

## Strategies for the Synthesis of Thiazolidinone Heterocycles

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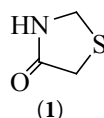
### Abstract

Thiazolidinones is the special class of heterocyclic compounds with a broad spectrum of biological activities such as anti-inflammatory, antiproliferative, antihistaminic, anti-HIV, hypnotic, anaesthetic, antifungal, anthelmintic and antiviral agents as well as CNS stimulants. Therefore researchers have synthesized these condensed heterocycles through different complex pathways as target structures for biological studies. This review focuses on the various strategies followed for the convenient synthesis of thiazolidinone based heterocyclic derivatives. The steps included condensation followed by cyclization of Schiff's bases, either in a step-wise manner or in one pot under different conditions. Mercaptoacetic acid, thiolactic acid, chloroacetyl chloride, potassium thiocyanate, ethylchloro acetate and ammonium thiocyanate are the most common reagents used for the synthesis thiazolidinone appended on different heterocyclic skeletons.

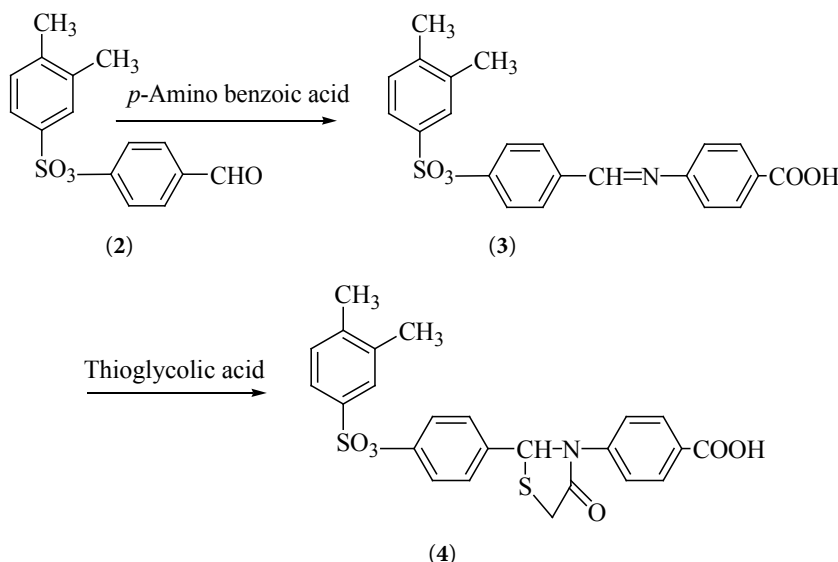
**Keywords:** Schiff's bases; Mercaptoacetic acid; Condensation; Heterocycles

### Thiazolidinones

Thiazolidinones and their derivatives display a large variety of activities such as antibiotic, diuretic, organoleptic, tuberculostatic, antileukaemic and antiparasitical [1,2]. As far as literature is concerned, little is known about thiazolidinones and their bioactivities. Thiazolidinones (1) are classified as doubly unsaturated five membered heterocyclic compounds contain one nitrogen, one sulphur and three carbon atoms including a carbonyl group.



Moawad et al. reported that reaction of Schiff base (3) with mercaptoacetic acid in dry benzene afforded thiazolidinone (4). Schiff base (3) was obtained by the condensation of, 3,4-xylene sulphonate ester of *p*-hydroxy benzaldehyde (2) with *p*-aminobenzoic acid [3].



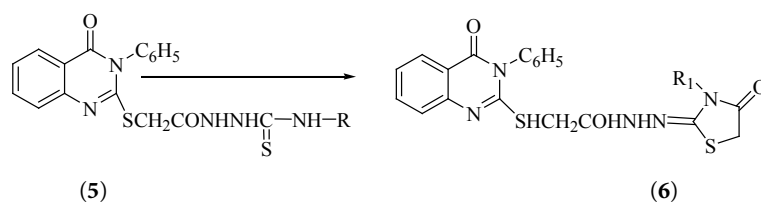
Gursoy et al. prepared new compounds (5) and (6) incorporating the quinazoline moiety [4].

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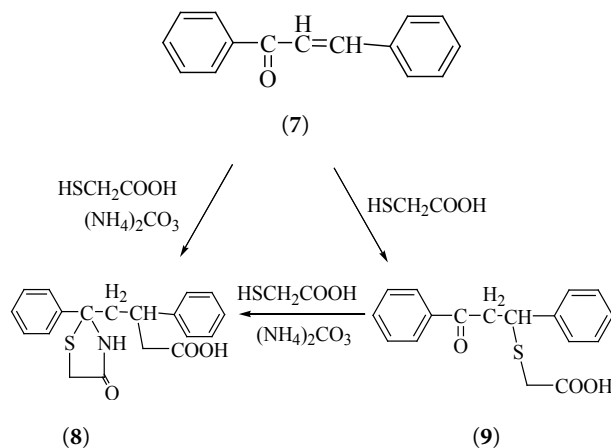
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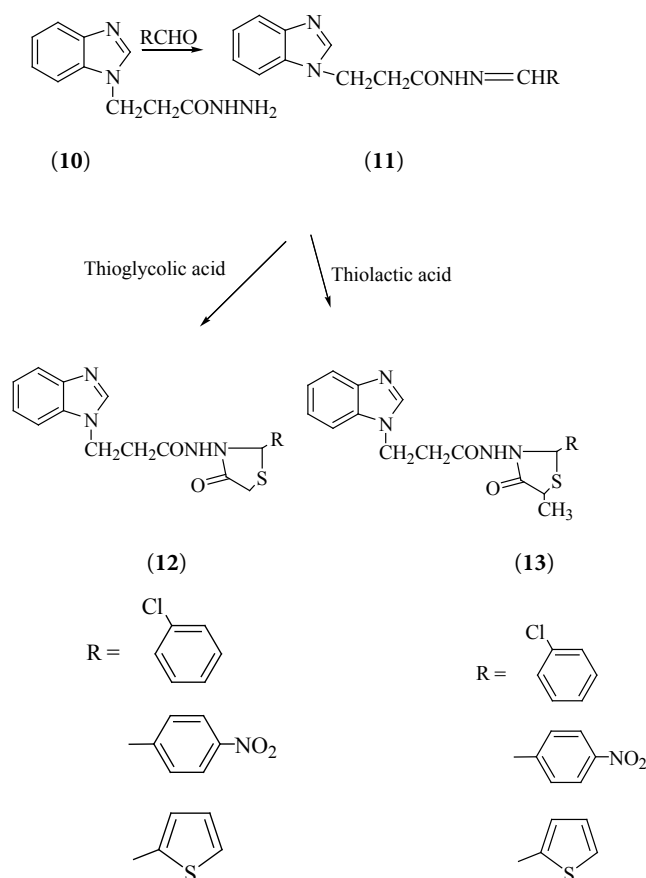
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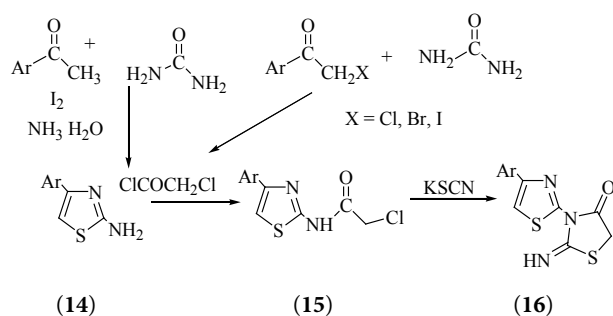
Ansari et al. synthesized 4-thiazolidinones (8, 9) starting from chalcone (7), by two different routes as shown in the following scheme [5].



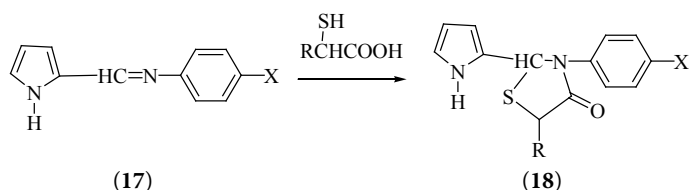
El-masry et al. reported that condensation of compound (10) with aromatic and heterocyclic aldehydes in absolute ethanol afforded the corresponding Schiff's bases (11). The cyclocondensation of some substituted Schiff's bases with thioglycolic acid and thiolactic acid afforded the corresponding thiazolidinone (12) and (13) [6].



Anthonsen et al. synthesized 2-imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones (16) via the key intermediates, 2-amino-4-arylthiazoles (14) which were reacted with chloroacetyl chloride to produce the corresponding 2-chloro-acetamido-4-arylthiazoles (15). The latter was treated with potassium thiocyanate in refluxing acetone to afford the product (16) [7].

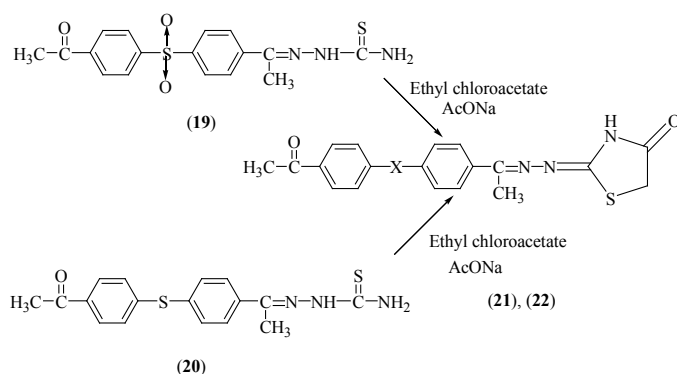


Ocal et al. synthesized substituted 4-thiazolidinones (18) by the reaction of mercaptoacids aldimines (19) which were obtained by the condensation of pyrrole-2-carbaldehyde with different aromatic amines [8].

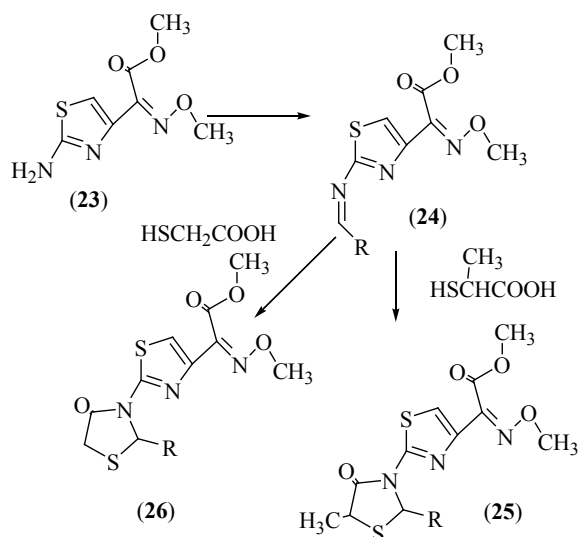


R= H,  $\text{CH}_3$

Abbadly et al. obtained 4-acetylthiosemicarbazone-4-acetyl diphenyl sulphone (19) and 4-acetylthiosemicarbazone-4-acetyldiphenyl sulphide (20) which on further reaction with ethylchloroacetate in the presence of fused AcONa gave 4-(4'-thiazolidinone-2''-acetylazino)-4'-acetyldiphenyl sulphone (21) and 4-(4'-thiazolidinone-2''-acetylazino)-4'-acetyldiphenyl sulphide (22), respectively [9].

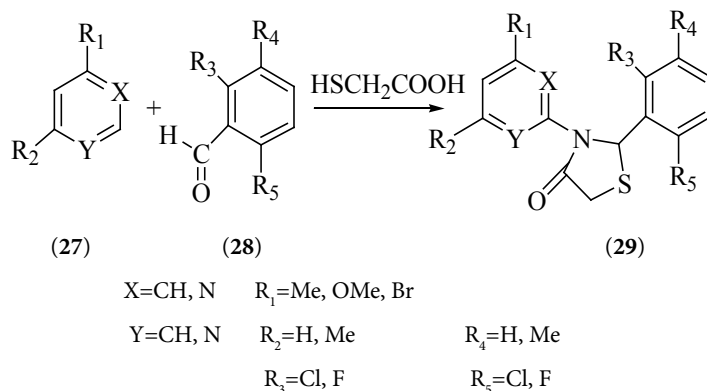


Parekh et al. prepared that substituted Schiff's bases (24) by the treatment of 2-amino-4-( $\alpha$ -methoxyiminocarbomethoxymethyl)-thiazole (23) with different aromatic mercaptopropionic acid in dry benzene furnished desired thiazolidinones of type (25) and (26) respectively. The products were evaluated for their *in vitro* growth inhibiting activity against several microbes. Some of them showed significant anti-tubercular and antifungal activity [10].

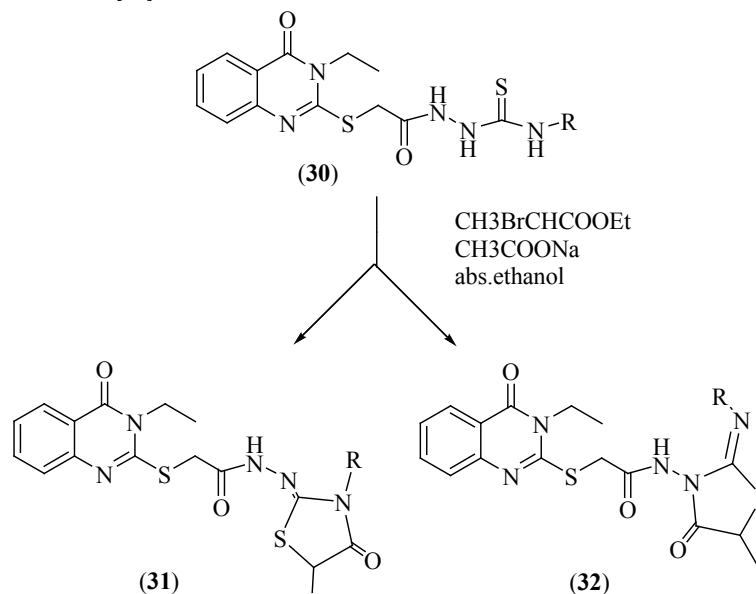


R=Ar

Monforte et al. reported the synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones (29) by reacting an aromatic aldehyde (28) with an equimolar amount of (hetero) aromatic amine (27) in the presence of an excess of mercaptoacetic acid. The microwave-irradiation dramatically shortened the reaction times, affording the desired products in high yields [11].

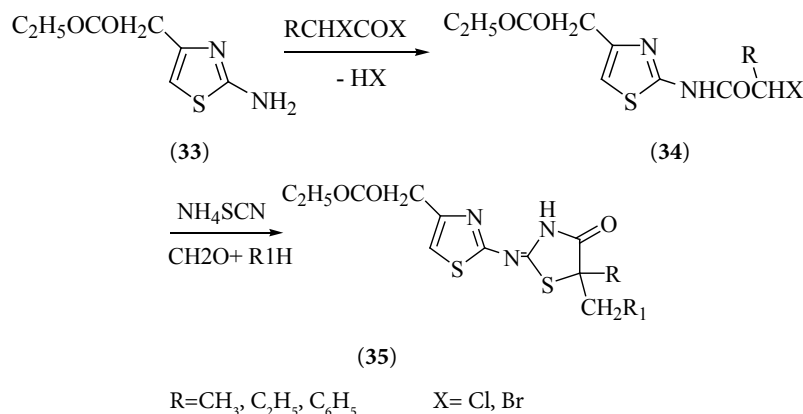


Terzioglu et al. synthesized the target compound, 2-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylhydrazono)-3-alkyl/aryl-5-methyl-4-thiazolidinones (31) and 2-arylimino-3-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylamino)-5-methyl-4-thiazolidinones (32) by the cyclization of 3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetyl-4-alkyl/arylthiosemicarbazides (30) with ethyl 2-bromopropionate in presence of anhydrous sodium acetate in absolute ethanol [12].

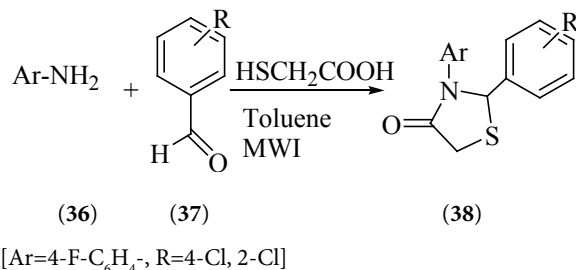


R = CH<sub>3</sub>, C<sub>6</sub>H<sub>11</sub>

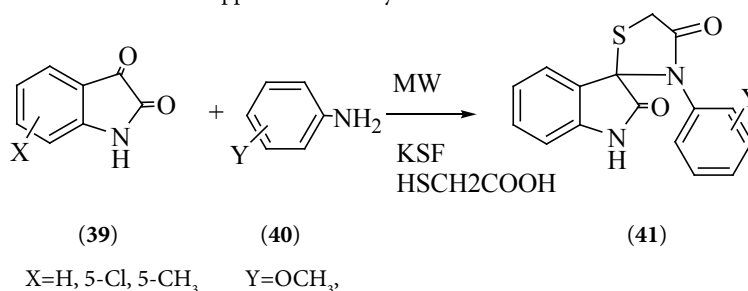
Altintas et al. synthesized by refluxing of 4-carboxymethyl-2-[(α-chloropropionyl/ α-bromobutyryl/ α-chloro-(phenyl)acetyl)amino]thiazoles (33) with ammonium thiocyanate to obtain 4-thiazolidinone (34). 5-(N,N-disubstitutedaminomethyl-2-[(4-carboxymethylthiazol-2-yl)imino] 4-thiazolidinones (34) was evaluated as antibacterial and antifungal activities [13].



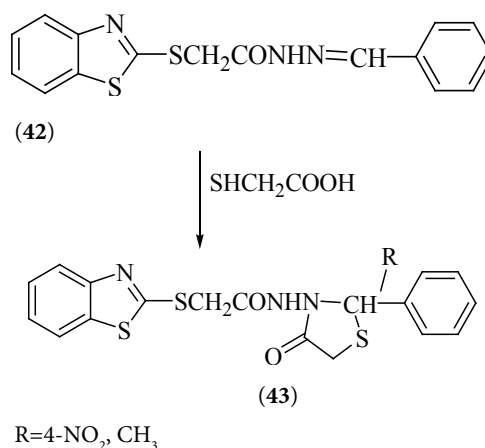
Sriram et al. reported that the synthesis of the 2,3-diaryl-1, 3-thiazolidin-4-ones (38) was accomplished by reacting substituted benzaldehyde (37) with equimolar amount of an appropriate substituted aromatic amine (36) in the presence of an excess of mercaptoacetic acid in toluene under microwave irradiation. Unlike the conventional methods (reaction time 48 h and yields of 30-70%), microwave-assisted reactions were very facile (6-8 min.) and provided very good yields (64-82%) [14].



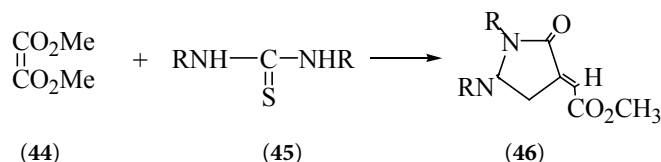
Arya et al. prepared *spiro*[indole-thiazolidines] (41) by the multicomponent condensation between indole-2,3-dione (39), amines (40) and mercaptoacetic acid using montmorillonite KSF as solid support in 85-90% yield in 4-5 min under MW reaction conditions [15].



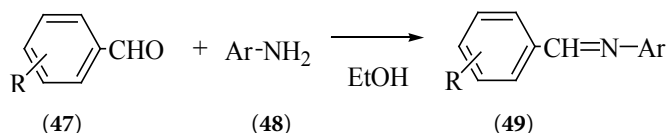
Desai et al. synthesized 4-thiazolidinones (43) in a good yields from the heterocyclization reaction of 2-(benzothiazol-2-ylthio)-N'-benzylideneacetohydrazide (42) with mercaptoacetic acid in DMF in the presence of catalytic amount of anhydrous ZnCl<sub>2</sub> under microwave irradiation and compared with conventional methods [16].

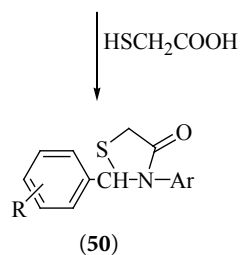


Nagarajan et al. synthesized *E*-thiazolidinone (46) by the cyclization of acetylene dicarboxylic ester (44) with thiocarbamoyl derivatives (45) [17].



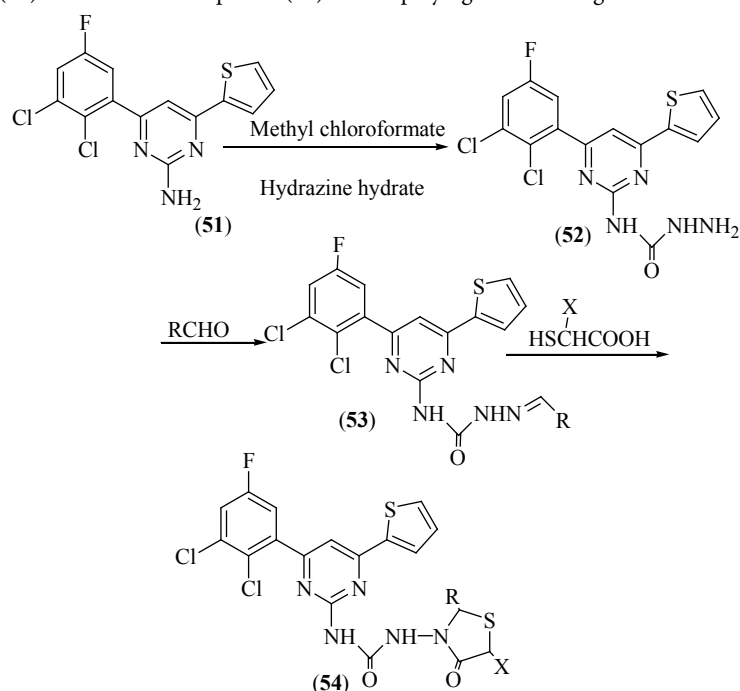
Sahu et al. reported that condensation of substituted benzaldehydes (47) with primary aryl amines (48) gave a series of Schiff bases (49) which, on reaction with mercaptoacetic acid, resulted in the formation of the corresponding 4-thiazolidinones (50) [18].





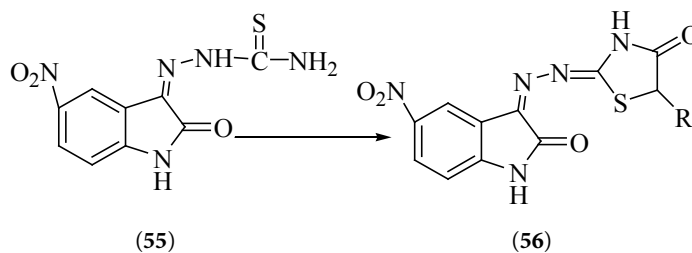
Ar=4-NO<sub>2</sub>, Phenyl, 4-Cl and Naphthyl R=2-OH, 4-N(CH<sub>3</sub>)<sub>2</sub>, 4-NO<sub>2</sub>, 4-Cl and 4-OCH<sub>3</sub>

Desai and Shah synthesized of 2-(substituted phenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido] 5H/ methyl/ carboxymethyl-4-thiazolidinones (54). It starts with compound (51) and employing the following reaction scheme [19].

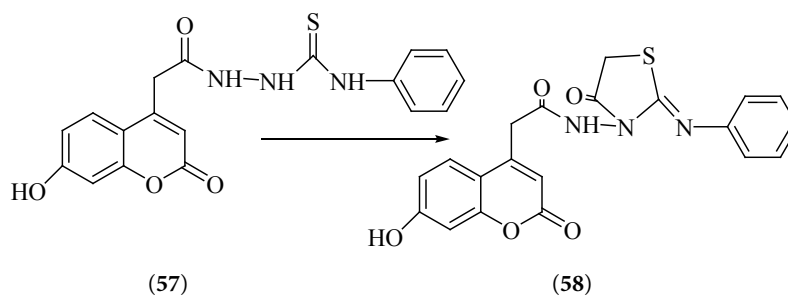


R=aryl; X=H, CH<sub>3</sub>, CH<sub>2</sub>COOH

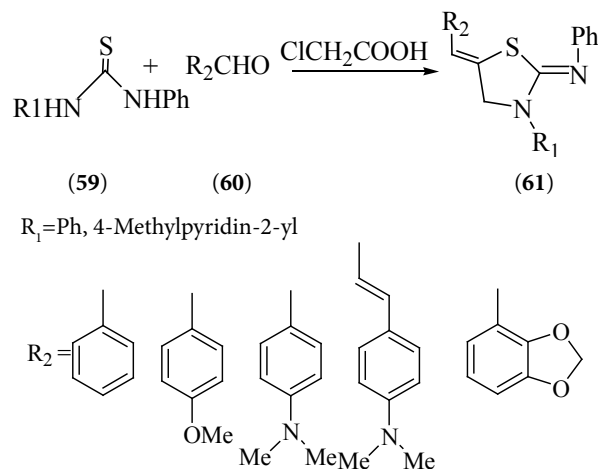
Terioglul et al. synthesized series of 5-nitro-3-[(5-nonsubstituted/methyl-4-thiazolidinone-2-ylidene) hydrazono]-1H-2-indolinones (56) by cyclization of 5-nitro-1H-indole-2,3-dione-3-thiosemicarbazone (55) with ethyl bromoacetate or ethyl 2-bromopropionate [20].



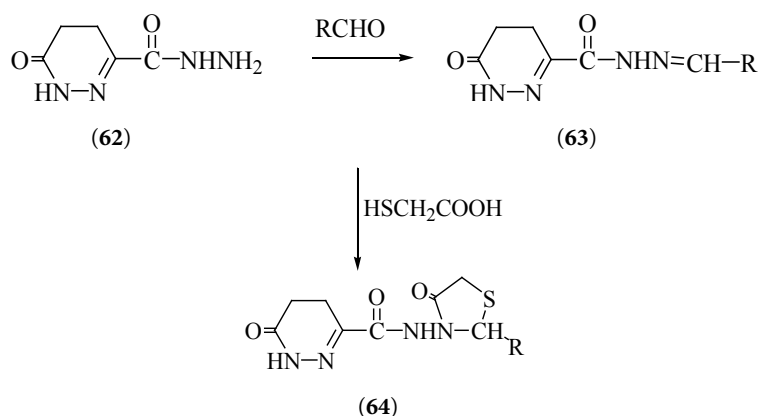
Cacic et al. reported the cyclization of thiosemicarbazide (57) with chloroacetylchloride in chloroform which afforded thiazolidinone derivative (58) [21].



Mir et al. reported a rapid and easy solvent free one-pot synthesis of 5-arylidne-2-imino-4-thiazolidinones (61) by condensation of the thioureas (59) with chloroacetic acid and an aldehyde (60) under microwave-irradiation [22].

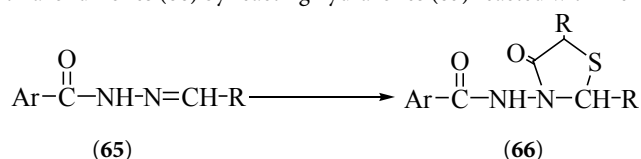


Cao et al. reported the reaction of 1,4,5,6-tetrahydro-6-pyridazinone-3-carboxylic acid hydrazides (62) with aromatic aldehydes which afforded 1,4,5,6-tetrahydro-6-pyridazinone-3-carbonyl aromatic aldehyde hydrazones (63). Hydrazones (63) cyclized with mercaptoacetic acid in DMF in the presence of anhydrous  $\text{ZnCl}_2$  to afford 1,3-thiazolidinone derivative (64) [23].

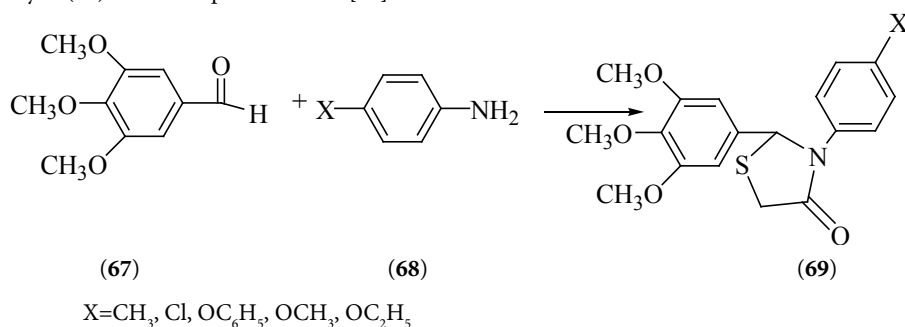


$\text{R} = \text{C}_6\text{H}_5, p\text{-MeOC}_6\text{H}_5, p\text{-NMe}_2\text{C}_6\text{H}_5, o\text{-NO}_2\text{C}_6\text{H}_4, m\text{-NO}_2\text{C}_6\text{H}_4, m\text{-Ome-}p\text{-OHC}_6\text{H}_5$

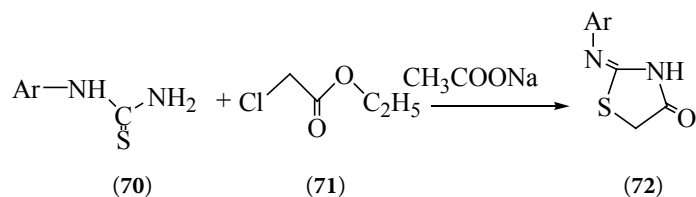
Rollas and Kucukguzel synthesized 4-thiazolidinones (66) by reacting hydrazones (65) reacted with mercaptoacetic acid/thiolactic acid [24].



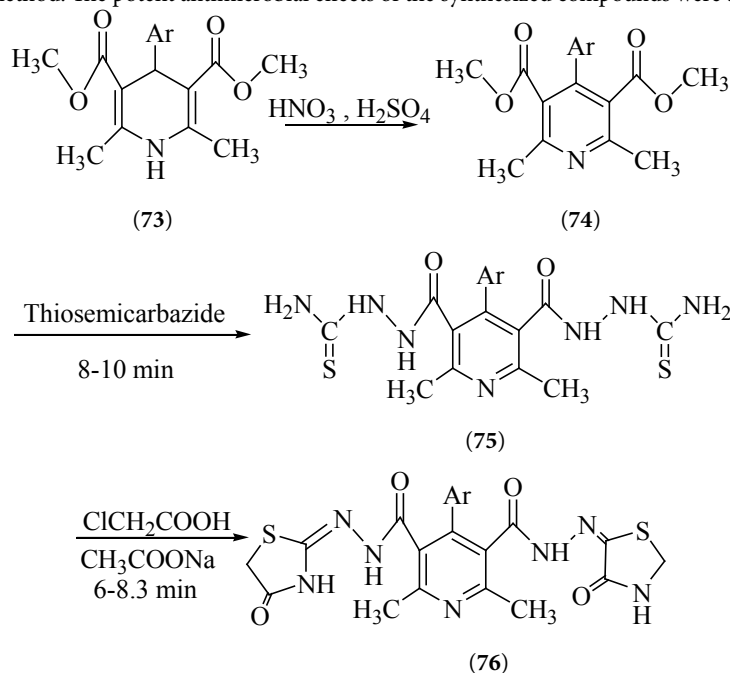
Turgut et al. prepared 4-thiazolidinones (69) by the Katti cabodiimide (DCC) mediated one-pot three component condensation reaction of an aromatic amine (68), an aldehyde (67) and mercaptoacetic acid [25].



Shiradkar reported that various aryl-thioureas (70) on treatment with ethyl chloroacetate (71) and fused sodium acetate in a ethanol gave 2-arylimino-4-thiazolidinones (72) [26].

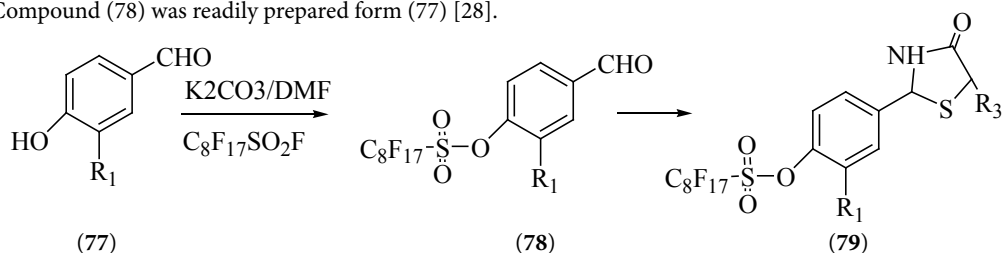


Ameta et al. reported a fast and facile procedure for the synthesis of pyridothiazolidinone (76) starting from dihydropyridine (73). Oxidation of (73) with nitrating mixture ( $\text{HNO}_3/\text{H}_2\text{SO}_4$ ) produced the anticipated 2,6-dimethylpyridine derivatives (74), which were subsequently condensed thiosemicarbazide in ethanol to produce the key intermediate 2,2-[4-(4-substitutedphenyl)-2,6dimethylpyridine-3,5diyl] dicarbonyldihydrazine carbothiomides (75). Compound (75) finally provided (76) on reacting with  $\text{ClCH}_2\text{COOH}$  and  $\text{CH}_3\text{COONa}$ . All the reaction were carried by conventional as well as microwave method. The potent antimicrobial effects of the synthesized compounds were also investigated [27].



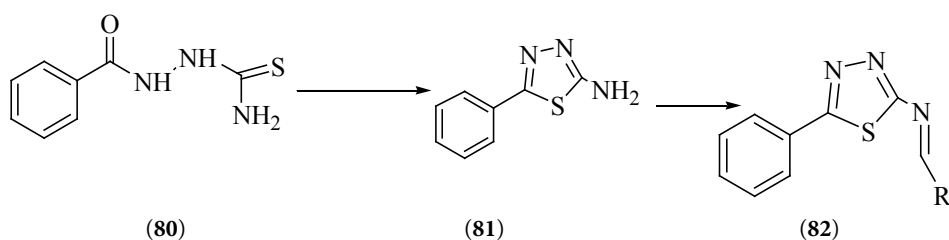
Ar=4-F-C<sub>6</sub>H<sub>4</sub>, 4-Cl-C<sub>6</sub>H<sub>4</sub>, 4-OCH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>, 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>, C<sub>6</sub>H<sub>5</sub>

Yan et al. reported the construction of 4-thiazolidinone ring (79) by a three component reaction of fluorosulfonyl benzaldehydes (78), an amine and mercaptoacetic acid. Compound (78) was readily prepared from (77) [28].

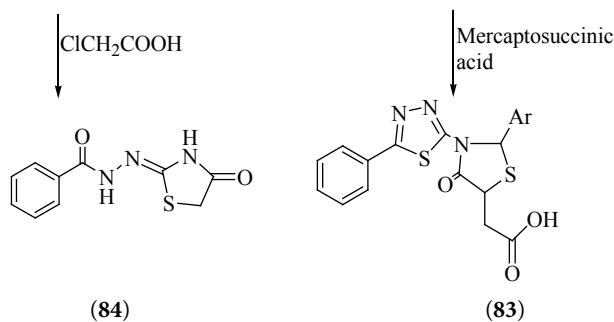


Talesara et al. also synthesized 2-amino-5-(4'-pyridyl)-1,3,4-thiaziazole (81) by cyclization of *iso* nicotinoyl thiosemicarbazide (80) with conc. sulphuric acid. When (81) was refluxed with various aldehydes. It gave the corresponding arylidene derivatives (82) which on further treatment with mercaptosuccinic acid furnished thiazolidinone derivative (83). Another thiazolidinone derivative 2-isonicotinoylhydrazido-1,3-thiazolidinone (84) was obtained by the successive treatment of isonicotinoylthiosemicarbazide (80) with chloroacetic acid in the presence of sodium acetate [29].

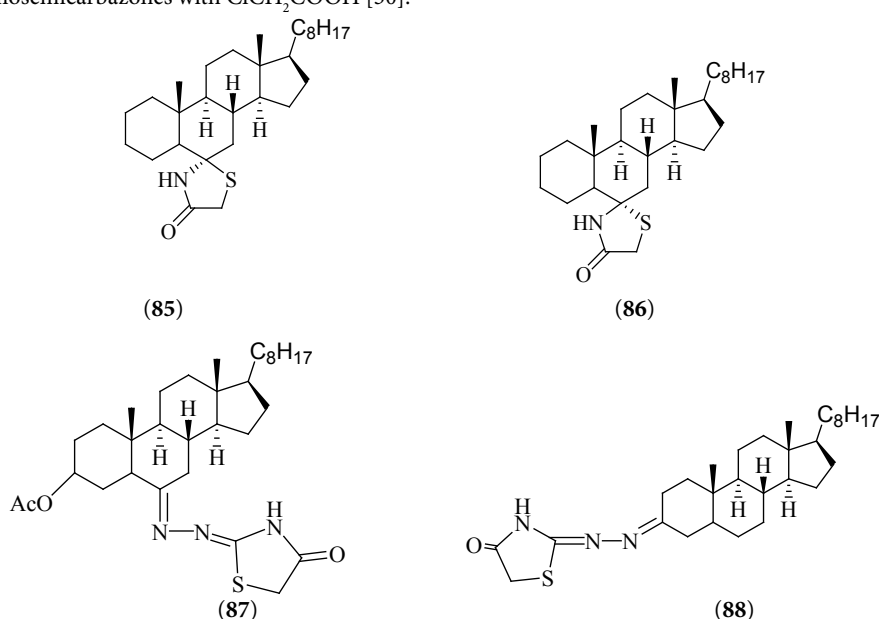
[Ar=4-OCH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>, 3,4,5-OCH<sub>3</sub>-C<sub>6</sub>H<sub>2</sub>, 3-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>, 4-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>, 4-(CH<sub>3</sub>)<sub>2</sub>NHC<sub>6</sub>H<sub>4</sub>, C<sub>6</sub>H<sub>5</sub>, C<sub>4</sub>H<sub>3</sub>O(2-furyl)].



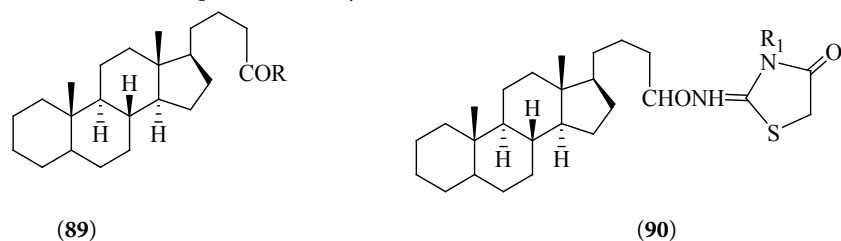




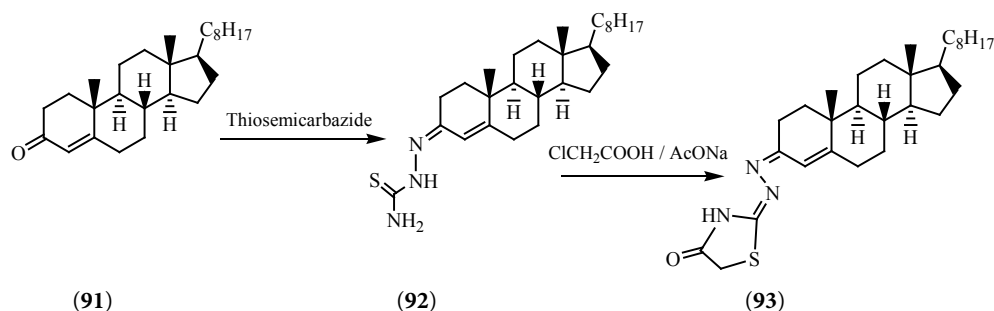
Literature has revealed that very few steroidal thiazolidinones have been prepared and studied so far. Shafullah and Ali reported the synthesis and mass spectral studies of the *spiro* thiazolidinones (85) and (86). Steroidal thiazolidinones of cholestane series (87) and (88) were also prepared by cyclizing the respective thiosemicarbazones with  $\text{ClCH}_2\text{COOH}$  [30].



Siddiqui et al. prepared C-24 thiazolidinone derivatives (90) [R=H, OH, R<sup>1</sup>=H] of bile acids from esters (89) [R<sup>2</sup>=OMe] in three steps involving hydrazinolysis with  $\text{NH}_2\text{NH}_2$  to give (89) [R<sup>2</sup>=NHNH<sub>2</sub>], reaction with potassium or ammonium thiocyanate to give (89) [R<sup>2</sup>=NHNHC(S)NH<sub>2</sub>] and finally cyclocondensation with chloroacetic acid in presence of anhydrous sodium acetate and AcOH [31].



Shamsuzzaman and Siddiqui reported the synthesis of 3-Diazo(4'-thiazolidinone) cholest-4-ene (93) from cholest-4-en-3-one thiosemicarbazone (92) and chloroacetic acid in presence of sodium acetate. The compound (92) was obtained by reacting cholest-4-en-3-one (91) with thiosemicarbazide in presence of conc. HCl [32].





## Conclusion

In this article we have mentioned the different routes for the synthesis of thiazolidinone derivatives. The steps included condensation followed by cyclization or multi component reaction (MCR), either in a step-wise manner or in one pot has been achieved successfully to obtain the aforementioned class of heterocycles under different conditions. Most of the preparative methods included mercaptoacetic acid, thiolactic acid, chloroacetyl chloride, potassium thiocyanate, ethylchloro acetate and ammonium thiocyanate are the most common reagents for the synthesis of thiazolidinone appended on different heterocyclic skeletons. Also many series of substituted thiazolidinone -fused five membered heterocycles possessing N-, S- and O- have been constructed in potential yields and with conventional methods. Hence these protocols provide convenient strategies to annelate different heterocyclic nuclei with widespread bioactive thiazolidinone thereby extending the categories of heterocyclic systems. These strategies may also provide valuable information for the further design and development of more active biological agents through various modifications and derivatizations.

## Acknowledgements

Authors (AMD and AM) thank Dr. Shamsuzzaman, Professor of Chemistry, AMU Aligarh, for useful discussions during the literature survey and University Grants Commission for providing research fellowship for successful completion of this work. Author (AM) is thankful to the Chairperson, Department of Pharmacy, UST, Sana'a, Yemen.

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