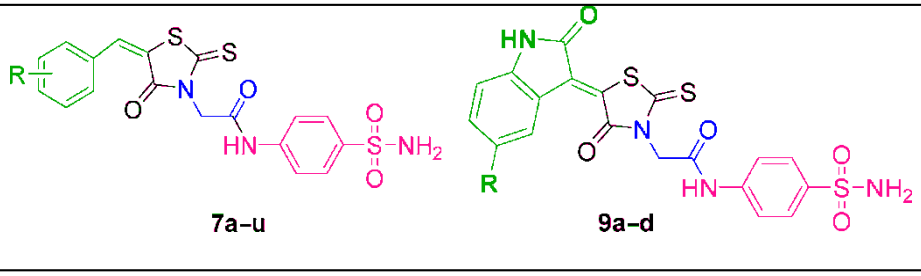
Reactions of Rhodanine:



Scheme 5: Reagent and conditions: (i) NaOH, EtOH, rt, 4–5 h; (ii) rt, 7–8 h; (iii) HCl, pH 1.0, rt, 2 h, 82%; (iv) EDCI, HOBt, DMF, rt; 7–8 h, 85%; (v) sodium acetate, acetic acid, EtOH, reflux, 4–5 h, 50–79%. For R substituents, please refer to Table 1.

The target molecules were designed using the tail approach as depicted in Scheme 5. The reactions involved the commercially available starting materials glycine (**1**) and chloroacetic acid (**2**). The intermediate 3, (2-(4-oxo-2-thioxothiazolidin-3-yl) acetic acid) was obtained via the one-pot, three component condensation of glycine, chloroacetic acid, and carbon disulfide by using a method identified in past literature [45]. The rhodamine- containing intermediate 3 (2-(4-oxo-2-thioxothiazolidin-3-yl)acetic acid) was then subjected to acid-amine coupling with sulfanilamide (**4**), according to a previously reported procedure [46], to produce intermediate **5**, which was further functionalized through Knoeve- nagel condensation [47] with the appropriated carbonyl compound (benzaldehydes (**6**) and isatins (**8**)) to produce the target compounds **7a**–**u** and **9a**–**d**, respectively, in good to excellent yield.

Table 1: Inhibition of hCA isoforms I, II, IX, and XII with *K*I (nM) data for compounds **7a**–**u** and **9a**–**d** and acetazolamide (AAZ) as the standard inhibitor by means of the stopped-flow carbon dioxide assays.



***K*I (nM) ***

Compound	R	hCA I	hCA II	hCA IX	hCA XII
7a	H	184.6	69.2	8.7	32.5
7b	4-Cl	349.0	51.6	35.7	9.1
7c	4-OCF3	2410	954.2	9.7	158.3
7d	2-F	223.7	139.6	14.3	65.4
7e	4-CF3	853.6	77.5	8.0	9.6
7f	4-allyloxy	688.5	320.1	5.6	67.6
7g	3,4,5-triOMe	173.0	31.6	4.2	46.0
7h	3-EtO-4-OH	22.4	7.3	5.6	63.7
7i	4-CN	124.9	56.6	7.3	9.0
7j	3-OMe	227.6	46.1	15.8	73.6
7k	4-OMe	78.6	12.7	9.3	58.2
7l	4-*i*Pr	430.3	68.6	51.5	41.6
7m	3-OPh	470.8	55.5	28.2	47.0

Table 1. *Cont.*

***K*I (nM) ***

Compound	R	hCA I	hCA II	hCA IX	hCA XII
7n	3,4-diOMe	84.0	15.4	8.1	38.5
7o	2,4,5-triOMe	338.9	176.3	34.7	9.5
7p	2,4-diOMe	385.6	8.0	17.7	9.8
7q	2,4,6-triOMe	298.5	53.1	23.6	26.3
7r	3,4-diF	212.7	19.6	13.5	9.6
7s	3-NO2	77.9	14.6	8.4	9.0
7t	4-OH-3,5-diOMe	77.5	9.6	7.2	30.2
7u	4-NO2	70.6	8.9	7.7	9.5
9a	H	41.6	4.3	4.7	56.2
9b	5-Me	92.2	5.5	8.9	40.6
9c	5-CF3	319.2	67.8	13.3	37.8
9d	5-Cl	35.8	5.2	6.0	26.3
AAZ		250.0	12.1	25.8	5.7

* The mean from three different assays using a stopped flow technique. Errors were in the range of ± 5–10% of the reported values.

Conclusion:

The present research work explained the comprehensive studies of various methodology of rhodanine and its derivatives including its synthesis and various reactions as well as various application including biological activities of rhodanine and its derivatives. This research work concluded that the Knoevenagel condensation is the best synthesis method to obtained Rhodanine and its derivatives with good yield. Also, rhodanine and its derivatives shows various biological activities like- antibacterial, antifungal, antiviral, anti-tubercular, anti-cancer etc.

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