

Thiadiazolo[3,2-*a*]pyridines and thiadiazolo[3,2-*a*]pyrimidines: A review on synthetic approaches for obtaining and chemical modification of their derivatives

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ABSTRACT

Condensed bicyclic systems with 1,3,4-thiadiazole core being annulated to pyridine or pyrimidine ones occupy prominent place in medicinal chemistry because of their broad spectrum of pharmacological properties. The combination of these heterocyclic systems into a bicyclic scaffold commonly provides much more interest in the enhanced activity profile of its analogs than their parent monocyclic constituents. Thus, a number of pyridines or pyrimidines fused to thiadiazoles are incorporated into a wide variety of therapeutically important compounds possessing a broad spectrum of biological activities. In the present review we highlight recent advances in the fast-growing research area of thiadiazolo[3,2-*a*]pyridines and thiadiazolo[3,2-*a*]pyrimidines chemistry summarizing the existing literature information with respect of their synthetic approaches. Considering such a significant pharmacological potential, as well as wide synthetic possibilities, mentioned fused heterosystems have received considerable attention from scientific community as perspective scaffold for the rational design of drug-like candidates.

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1. Introduction

Heterocyclic compounds play a crucial role in producing organic and medicinal compounds and are frequently found in a wide variety of physiologically important biomolecules such as enzyme, vitamins, natural products and biological active compounds.¹⁻² The majority of biologically active pharmaceuticals and agrochemicals belong to heterocycles. In the field of medicinal chemistry research, heterocyclic compounds hold a distinguished position due to their pharmacological significance.³⁻¹⁰ An equally important place as one of the most important building blocks in heterocyclic chemistry is occupied by fused heterocycles, which have received attention in medicinal chemistry due to their proven therapeutic and synthetic relevance.¹¹⁻¹⁷

Pyridine and pyrimidine derivatives represent an important class of heterocyclic compounds possessing a wide spectrum of biological activities. In particular, pyridines have received much significant attention in last few decades on the field of medicinal chemistry because of their diversified biological properties like anticancer,¹⁸ antimicrobial and antiviral,¹⁹ antifungal,²⁰ anti-inflammatory,²¹ antioxidant,²² HDAC inhibitory²³ action etc. In return, pyrimidines and fused pyrimidines,²⁴⁻²⁶ being an integral part of DNA and RNA, play a vital role in a in the metabolism of all living cells. They are valuable leads for drug discovery because of their important role in cellular processes. Annulated pyridines and pyrimidines are of considerable relevance as lead structures in medicinal chemistry due to their wide range of pharmacological properties.²⁷⁻³¹ In addition, pyrimidine as well as pyridine motifs have received significant attention as valuable building blocks for obtaining of many fused scaffolds.^{32,33}

On the other hand, 1,3,4-thiadiazole is a versatile moiety that is well known for its biological activity.³⁴⁻³⁶ For instance, 1,3,4-thiadiazole derivatives exhibit good to excellent anticancer,³⁷ anti-inflammatory,³⁸ antitubercular,³⁹ antibacterial,⁴⁰ antiprotozoal,⁴¹ antifungal,⁴² antiviral,⁴³ antioxidant,⁴⁴ antidiabetic,⁴⁵ anticonvulsant⁴⁶ action etc. In addition, many certain

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approved drugs based on thiaziazole nuclei are available in medicine such as sulfamethiazole, acetazolamide, and methazolamide. Thus, combining a 1,3,4-thiaziazole ring with a pyrimidine or pyrimidine ones in the same molecule may be a great value in designing and identification of new potent drug candidates.

In the present review, we summarized the literature data about the main synthetic approaches for obtaining of heterocyclic compounds based on fused thiaziazolo[3,2-*a*]pyridine and thiaziazolo[3,2-*a*]pyrimidine systems. This work is a continuation of our numerous review researches, which provide a detailed analysis of synthetic methods of the obtaining and discourse of pharmacological significance for some oxa/thia-containing diazaheterocycles.⁴⁷⁻⁵⁰

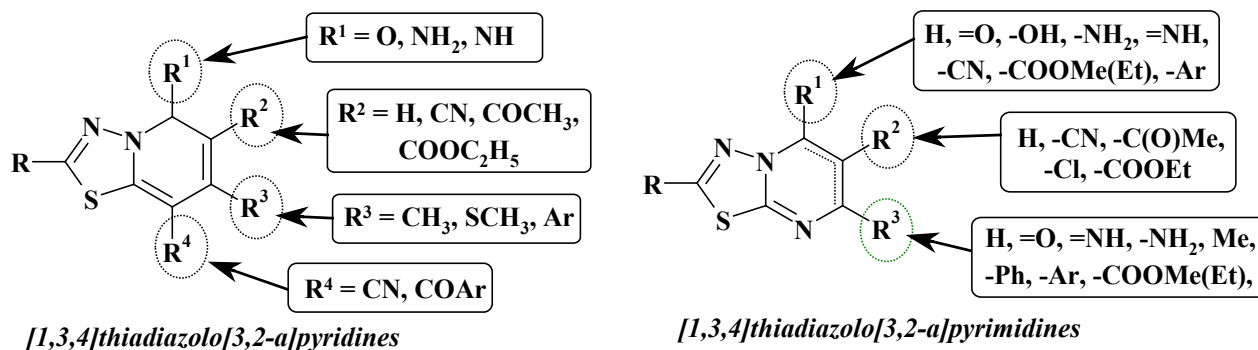
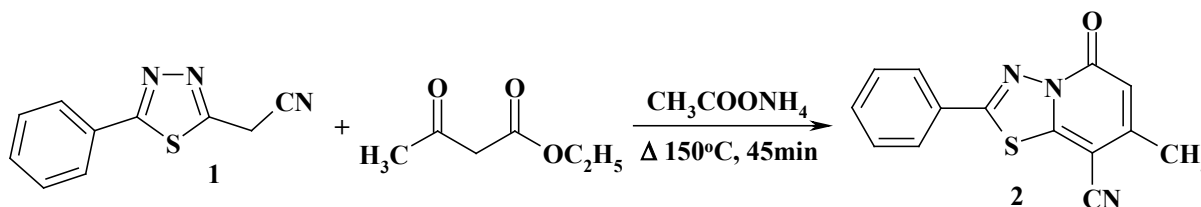


Fig. 1. Diversity of chemical structure of thiaziazolo[3,2-*a*]pyridines and thiaziazolo[3,2-*a*]pyrimidines.

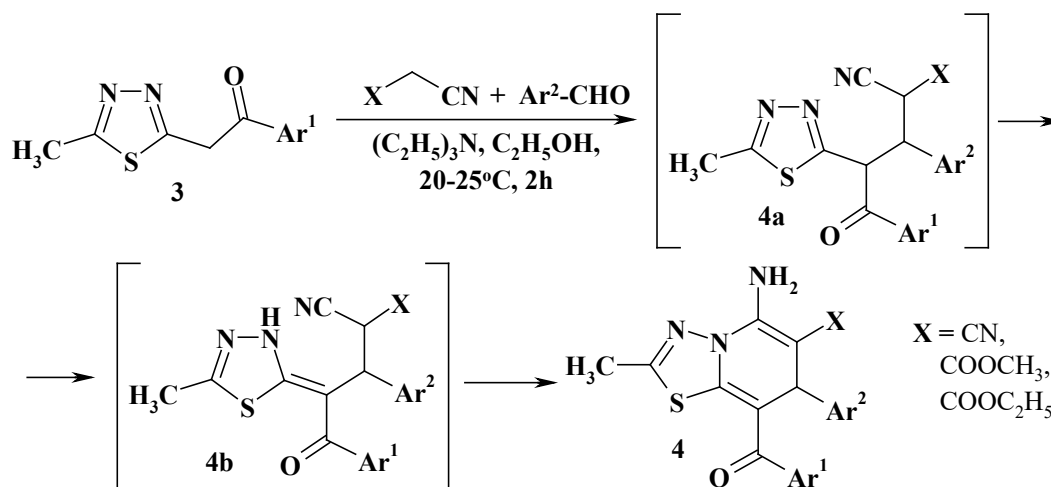
2. Approaches for synthesis and structural modification of functionally substituted thiaziazolo[3,2-*a*]pyridine and thiaziazolo[3,2-*a*]pyrimidine derivatives

2.1. Synthesis of [1,3,4]thiaziazolo[3,2-*a*]pyridines

The reaction of 4-phenyl-2-cyanomethyl-1,3,4-thiaziazole **1** with ethyl acetoacetate and two equivalent amounts of ammonium acetate at 150°C over 30-45 min (Scheme 1) gives a target bicyclic product – 7-methyl-5-oxo-2-phenyl-5*H*-[1,3,4]thiaziazolo[3,2-*a*]pyridine-8-carbonitrile **2**.⁵¹



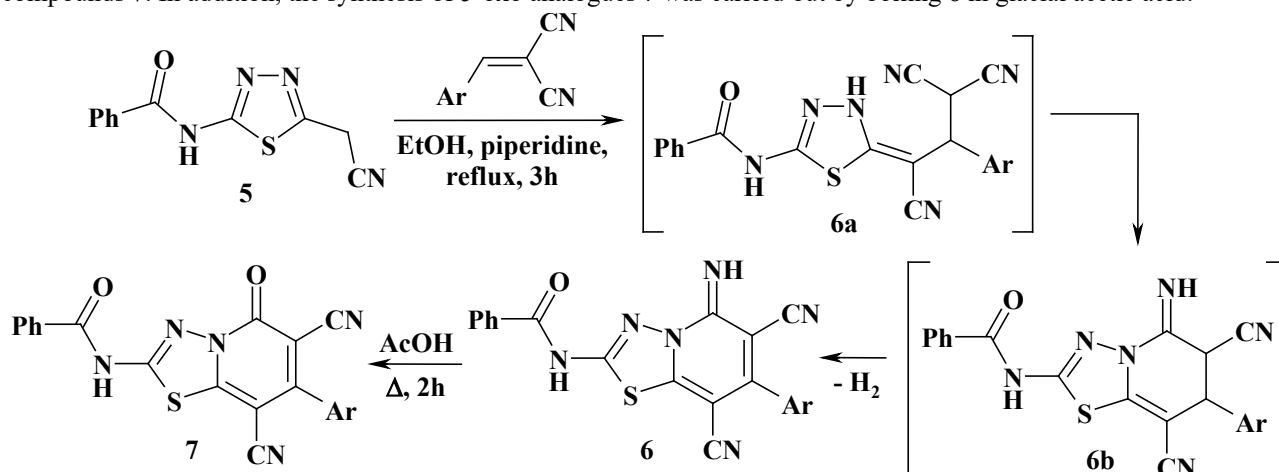
Scheme 1. Synthesis of 7-methyl-5-oxo-2-phenyl-5*H*-[1,3,4]thiaziazolo[3,2-*a*]pyridine-8-carbonitrile by reaction of 4-phenyl-2-cyanomethyl-1,3,4-thiaziazole with ethyl acetoacetate and ammonium acetate.



Scheme 2. Synthesis of 5-amino-2-methyl-7*H*-[1,3,4]thiaziazolo[3,2-*a*]pyridine derivatives by one-pot condensation of 2-methyl-5-phenacyl-1,3,4-thiaziazoles with malononitrile derivatives and aromatic aldehydes.

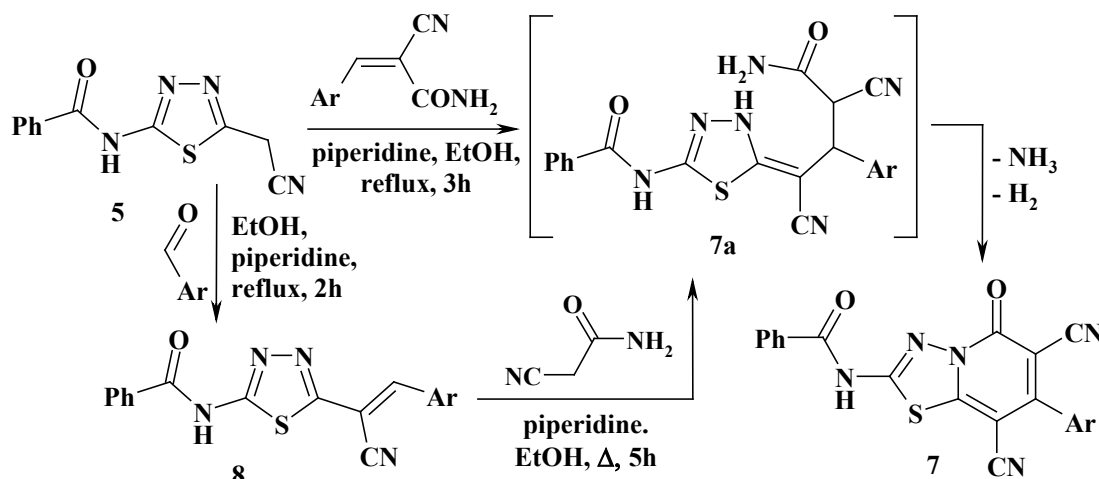
A series of 5-amino-2-methyl-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridine derivatives **4** were prepared through the one-pot three-component procedure based on condensation of 2-methyl-5-phenacyl-1,3,4-thiadiazoles **3** with malononitrile and aromatic aldehydes in ethanol for 2h at ambient temperature in the presence of triethylamine (**Scheme 2**). It was found that such conditions provide rather high yields than with direct interaction of compounds **3** with one equivalent of corresponding benzylidene-malononitriles.⁵²

Due to the presence of an active methylene group, *N*-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)benzamide **5** readily reacted with arylidenemalononitriles in ethanolic/piperidine with hydrogen elimination with the formation of 5-imino-6,8-dicyano-7-aryl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridines **6** (**Scheme 3**). The formation of **7** was assumed to proceed *via* Michael type addition to give intermediate Michael adducts **6a**, which readily cyclized to **6b** and dehydrogenated to afford the target compounds **7**. In addition, the synthesis of 5-oxo analogues **7** was carried out by boiling **6** in glacial acetic acid:⁵³



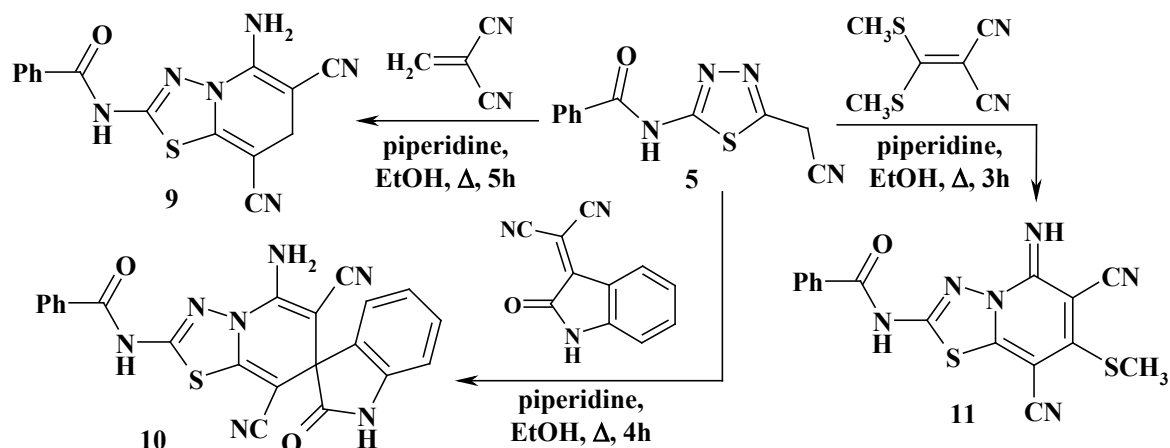
Scheme 3. Synthesis of 5-imino(oxo)-6,8-dicyano-7-aryl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridines by interaction of *N*-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)benzamide with arylidenemalononitriles.

Moreover, the synthesis of 5-oxo-6,8-dicyano-7-aryl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridines **7** was carried out by the alternative method (**Scheme 4**) by reacting **5** with arylidenecyanoacetamides (**1**) or arylidene derivatives **8**, obtained from starting 5-(cyanomethyl)-1,3,4-thiadiazole and aryl carbaldehydes, with cyanoacetamide (**2**) in ethanol/piperidine medium *via* ammonia and hydrogen elimination:⁵³



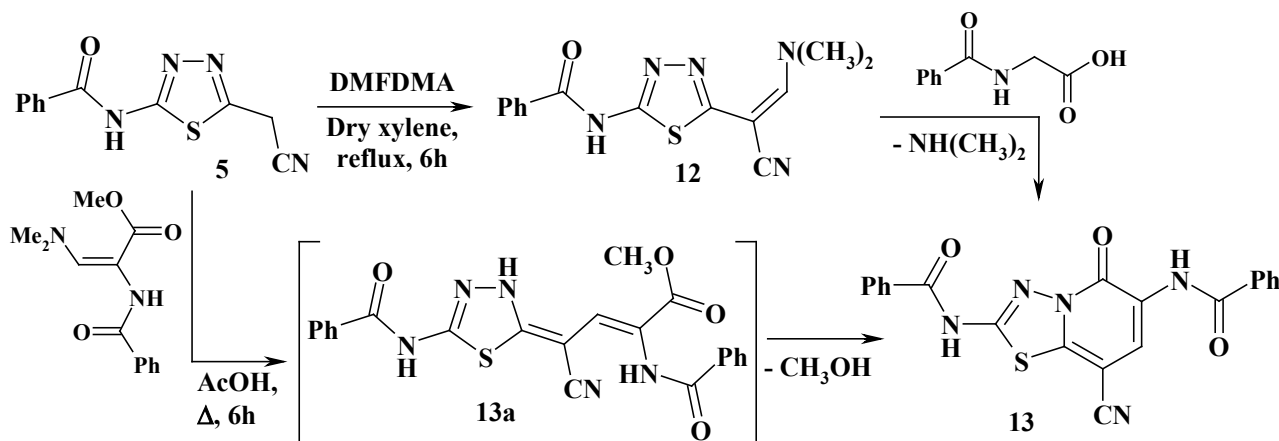
Scheme 4. Synthesis of 5-oxo-6,8-dicyano-7-aryl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridines by cyclocondensation of 5-(cyanomethyl)-1,3,4-thiadiazole-2-amine with arylidenecyanoacetamides.

Also, the starting 5-cyanomethyl-1,3,4-thiadiazole **5** reacted with the mixture of formaldehyde and malononitrile as a synthetic equivalent of methylidenemalononitrile in refluxing ethanol/piperidine to afford 7-unsubstituted 5-amino-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridine **9** (**Scheme 5**). Further interaction of compound **5** with 2-oxoindol-3-ylidene substituted malononitrile in ethanol catalyzed by piperidine gave spiro indolono-thiadiazolo[3,2-*a*]pyridine **10**. In addition, the cyclocondensation of compound **5** with ketenedithioacetal accompanied by thiomethanol elimination resulted in the formation of 7-methylsulfanyl substituted 5-amino-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridine-6,8-dicarbonitriles **11**.⁵³



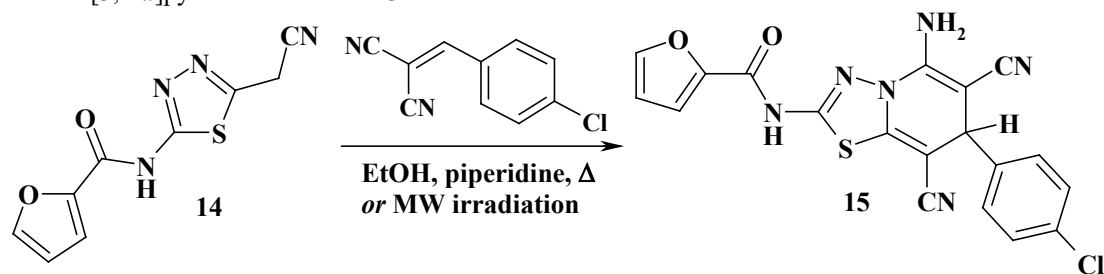
Scheme 5. Synthesis of 5-amino(imino)-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridine-6,8-dicarbonitriles by reaction of 5-cyanomethyl-1,3,4-thiadiazole with ylidene substituted malononitriles.

As a continuation, the treatment of *N*-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)benzamide **5** with dimethylformamidedimethylacetal (DMFDMA) in dry xylene under the reflux gave the corresponding 3-(*N,N*-dimethylamino)propenenitrile **12**. The interaction of **12** with benzoylaminoacetic acid in dry acetic anhydride at a reflux temperature afforded a cyclic product – 2,6-di-(benzoylamino)-8-cyano-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridine-5-one **13** (**Scheme 6**). Compound **13** was also prepared by reacting **5** with methyl 2-benzoylamino-3-(*N,N*-dimethylamino)-propenoate in glacial acetic acid under the reflux conditions *via* dimethylamine and methanol elimination:⁵³



Scheme 6. Synthesis of 2,6-di-(benzoylamino)-8-cyano-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridine-5-one by reaction of *N*-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)benzamide with 2-benzoylamino-3-(*N,N*-dimethylamino)-propenoate.

Finally, the interaction of *N*-(1,3,4-thiadiazol-2-yl)furan-2-carboxamide derivative **14** with 2-(4-chlorobenzylidene)malononitrile in the presence of catalytic amounts of piperidine in refluxing ethanol (**Scheme 7**) followed by acidification of the reaction mixture with cold dilute HCl furnished the target 5-amino-6,8-dicyano-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridine derivative **15**:⁵⁴

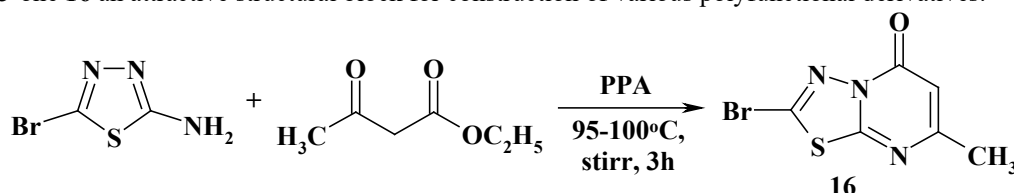


Scheme 7. Synthesis of 5-amino-6,8-dicyano-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyridine by reaction of *N*-(1,3,4-thiadiazol-2-yl)furan-2-carboxamide with 2-(4-chlorobenzylidene)malononitrile.

2.2. Synthesis of [1,3,4]thiadiazolo[3,2-*a*]pyrimidines

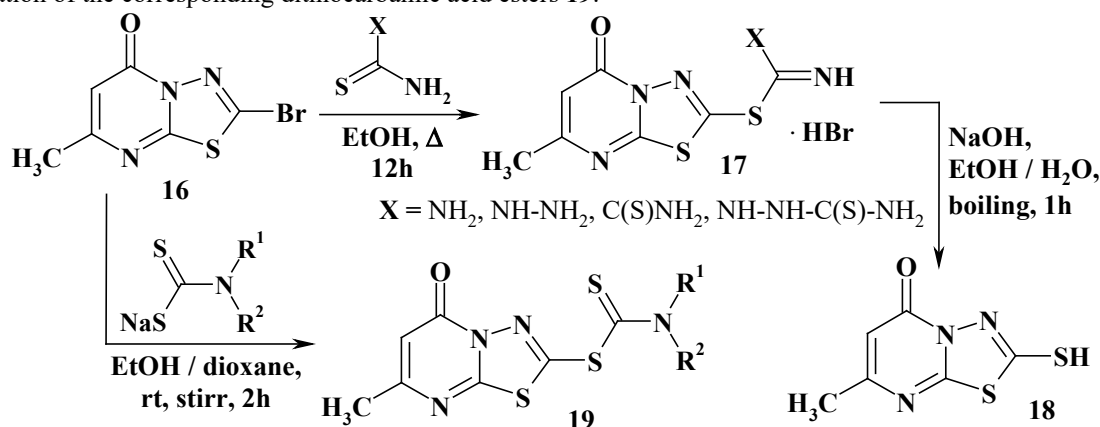
The condensation of 2-amino-5-bromo-1,3,4-thiadiazole with ethyl acetoacetate in polyphosphoric acid (PPA) leads to the formation of the target 2-bromo-7-methyl-5-oxo-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine **16** (**Scheme 8**). The bromine

atom in position 2 can be easily replaced by various nucleophilic substituents, which makes the obtained thiadiazolo[3,2-*a*]pyrimidin-5-one **16** an attractive structural block for construction of various polyfunctional derivatives.⁵⁵



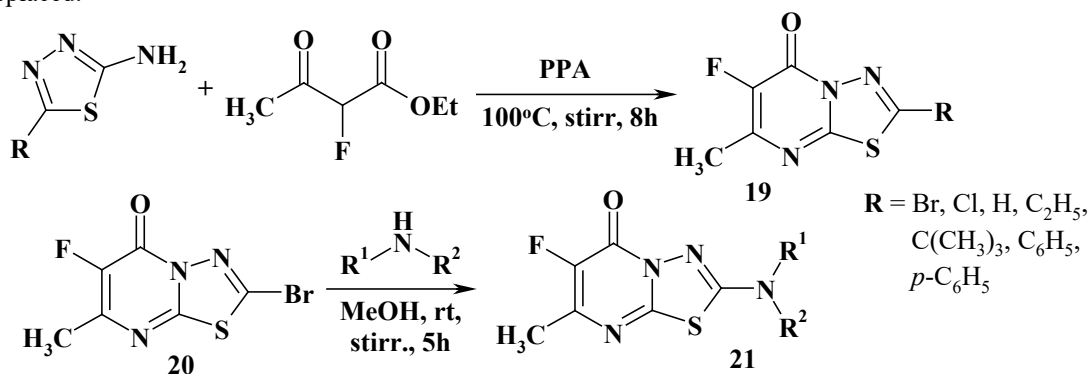
Scheme 8. Synthesis of 2-bromo-7-methyl-5-oxo-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine by condensation of 2-amino-5-bromo-1,3,4-thiadiazole with ethyl acetoacetate in polyphosphoric acid.

Thus, a series of thiuronium salts **17** were synthesized by reaction of 2-bromo-5*H*-thiadiazolo[3,2-*a*]pyrimidin-5-one **16** with various thioamides (such as thiourea, thiosemicarbazide, dithiocarbonylhydrazine, and dithiooxamide) in boiling ethanol with a high yields (**Scheme 9**). Further hydrolysis of the obtained thiuronium salts **17** in sodium hydroxide aqueous/ethanol medium forms the expected 7-methyl-5-oxo-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-2-thiol **18**. In addition, the interaction of compound **16** with alkali metal salts of dithiocarbamates in aqueous ethanol solutions provides the formation of the corresponding dithiocarbamic acid esters **19**.⁵⁶



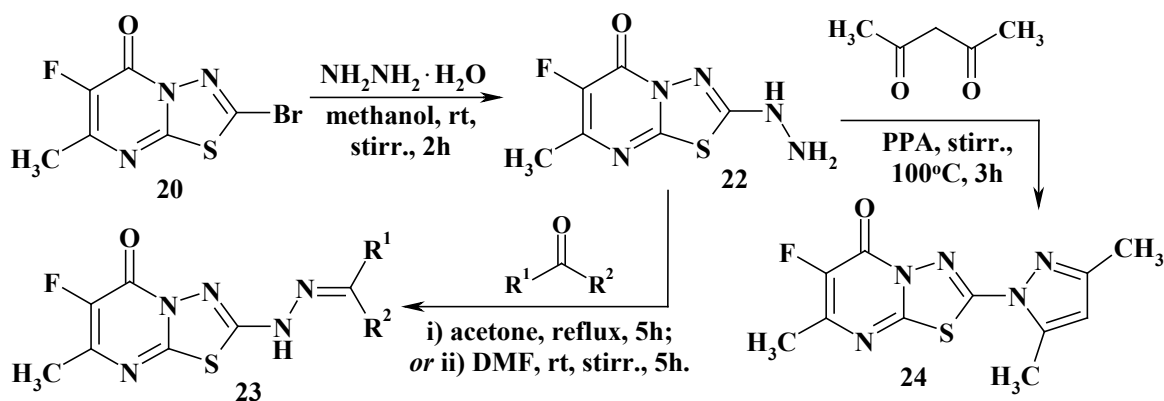
Scheme 9. Synthesis of thiuronium salts and dithiocarbamic acid esters by reaction of 2-bromo-5*H*-thiadiazolo[3,2-*a*]pyrimidin-5-one with thioamides or alkali metal salts of dithiocarbamates.

Similarly, following the reaction of 2-*R*-5-amino-1,3,4-thiadiazoles with ethyl 2-fluoroacetoacetic ester in polyphosphoric acid (PPA) a series of 2-substituted 6-fluoro-7-methyl-5-oxo-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidines **19** were obtained (**Scheme 10**). Further interaction of 2-bromo-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine **20** with nucleophiles such as ammonia, primary and secondary amines led only to selective substitution of the bromine atom located in the position 2 giving the corresponding derivatives **21**. It was also established that the fluorine atom located in the position 6 of the ring was not replaced.⁵⁷



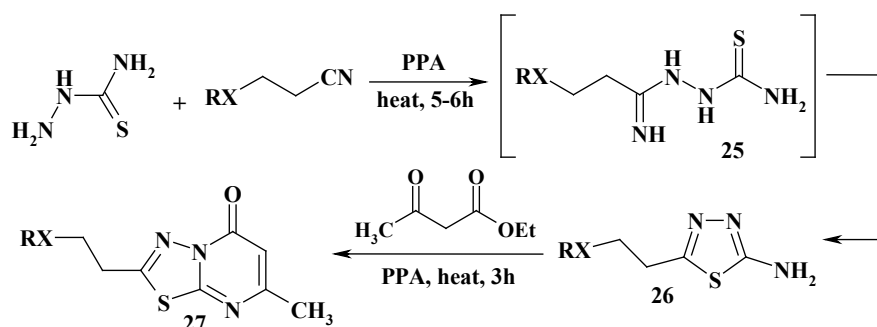
Scheme 10. Synthesis of 2-substituted 6-fluoro-7-methyl-5-oxo-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidines by reaction of 2-*R*-5-amino-1,3,4-thiadiazoles with ethyl 2-fluoroacetoacetic ester.

As a continuation, the synthesis of 2-hydrazino-6-fluoro-7-methyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one **22** was performed based on reaction of 2-bromo derivative **20** with hydrazine hydrate in methanol at room temperature (**Scheme 11**). Further utilization of compound **22** upon interaction with (i) acetone under the reflux or (ii) benzaldehyde in anhydrous dimethyl formamide provided the corresponding hydrazones **23**. Whereas, the condensation of **22** with acetylacetone in PPA with stirring at 100°C afforded the target 2-pyrazole substituted [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one **24**.⁵⁸



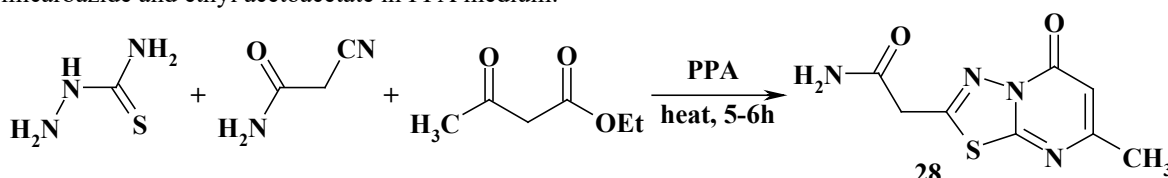
Scheme 11. Synthesis of 2-hydrazino-6-fluoro-7-methyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one and further utilization upon interaction with acetone, benzaldehyde or acetylacetone.

A one-pot method based on condensation of β -alkylthio(alkoxy)propionitriles with thiosemicarbazide and ethyl acetoacetate in PPA medium has been developed for the synthesis of 2-R-7-methyl-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidines **27** by Kukaniev *et al.*⁵⁹ Primarily the starting nitriles in a PPA medium on reaction with thiosemicarbazide are converted into amidrazones **25**, followed by loss of a molecule of ammonia to give 5-(β -alkylthioethyl)-2-amino-1,3,4-thiadiazoles **26** (Scheme 12). Then compounds **26** were cyclized with ethyl acetoacetate to give the target products **27**:

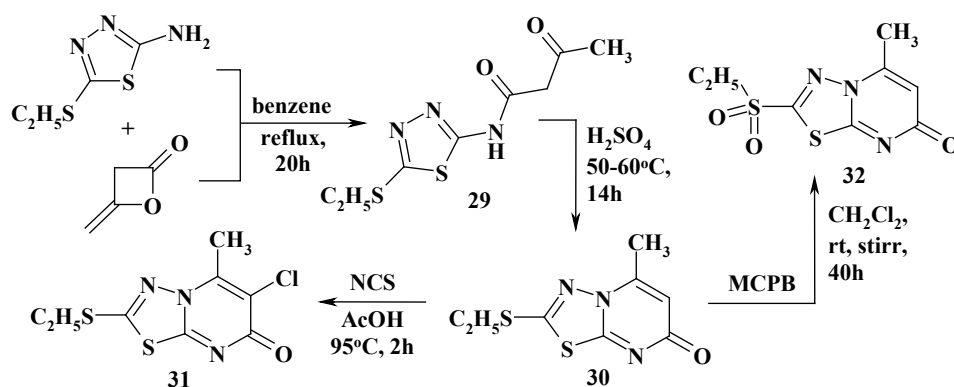


Scheme 12. Synthesis of 2-R-7-methyl-5-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidines by condensation of β -alkylthio(alkoxy)propionitriles with thiosemicarbazide and ethyl acetoacetate.

In above mentioned conditions, the synthesis of 2-(7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-a]pyrimidin-2-yl)acetamide **28** (Scheme 13) was carried out by one-step three-component condensation of cyanoacetamide, thiosemicarbazide and ethyl acetoacetate in PPA medium:⁵⁹



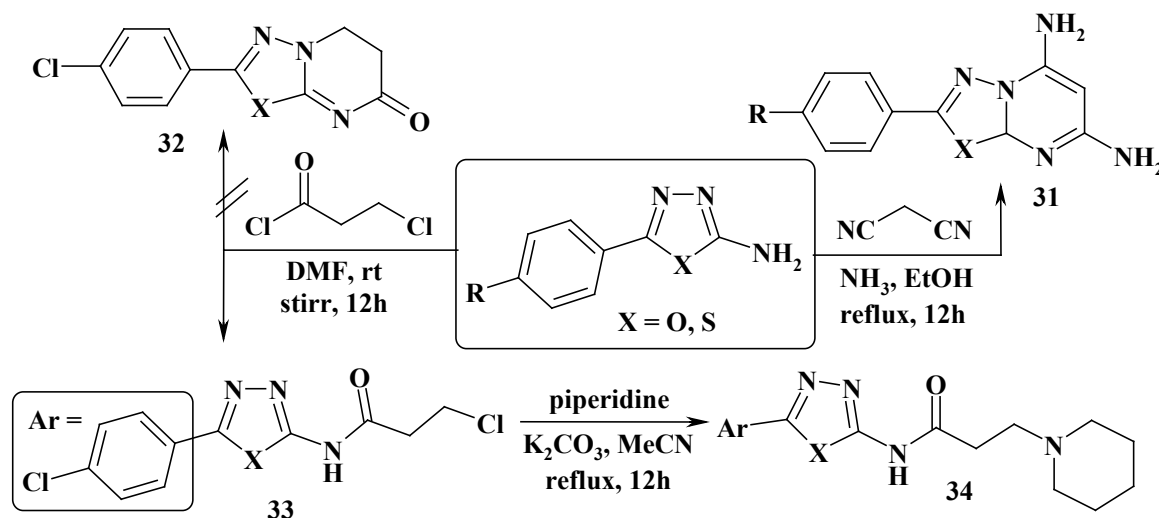
Scheme 13. Synthesis of 2-(7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-a]pyrimidin-2-yl)acetamide by condensation of cyanoacetamide, thiosemicarbazide and ethyl acetoacetate.



Scheme 14. Synthesis of 2-ethylthio-5-methyl-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-one by cyclization of *N*-(thiadiazol-2-yl) substituted 3-oxobutanamide with sulphuric acid.

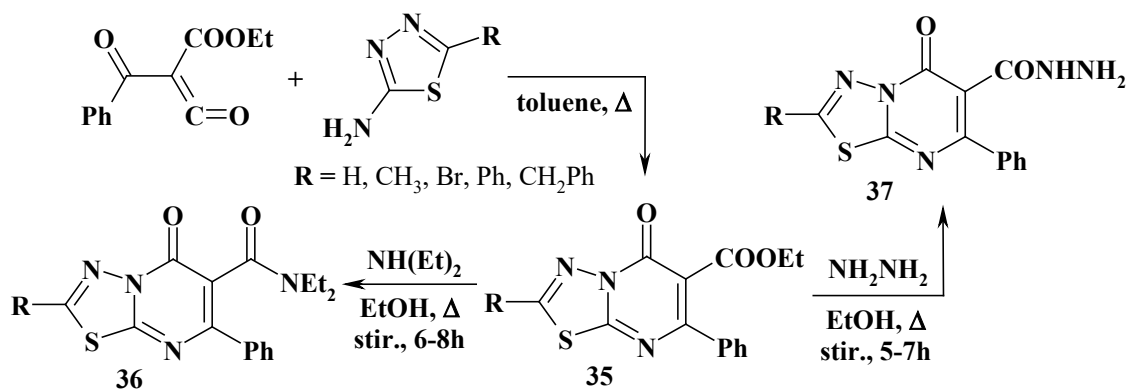
Interaction of 2-amino-5-ethylthio-1,3,4-thiadiazole with diketene in refluxing benzene resulted in *N*-(thiadiazol-2-yl) substituted 3-oxobutanamide **29**, which under the action of sulphuric acid cyclized into the target 2-ethylthio-5-methyl-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-7-one **30** (Scheme 14). Further chlorination of compound **30** with *N*-chlorosuccinimide (NCS) in acetic acid at 95°C led to the formation of 6-chloro derivative **31**. In addition, oxidation of **30** with *m*-chloroperoxybenzoic acid (MCPB) with stirring for 40 h. at room temperature gave the corresponding 2-ethylsulfone **32**.⁶⁰

Following the reaction of 5-aryl-1,3,4-oxa or thiadiazol-2-amines with malononitrile in absolute ethanol and the presence of triethylamine the appropriate 2-aryl-8*aH*-[1,3,4]oxa- or thiadiazolo[3,2-*a*]pyrimidine-5,7-diamines **31** were obtained (Scheme 15). Furthermore, the interaction of 4-chlorophenyl substituted derivative with 3-chloropropionyl chloride using different reaction conditions yielded 3-chloro-*N*-(5-(4-chlorophenyl)-1,3,4-oxa or thiadiazol-2-yl) propanamide **33** rather than more expected cyclized product **32**. In addition, the reaction of compound **33** with piperidine in dry acetonitrile gave the bicyclic non-condensed analogue **34**.⁶¹



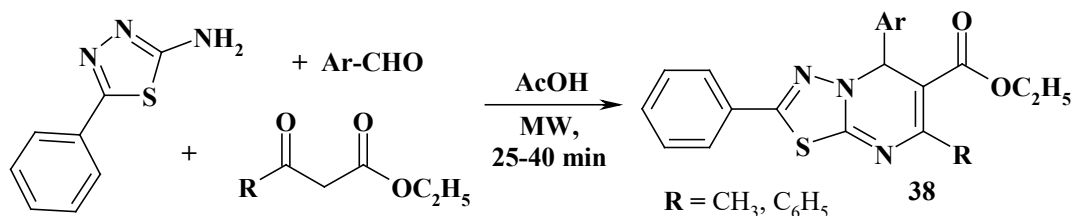
Scheme 15. Synthesis of 2-aryl-[1,3,4]oxa(thia)diazolo[3,2-*a*]pyrimidine-5,7-diamines by reaction of 5-aryl-1,3,4-oxa or thiadiazol-2-amines with malononitrile.

The use of various 2-substituted 5-amino-1,3,4-thiadiazoles in the reaction with ethyl 2-formyl-3-oxo-3-phenylpropanoate (Scheme 16) allowed Moradivalikboni *et al.*⁶² to synthesize 2-*R*-5-oxo-7-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-ethylcarboxylates **35**. Further, the corresponding 6-*N,N*-diethylcarboxamides **36** were obtained following the reaction of compounds **35** with *N,N*-diethylamine in ethanol medium under reflux conditions. In addition, the interaction of compounds **35** with hydrazine in similar conditions provides the formation of the target 5-oxo-7-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carbohydrazide derivatives **37**.⁶³



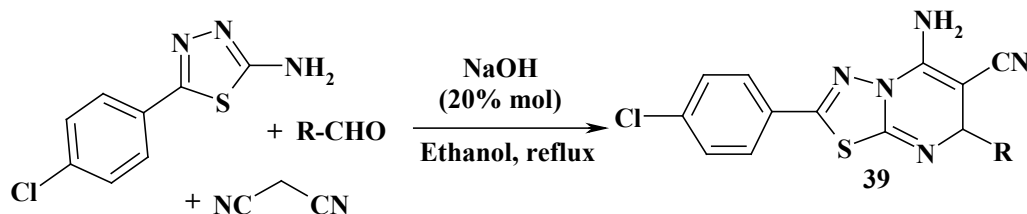
Scheme 16. Synthesis of 6-diethylcarboxamides or 6-carbohydrazide derivatives by reaction of 2-*R*-5-oxo-7-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-ethylcarboxylates with *N,N*-diethylamine or hydrazine in ethanol medium.

An efficient synthetic method based on one-pot three component condensation reaction of 2-amino-1,3,4-thiadiazole with various aldehydes and ethyl acetoacetate or benzoylacetate in acetic acid medium under microwave irradiation (Scheme 17) was proposed by Zhao *et al.*⁶⁴ As result, a series of 5-aryl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carboxylates **38** were obtained using mentioned conditions:



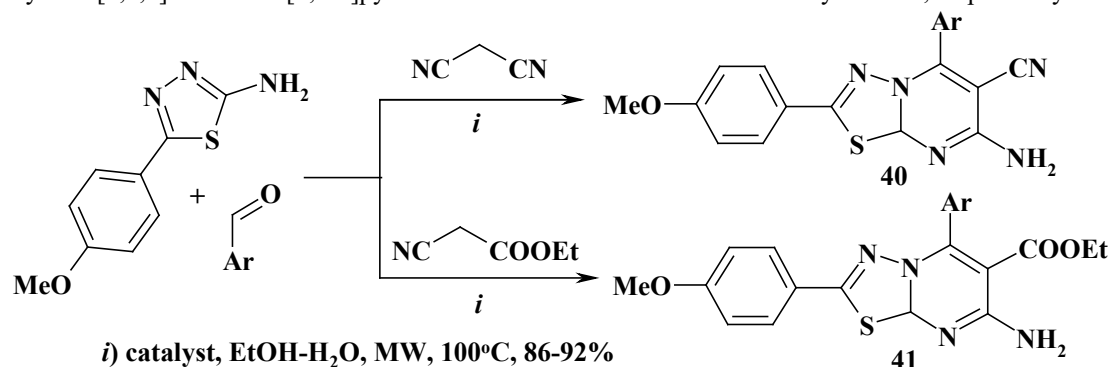
Scheme 17. Synthesis of 5-aryl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carboxylate by one-pot condensation of 2-amino-1,3,4-thiadiazole with aldehydes and ethyl acetoacetate or benzoylacetate.

The synthesis of novel 5-amino-2-(4-chlorophenyl)-7-substituted phenyl-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carbonitriles **40** (Scheme 18) was carried out through the one-pot three component reactions between 5-(4-chlorophenyl)-1,3,4-thiadiazol-2-amine, aromatic aldehydes and malononitrile in presence of NaOH under reflux and ultrasonic irradiation:⁶⁵



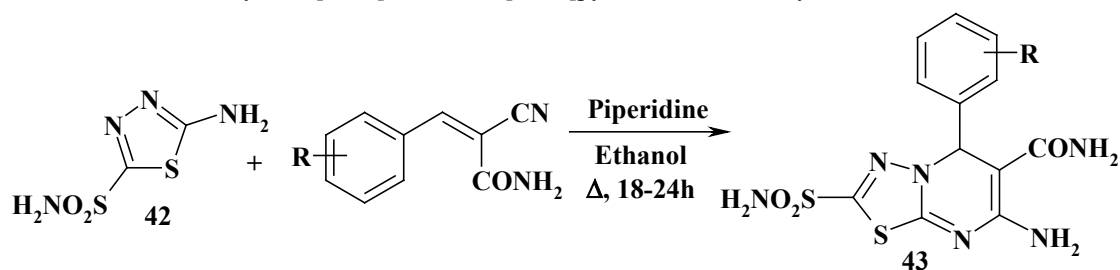
Scheme 18. Synthesis of 7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carbonitriles by reaction of 5-(4-chlorophenyl)-1,3,4-thiadiazol-2-amine with aromatic aldehydes and malononitrile.

Based on the reaction between 2-amino-1,3,4-thiadiazole, appropriate aromatic aldehyde and malononitrile or ethyl cyanoacetate in ethanol-water mixture under microwave irradiation (**Scheme 19**) using 2-[5-(4-methoxyphenyl)-4*H*-1,2,4-triazole-3-ylthio]acetic acid as organocatalyst Sahi *et al.*⁶⁶ performed the synthesis of 2-(4-methoxyphenyl) substituted 7-amino-5-aryl-9*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carbonitriles **40** and 6-carboxylates **41**, respectively:



Scheme 19. Synthesis of 7-amino-9*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carbonitriles and 6-carboxylates by reaction of 2-amino-1,3,4-thiadiazole with aromatic aldehydes and malononitrile.

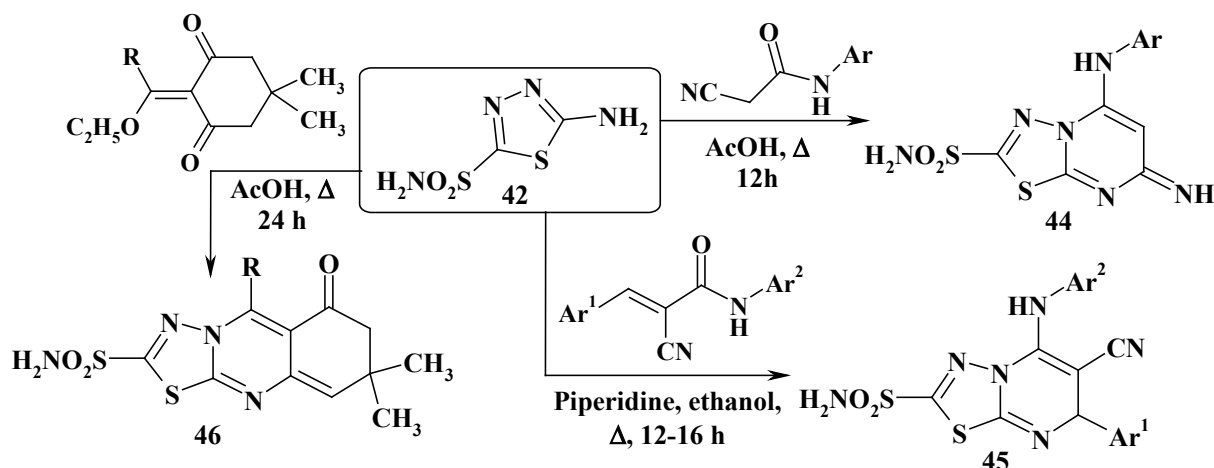
Whereas, the condensation of 5-amino-1,3,4-thiadiazole-2-sulfonamide **42** with the appropriate benzylidenecyanoacetamide in absolute ethanol in the presence of piperidine as a catalyst (**Scheme 20**) afforded 7-amino-5-phenyl substituted 2-sulfamoyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carboxylic acid amides **43**:⁶⁷



Scheme 20. Synthesis of 2-sulfamoyl-7-amino-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carboxylic acid amides by reaction of 5-amino-1,3,4-thiadiazole-2-sulfonamide with benzylidenecyanoacetamides.

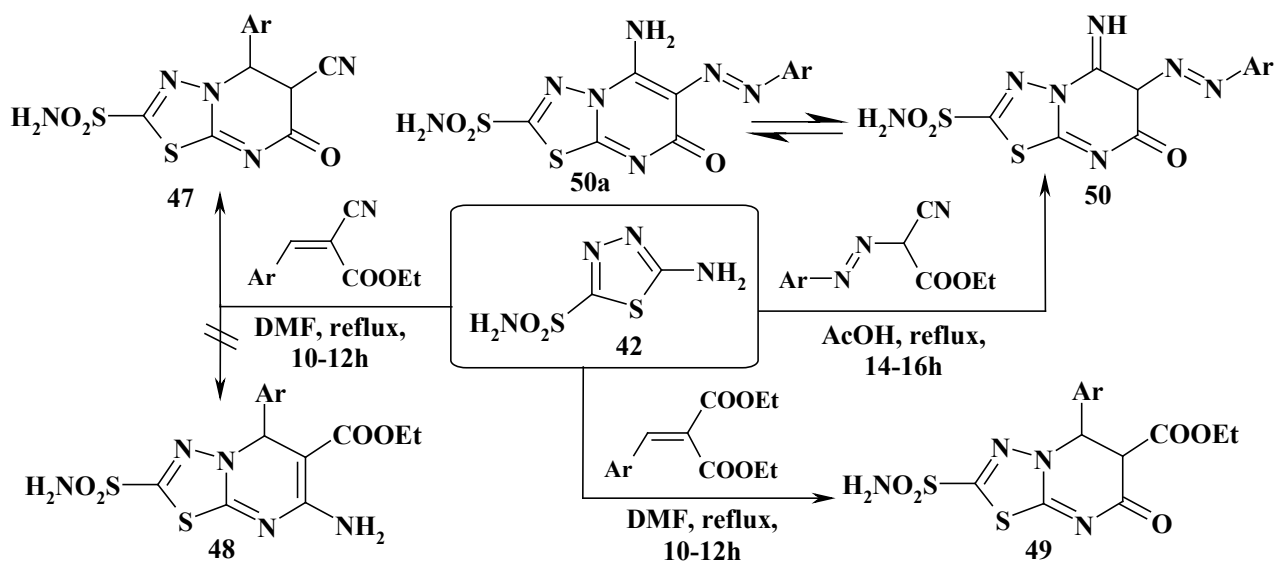
Similarly, cyclocondensation of starting 5-amino-1,3,4-thiadiazole-2-sulfonamide **42** with *N*-arylcycanoacetanilide derivatives in glacial acetic acids under the reflux afforded the title 7-imino-5-(substituted phenyl)amino-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-2-sulfonamides **44** (**Scheme 21**). Whereas, interaction of compound **42** with various 2-arylidene substituted *N*-arylcycanoacetanilide in absolute ethanol in the presence of catalytic amount of piperidine gave the

respective 6-cyano-7-aryl-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-2-sulfonamide derivatives **45**. In addition, the treating of compound **42** with 2-(ethoxymethylene)-5,5-dimethylcyclohexane-1,3-dione in refluxing acetic acid yielded the corresponding [1,3,4]thiadiazolo[2,3-*b*]quinazoline derivatives **46**.⁶⁸



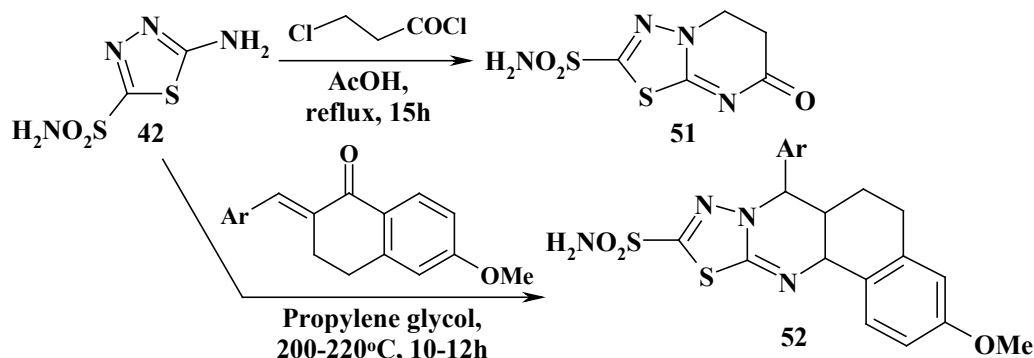
Scheme 21. Synthesis of 5-(substituted phenyl)amino-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-2-sulfonamides and [1,3,4]thiadiazolo[2,3-*b*]quinazoline derivatives by reaction of 1,3,4-thiadiazole-2-sulfonamide with cyanoacetanilides or 2-(ethoxymethylene)-5,5-dimethylcyclohexane-1,3-dione.

In addition, the condensation of 1,3,4-thiadiazole-5-sulfonamide **42** with arylidene substituted cyanoacetates or diethyl malonates in DMF medium under the reflux conditions gives the expected 5,6-dihydro-7-oxo-5-(substituted)phenyl-2-sulfamoyl-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carbonitriles **47** or 6-carboxylates **49** (**Scheme 22**), respectively. Interestingly, in the case of interaction with arylidene cyanoacetates, the formation of only one of the two possible target products was observed, namely **47** as opposed to **48**. Moreover, by reacting of starting 2-amino-1,3,4-thiadiazole with ethyl 2-cyano-2-[4-(substituted)phenyldiazenyl]acetates the corresponding 5-amino-7-oxo-6-[4-(substituted)phenyldiazenyl]-5*H*,7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-2-sulfonamides **50** were obtained.⁶⁹



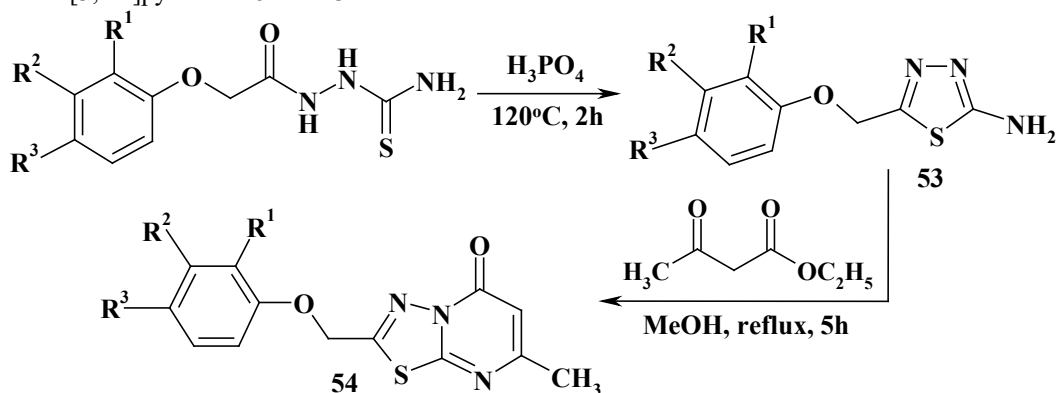
Scheme 22. Synthesis of 5,6-dihydro-7-oxo-2-sulfamoyl-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carbonitriles or 6-carboxylates by reaction of 2-amino-1,3,4-thiadiazole-5-sulfonamide with arylidene substituted cyanoacetates or diethyl malonates.

Also, the reaction of 2-amino-1,3,4-thiadiazole-5-sulfonamide **42** with 3-chloropropionyl chloride in refluxing glacial acetic acid afforded 6,7-dihydro-7-oxo-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-2-sulfonamide **51** (**Scheme 23**). As a continuation, the interaction of equimolar amounts of starting thiadiazole-2-amine **42** with benzylidenetetralones in refluxing propylene glycol gave the original polycyclic benzo[*h*][1,3,4]thiadiazolo[2,3-*b*]quinazoline derivatives **52**.⁶⁹



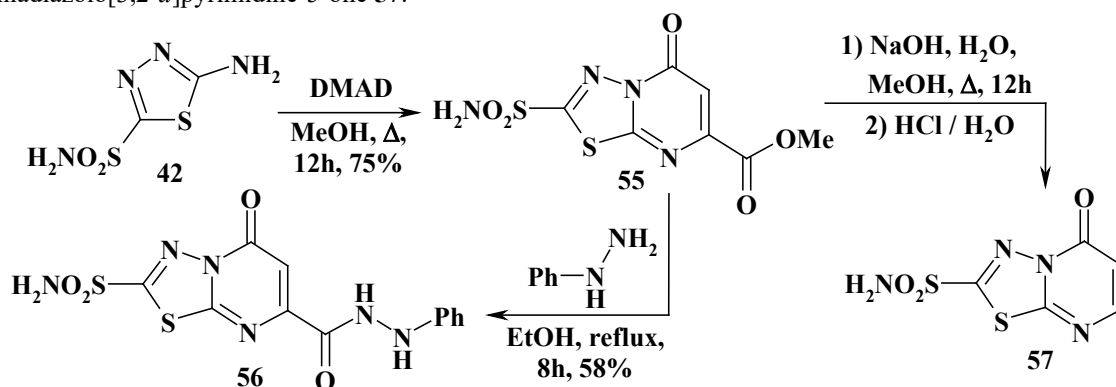
Scheme 23. Synthesis of 6,7-dihydro-7-oxo-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-sulfonamide and benzo[h][1,3,4]thiadiazolo[2,3-b]quinazoline derivatives by reaction of 2-amino-1,3,4-thiadiazole-5-sulfonamide with 3-chloropropionyl chloride or benzylidene tetralones.

Condensation of 5-phenoxy methyl-1,3,4-thiadiazole-2-amines **53** (Scheme 24), previously obtained by intramolecular cyclization of substituted phenoxy acetyl-*N*-hydrazine carbothioamides with anhydrous orthophosphoric acid, with ethylacetoacetate in methanol medium under the reflux afforded the target 7-methyl-2-(phenoxy methyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-ones **54**.⁷⁰



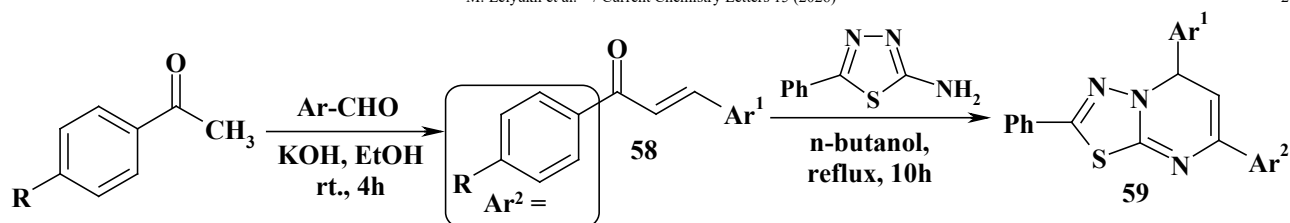
Scheme 24. Synthesis of 7-methyl-2-(phenoxy methyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-ones by condensation of 5-phenoxy methyl-2-amino-1,3,4-thiadiazoles with ethylacetoacetate.

Treating of 2-amino-1,3,4-thiadiazole-5-sulfonamide **42** with dimethyl acetylene dicarboxylate (DMAD) in methanol to afford the corresponding 5-oxo-2-sulfamoyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-7-carboxylate **55** (Scheme 25). Compound **55** was reacted with phenylhydrazine in refluxing absolute ethanol to give the target *N*-phenyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-7-carbohydrazide **56**. In addition, the hydrolysis of thiadiazolo[3,2-a]pyrimidine-7-carboxylate **55** using 12% sodium hydroxide followed by acidification with hydrochloric acid yielded 6,7,8-unsubstituted [1,3,4]thiadiazolo[3,2-a]pyrimidine-5-one **57**.⁷¹



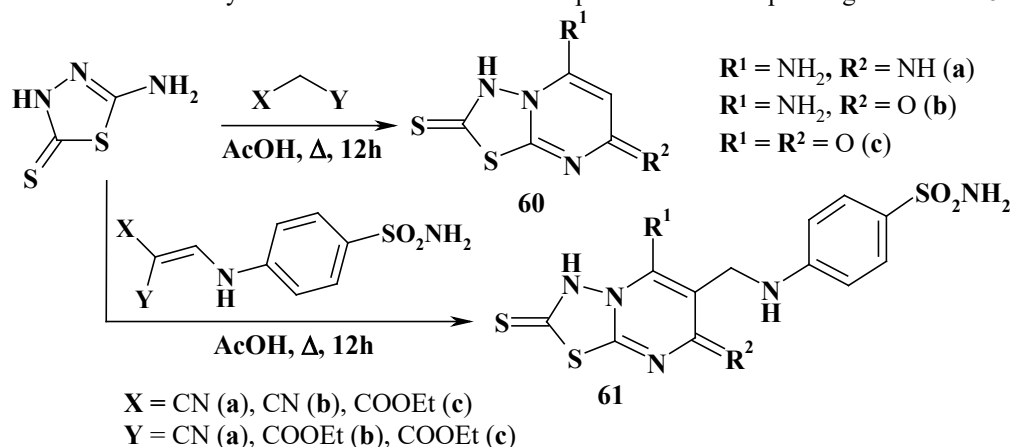
Scheme 25. Synthesis of 5-oxo-2-sulfamoyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-7-carboxylate by reaction of 2-amino-1,3,4-thiadiazole-5-sulfonamide with dimethyl acetylene dicarboxylate.

According to the Claisen-Schmidt condensation procedure between substituted acetophenones with different aromatic aldehydes the corresponding chalcones **58** were obtained (Scheme 26), which upon reaction with 5-phenyl-1,3,4-thiadiazole-2-amine furnished the target 5,7-disubstituted 2-phenyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine derivatives **59**.⁷²



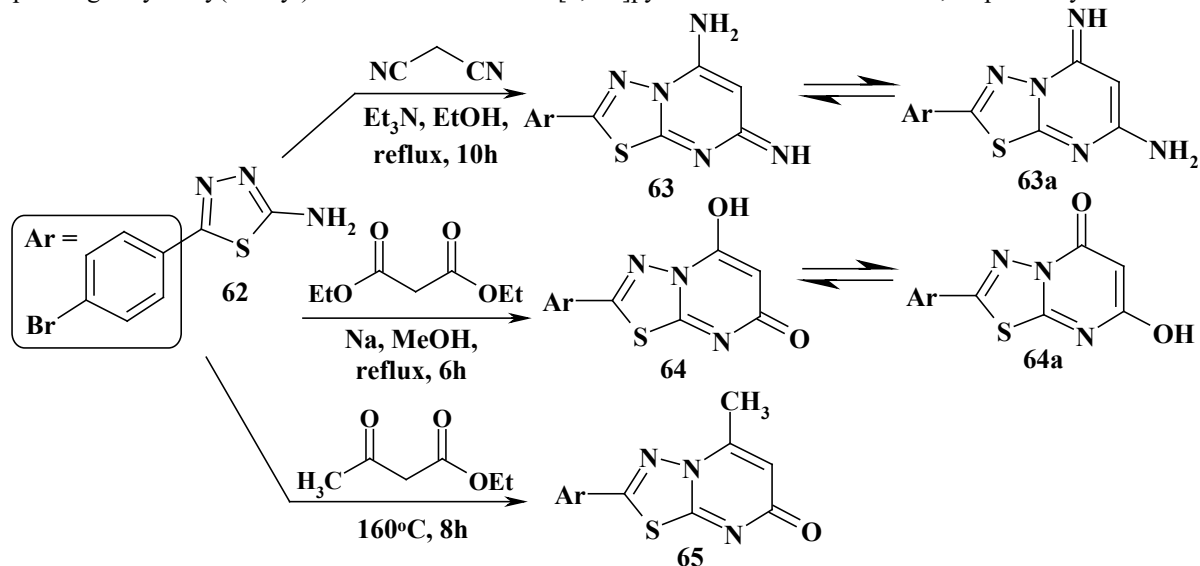
Scheme 26. Synthesis 5,7-disubstituted 2-phenyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidines by reaction of 5-phenyl-1,3,4-thiadiazole-2-amine with different chalcones.

A series of 5-oxo(imino)-[1,3,4]thiadiazolo[3,2-a]pyrimidine-7-ones(imines) **60** were synthesized through the reaction of 5-amino-3H-1,3,4-thiadiazole-2-thione with methylene active compounds such as malononitrile, ethylcyanoacetate or diethylmalonate in refluxing glacial acetic acid (**Scheme 27**). Whereas, reacting of starting 5-amino-1,3,4-thiadiazole with 5-benzenesulfonamide aminomethylidene substituted malonates to provide the corresponding derivatives **61**.⁷³



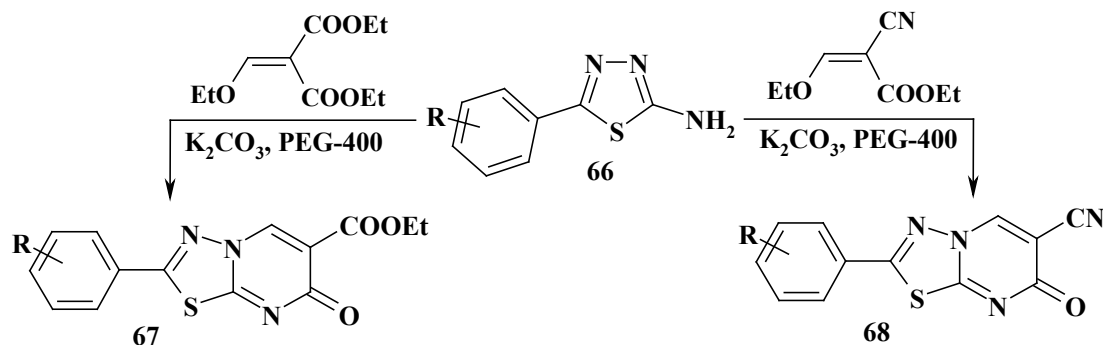
Scheme 27. Synthesis of 5-oxo(imino)-[1,3,4]thiadiazolo[3,2-a]pyrimidine-7-ones(imines) by reaction of 5-amino-3H-1,3,4-thiadiazole-2-thione with methylene active compounds.

2-Aryl-5-amino-[1,3,4]thiadiazolo[3,2-a]pyrimidine-7-imine/amine derivatives **63** were achieved *via* reaction of 5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine **62** with malononitrile in ethanol medium in the presence of triethylamine (**Scheme 28**). In return, the reaction of compound **62** with diethyl malonate or ethyl acetoacetate under the heating afforded the corresponding 5-hydroxy(methyl) substituted thiadiazolo[3,2-a]pyrimidine-7-ones **64** and **65**, respectively.⁷⁴



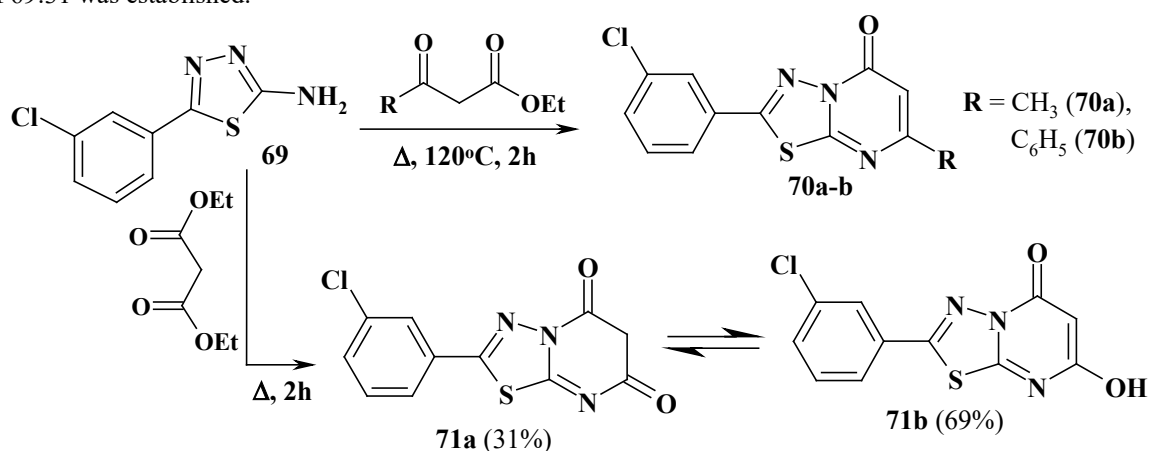
Scheme 28. Synthesis of 2-aryl-5-amino(hydroxy)-[1,3,4]thiadiazolo[3,2-a]pyrimidine-7-imines(ones) by reaction of 5-(4-bromophenyl)-1,3,4-thiadiazol-2-amine with malononitrile, diethyl malonate or ethyl acetoacetate.

The synthesis of ethyl 2-aryl-7-oxo-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carboxylates **67** and 6-carbonitriles **68** through intramolecular cyclo-elimination of Michael adducts formed (**Scheme 29**) was achieved *via* interaction of 2-amino-5-substituted 1,3,4-thiadiazoles **66** with diethyl-2-(ethoxymethylene) malonate or ethyl-2-cyano-3-ethoxyacrylate, respectively.⁷⁵



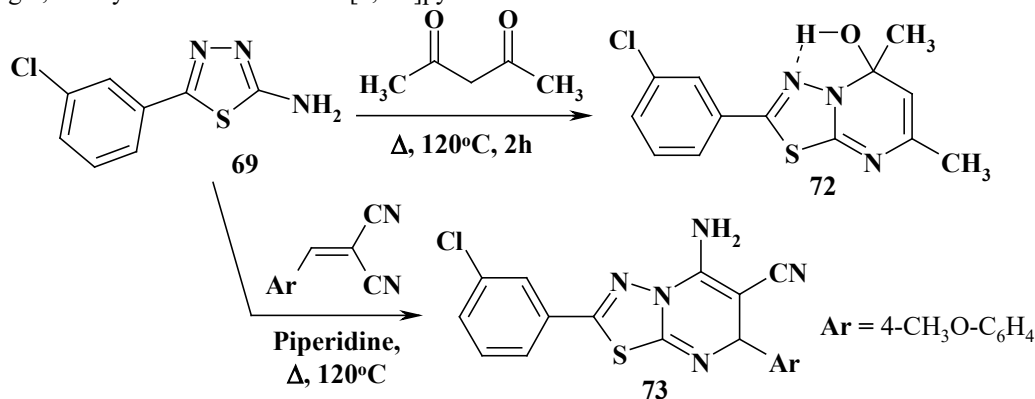
Scheme 29. Synthesis of 2-aryl-7-oxo-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-ethylcarboxylates and 6-carbonitriles by reaction of 2-amino-5-1,3,4-thiadiazoles with diethyl-2-(ethoxymethylene) malonate and ethyl-2-cyano-3-ethoxyacrylate.

The reaction of 5-(3-chlorophenyl)-1,3,4-thiadiazol-2-amine **69** with ethyl acetoacetate or benzoyl acetoacetate gave 7-methyl/phenyl substituted thiadiazolo[3,2-a]pyrimidin-5-ones **70a-b** in an excellent yields (**Scheme 30**). Similarly, the fusion of starting 2-aminothiadiazole **69** with diethyl malonate afforded thiadiazolo[3,2-a]pyrimidin-5-one derivative **71**. Based on the IR and 1H NMR spectra the presence of prototropic keto-enol tautomerism of the compound **71** with a tautomer ratio of 69:31 was established.⁷⁶



Scheme 30. Synthesis of 7-methyl/phenyl-thiadiazolo[3,2-a]pyrimidin-5-ones and thiadiazolo[3,2-a]pyrimidin-5,7-diones by reaction of 5-(3-chlorophenyl)-1,3,4-thiadiazol-2-amine with ethyl/benzoyl acetoacetates or diethyl malonate.

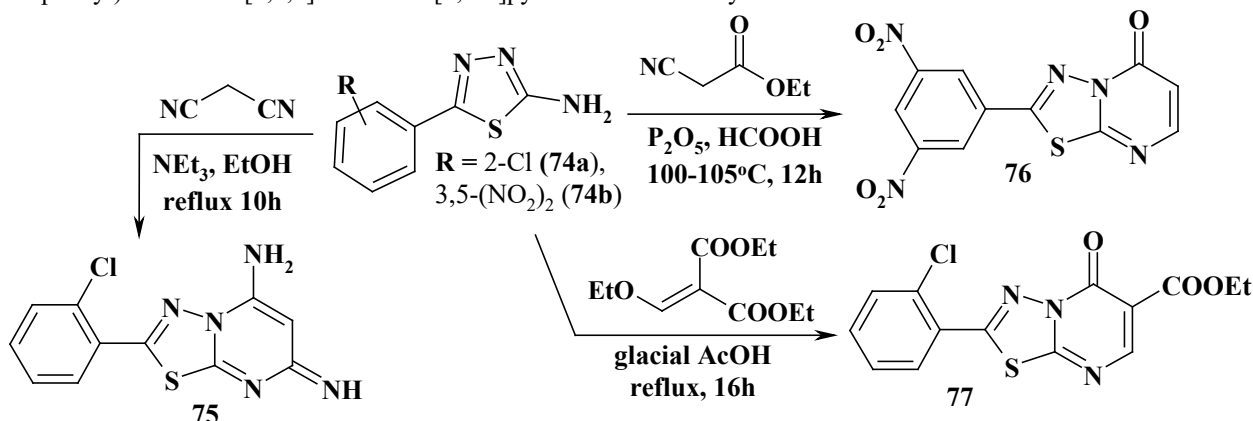
Also, the reaction of compound **69** with acetylacetone provides the formation of 5,7-dimethyl-5-hydroxythiadiazolo[3,2-a]pyrimidine **72** as the sole product (**Scheme 31**). The predictable structure of compound **72** was confirmed based on the spectral data showing the presence of a hydroxyl (absorption band at 3387 cm^{-1} in the IR spectrum) and two methyl groups (two singlet peaks at 2.42 and 1.90 ppm the 1H NMR and 25.4 and 23.2 ppm the ^{13}C NMR spectra) in target molecule. In addition, the reaction of starting 2-aminothiadiazole **69** with 2-(4-methoxybenzylidene)malononitrile furnished the corresponding 2,7-diaryl-5-aminothiadiazolo[3,2-a]pyrimidine-6-carbonitrile derivative **73**.⁷⁶



Scheme 31. Synthesis of 5,7-dimethyl-5-hydroxythiadiazolo[3,2-a]pyrimidine and 5-aminothiadiazolo[3,2-a]pyrimidine-6-carbonitrile by reaction of 5-(3-chlorophenyl)-1,3,4-thiadiazol-2-amine with acetylacetone or 2-(4-methoxybenzylidene)malononitrile.

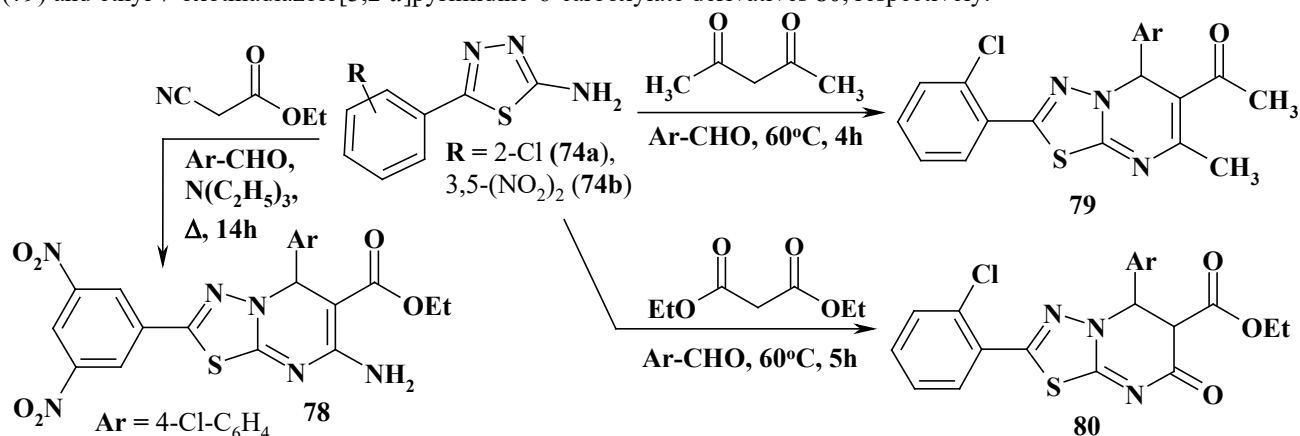
Azab *et al.*⁷⁷ described the synthesis of some [1,3,4]thiadiazolo[3,2-a]pyrimidine derivatives based on the reaction of 5-(2-chlorophenyl)- (**74a**) or 5-(3,5-dinitrophenyl)- 1,3,4-thiadiazol-2-amine (**74b**) with different methylene active

compounds (**Scheme 32**). Thus, the interaction of starting compound **74a** with malononitrile in ethanol/triethylamine mixture gives the expected 7-imino-7*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-amine **75**. Whereas, refluxing of compound **74b** with ethyl cyanoacetate in the presence of phosphorus pentoxide and formic acid mixture as a catalyst the corresponding 2-(3,5-dinitrophenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one **76** was afforded. Finally, compound **74a** was allowed to react with diethyl 2-(ethoxymethylene) malonate in refluxing glacial acetic acid to yield the desired ethyl 2-(2-chlorophenyl)-5-oxo-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carboxylate **77**:



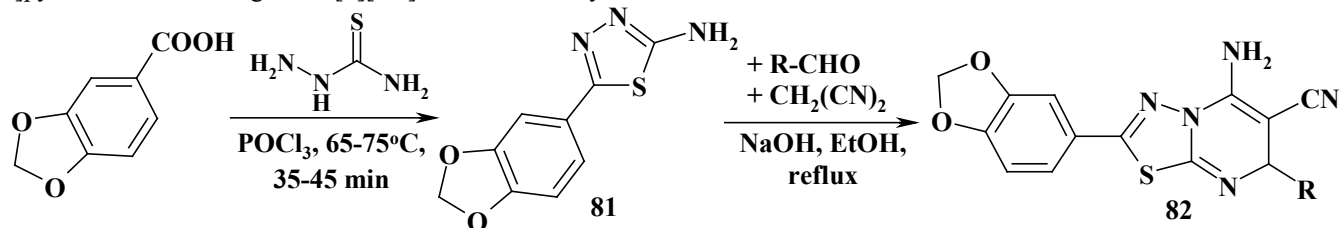
Scheme 32. Synthesis of [1,3,4]thiadiazolo[3,2-*a*]pyrimidine derivatives by reaction of corresponding 1,3,4-thiadiazol-2-amine with malononitrile, ethyl cyanoacetate or diethyl 2-(ethoxymethylene) malonate.

Respectively, through the one-pot three-component condensation of 2-aminothiadiazole derivative **74b** with ethyl cyanoacetate and *p*-chlorobenzaldehyde in refluxing ethanol in the presence of catalytic amount of trimethylamine the corresponding ethyl 5-aryl-7-amino[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-6-carboxylate **78** was obtained (**Scheme 33**). Ultimately, the similar condensation between 2-aminothiadiazole derivative **74a** and *p*-chlorobenzaldehyde with acetyl acetone or diethyl malonate without using any solvent or catalyst resulted in both of 6-acetylthiadiazolo[3,2-*a*]pyrimidine (**79**) and ethyl 7-oxothiadiazolo[3,2-*a*]pyrimidine-6-carboxylate derivatives **80**, respectively.⁷⁷



Scheme 33. Synthesis 6-acetylthiadiazolo[3,2-*a*]pyrimidine or ethyl 7-oxo/aminothiadiazolo[3,2-*a*]pyrimidine-6-carboxylate derivatives by one-pot three-component reaction of 2-aminothiadiazoles and *p*-chlorobenzaldehyde with ethyl cyanoacetate, acetyl acetone or diethyl malonate.

Following the reaction of piperonylic acid with thiosemicarbazide in phosphorus oxochloride under the heating the intermediate 5-(benzo[*d*][1,3]dioxol-5-yl)-1,3,4-thiadiazol-2-amine **81** was obtained (**Scheme 34**). Further, one-pot three-component condensation of compounds **81** with propanedinitrile and corresponding aromatic or heteroaromatic aldehydes in absolute ethyl alcohol and NaOH as catalyst provides the formation of the target 5-amino-6-cyano-[1,3,4]thiadiazolo[3,2-*a*]pyrimidines **82** having benzo[*d*][1,3]dioxolane moiety:⁷⁸



Scheme 34. Synthesis benzo[*d*][1,3]dioxolane substituted 5-amino-6-cyano-[1,3,4]thiadiazolo[3,2-*a*]pyrimidines by one-pot three-component reaction of 5-(benzo[*d*][1,3]dioxol-5-yl)-1,3,4-thiadiazol-2-amine with propanedinitrile and aromatic or heteroaromatic aldehydes.

3. Conclusions

Thiadiazolo[3,2-*a*]pyridines and thiadiazolo[3,2-*a*]pyrimidines are an important classes of fused heterocyclic compounds that have a wide range of biological activity and, as a result, have become a focus of interest for scientists. They are fused heterocyclic ring-systems consists of 1,3,4-thiadiazole cycle annulated to pyridine or pyrimidine ring and can be viewed at the first glance as purine isosteres. The combination of these heterocyclic systems into a bicyclic scaffold commonly provides much more interest in the enhanced activity profile of its analogs than their parent monocyclic constituents. The chemical features of thiadiazolo[3,2-*a*]pyridines and thiadiazolo[3,2-*a*]pyrimidines were described in a numerous research papers focusing on the main approaches for their synthesis and modification as well as theirs biological activity. Thus, broad synthetic possibilities of mentioned condensed heterosystems generation and functionalization, their high pharmacological potential found a strong basis for the systematic research of these compounds.

In the present review we performed the literature search and highlighted the recent synthetic strategies for obtaining of heterocyclic compounds based on fused thiadiazolo[3,2-*a*]pyridine and thiadiazolo[3,2-*a*]pyrimidine systems. The available synthetic protocols were divided and structured according to the chemical structure of the target products. All of things, the wide synthetic capabilities and essential biological properties of thiadiazolo[3,2-*a*]pyridine and thiadiazolo[3,2-*a*]pyrimidine derivates promote the scientists to further investigation and appliance of this heterocyclic systems as a perspective building blocks for organic and medicinal chemistry.

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Conflicts of Interest

The authors declare no conflict of interest.

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