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REVIEW ARTICLE

Recent Development in the Synthesis of Thiazoles

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ARTICLE HISTORY

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Abstract: ***Background*:** Thiazole-containing compounds are widely found in natural products as well as synthetic sources. Many thiazole-based compounds possess a broad spectrum of bioactivities, and some of them are well-known drugs in the markets. The use of thiazole derivatives in other fields such as organic materials, cosmetics, and organic synthesis has also been widely reported. Due to a wide range of applicability, the synthesis of thiazole-containing compounds has attracted extensive interest from chemists, and many studies in the synthesis of thiazole skeleton have been reported recently.

***Objective*:** This review article will discuss recent studies in the synthesis of thiazoles (from 2012). Besides the well-established Hantzsch thiazole synthesis, a large number of novel methods have been developed for the synthesis of thiazole derivatives. In most cases, reaction mechanisms have also been described.

***Conclusion*:** The synthesis of thiazole derivatives has drawn great attention from chemists, and many studies in the synthesis of these heterocycles have been reported recently. The classical method, the Hantzsch thiazole synthesis has received great research interest from chemists. Moreover, many new methods have been established to synthesize thiazole-derived compounds. Unquestionably, more and more approaches to access thiazole skeleton will appear in the literature. The application of well-established thiazole synthesis methods to the synthesis of drugs, organic materials, and natural products will almost certainly be studied.

Keywords: α-haloketones, thioamides, acetophenones, isocyanides, thioureas, Hantzsch cyclization, thiosemicarbazides, thiazoles.

1. INTRODUCTION

Thiazole derivatives are aromatic five-membered ring heterocyclic compounds that contain both sulfur and nitrogen at 1 and 3 positions (Fig. **1**). Thiazoles are members of the azoles or 1,3-azoles, heterocyclic compounds that include imidazoles and oxazoles. Thiazole-containing compounds are found in a wide variety of bioactive molecules and natural products as well as synthetic sources. Some naturally occurring thiazoles play important roles in human life, such as vitamin B1 (thiamin) and the penicillin antibiotic family. Many thiazoles possess a wide spectrum of bioactivities such as antibacterial, antiprotozoal, antimalarial, anticancer, anti-allergic, gene modulating, anti-schizophrenia, antihypertension, anti-inflammation, and anti-HIV activities. The use of thiazole derivatives in other fields such as organic materials, cosmetics, and organic synthesis has also been widely reported.

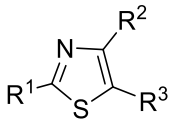

Fig. (1). Structure of thiazole derivatives.

1.1. Antimicrobial Activity

Sulfathiazole **1** is a thiazole-based compound used as a short-acting sulfa drug. Sulfathiazole is effective against a wide range of gram-positive and gram-negative pathogenic microorganisms (Fig. **2**). Today it is rarely used in humans due to the appearance of more effective and less toxic drugs. Cefixime **2** is an antibiotic medication used to treat a number of bacterial infections such as otitis media, strep throat, pneumonia, urinary tract infections, gonorrhea, and Lyme disease (Fig. **2**). Cefovecin **3** is a broad-spectrum, third-generation cephalosporin antibiotic administered by subcutaneous injection. Abafungin **4** is a broad-spectrum antifungal agent used for the treatment of dermatomycoses (Fig. **2**) [1].

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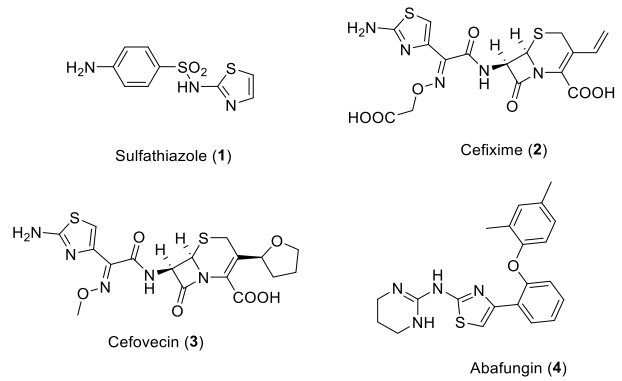


Fig. (2). Thiazole derivatives as antimicrobial agents.

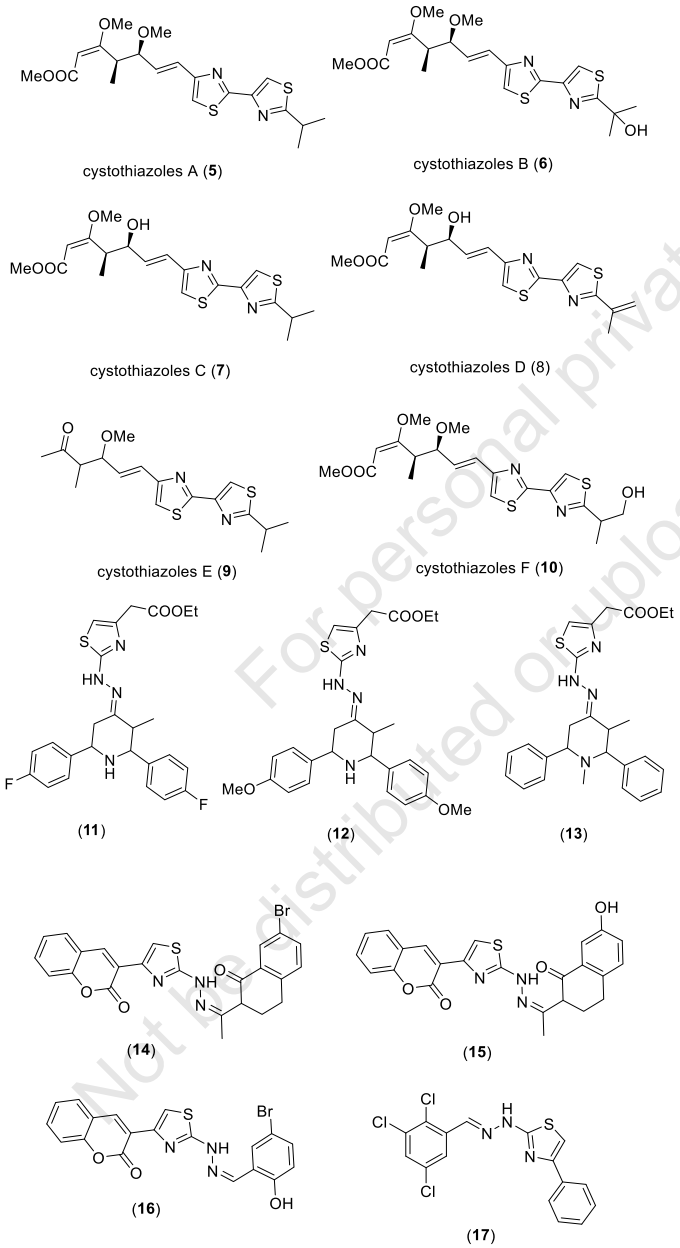
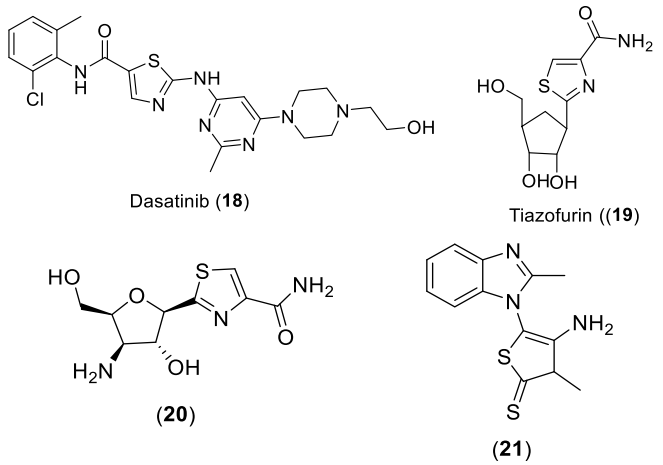


Fig. (3). Thiazole derivatives with antimicrobial activity.

Sakagami *et al*. isolated cystothiazoles A-F (**5-10**) from the myxobacterium culture broth of *Cystobacter fuscus*. Bioactive investigation revealed that these compounds have potent antifungal activity against the phytopathogenic fungus *Phytophthora capsici* (0.05-5 mg/disk) and can serve as a series of new antibiotics (Fig. **3**) [2]. Aridoss *et al.* reported the stereospecific synthesis of some thiazole derivatives and the examination for antimicrobacterial activity against *Mycobacterium tuberculosis*. The result indicated that compounds **11-13** exhibited two-fold enhanced potency than rifampicin, the reference drug (Fig. **3**) [3]. Arshad *et al.* prepared a new series of thiazolylcoumarin derivatives and examined *in vitro* for antibacterial activity against *Mycobacterium tuberculosis* and *Candida albicans*. Three compounds **14-16** showed significant activity (Fig. **3**) [4]. Sarojini *et al*. prepared a diverse range of 2-substituted 4-(2,5-dichloro thienyl)-1,3-thiazoles and screened for their antifungal and antibacterial activities. Among tested compounds, compound **17** exhibited good antifungal and antimicrobial activities (Fig. **3**) [5].

1.2. Anticancer and Antitumor Activity

Dasatinib **18** is a thiazole derivative used to treat people with chronic myeloid leukemia and people with acute lymphoblastic leukemia who are positive for the Philadelphia chromosome [6]. Tiazofurin **19** is a drug that acts as an inhibitor of the enzyme IMP dehydrogenase (Fig**. 4**). Popsavin *et al*. prepared a novel tiazofurin analog, 2-(3-amino-3-deoxy-β-D xylofuranosyl) thiazole-4- carboxamide **20,** and tested *in vitro* for antiproliferative activity against a panel of human tumor cells. This heterocycle is approximately 100 times more potent than tiazofurin in terms of cytotoxicity against K562 cells (Fig. **4**) [7]. Ramla *et al*. prepared a diverse range of 1-substituted- 2-methyl-5-nitrobenzimidazoles and evaluated them for antitumor activity. Compound **21** was found to exhibit significant anti-tumor activity [8]. A new series of 3,4-diarylthiazol-2(3*H*)-ones and 3,4-diarylthiazol-2(3H)-imines were prepared and examined by Liu *et al*. for their cytotoxicity in a panel of human cancer cell lines (Fig. **3**). Two compounds, **22** and **23,** possessed potential anticancer activity against human CEM cells with IC_{50} values of 0.12 and 0.24 μM, respectively (Fig. **4**) [9].



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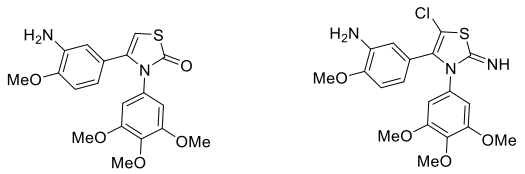


Fig. (4). Thiazole derivatives with anticancer and antitumor activity.

1.3. Anthelmintic Activity

Levamisole **24** is an anthelmintic drug used for the treatment of parasitic worm infections. Specifically, it is used for ascariasis and hookworm infections. Levamisole acts as a nicotinic acetylcholine receptor agonist that causes continued stimulation of the parasitic worm muscles, leading to paralysis (Fig. **5)** [10]. Niridazole **25** is a schistosomicide used to treat schistosomiasis, the helminthic disease caused by certain flatworms from the genus *Schistosoma* (Fig. **5**) [11]. Thiabendazole **26** is an antiparasitic agent used to control roundworms, hookworms, and other helminth species which infect wild animals, livestock, and humans (Fig. **5**) [12, 13]. Cambendazole **27** is a veterinary anti-parasitic drug, which was approved by the FDA for the treatment of worm infections in horses. Nitazoxanide **28** has been marketed as a broad-spectrum antiparasitic medication that is used in medicine for the treatment of various helminthic, protozoal, and viral infections (Fig. **5)** [14].

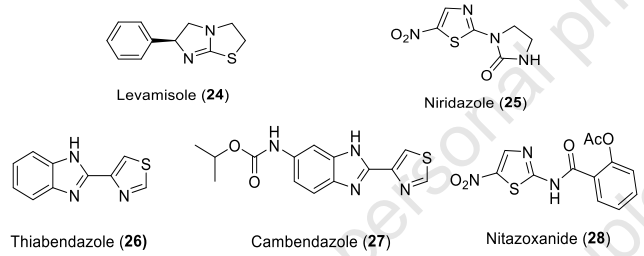


Fig. (5). Thiazole derivatives as anthelmintic agents.

1.4. Anti-inflammatory Activity

Meloxicam **29** has been marketed as a nonsteroidal anti-inflammatory drug to treat pain and inflammation in rheumatic diseases and osteoarthritis by blocking cyclooxygenase, the enzyme responsible for converting arachidonic acid into prostaglandin H_2-the first step in the synthesis of rostaglandins, which are mediators of inflamemation (Fig. **6)**. Fentiazac **30** is a nonsteroidal antiinflammatory agent used for joint and muscular pain (Fig. **6)**. Kalkhambkar *et al*. demonstrated the synthesis of a series of triheterocyclic thiazoles containing coumarin and carbostyril (1-aza coumarin) and the evaluation for their *in vitro* analgesic and anti-inflammatory activities using acetic acid-induced writhing. Among the studied heterocycles, compounds **31** and **32** exhibited significant analgesic and anti-inflammatory activities (Fig. **6**) [15]. Giri *et al*. synthesized a variety of 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl- 3*H*-quinazoline-4-one derivatives and evaluated for anti-inflammatory activity *in vivo* for acute inflammation. Among them, compounds **33** and **34** were found to be the most promising dual inhibitors of NF-kB and AP-1 mediated transcriptional activation with an IC_{50} of 3.3 mM for both (Fig. **6)** [16]. Holla *et al*. described the construction of a series of arylaminothiazoles and a series of arylidene/5-aryl-2-furfurylidene hydrazinothiazoles and the examination for their anti-inflammatory activities, using the carrageenan-induced rat paw edema method. Compounds **35** and **36** displayed good anti-inflammatory activity in comparison to the standard ibuprofen drug (Fig. **6)** [17].

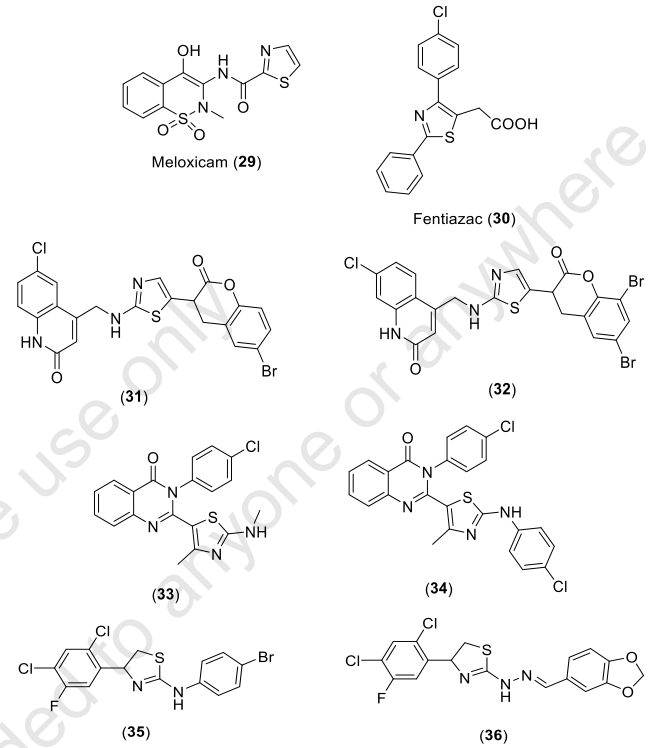


Fig. (6). Thiazole derivatives with anti-inflammatory activity.

1.5. Antidiabetic Activity

Troglitazone is **37,** a thiazolidinediones antidiabetic drug, used for people with diabetes mellitus type 2 (Fig. **7**) [18]. Rosiglitazone **38** is a thiazolidinedione antidiabetic drug. It functions as an insulin sensitizer by binding to the PPAR in fat cells and making the cells more responsive to insulin (Fig. **7)** [19]. Pioglitazone is another thiazolidinedione anti-diabetic medication used to **39** treat type 2 diabetes. Lobeglitazone **40** is a thiazolidinedione antidiabetic drug functioning in the same way as rosiglitazone (Fig. **7)** [20].

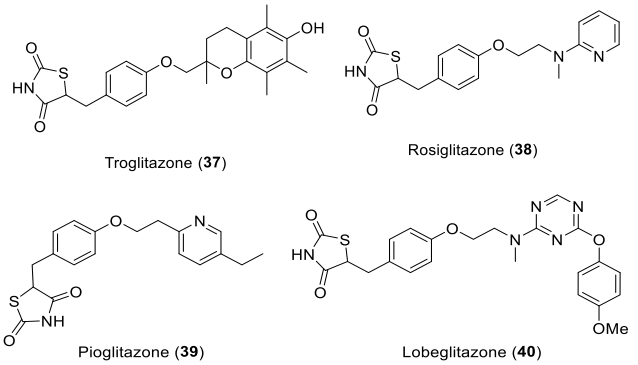


Fig. (7). Thiazole derivatives with antidiabetic activity.

1.6. Anti-HIV Activity

Ritonavir **41** has been marketed as an antiretroviral medication used in combination with other medications to treat HIV/AIDS (Fig. **8**) [21]. Turan-Zitouni *et al*. reported the synthesis of a series of 3,4-diaryl-3*H*-thiazol-2-ylidene) pyrimidin-2-yl amine derivatives and the evaluation them for anti-HIV activity. Among the examined compounds, compound **42** showed excellent activity (Fig. **8**) [22]. Barreca *et al*. described the synthesis of a diverse range of 2,3-diaryl-1,3-thiazolidin-4-ones and the screening for anti-HIV activity. The bioassay revealed that compounds **43** and **44** are effective for inhibiting HIV-1 replication at nanomolar concentrations (Fig. **8**) [23].

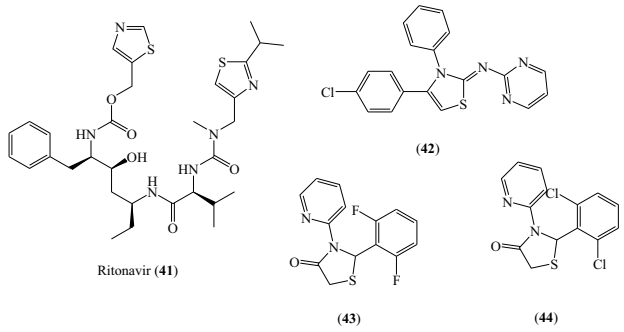


Fig. (8). Thiazole derivatives with anti-HIV activity.

1.7. Anticonvulsant Activity

Dawood *et al*. synthesized a novel series of thiazoline derivatives and evaluated them for their anticonvulsant activities. Among tested compounds, compound **45** was found to exhibit good anticonvulsants (Fig. **9**) [24]. Siddiqui *et al*. prepared a variety of 3-[4- (substituted phenyl)-1,3-thiazol-2-ylamino]-4-(substituted phenyl)-4,5-dihydro-1*H*-1,2,4-triazole-5-thiones and examined them for *in vivo* anticonvulsant activity *via* MES and scPTZ. Among them, compounds **46** and **47** displayed significant anticonvulsant activity with ED50 values 23.9 mg/kg and 13.4 mg/kg respectively in the MES screen and 178.6 mg/kg and 81.6 mg/kg respectively in scPTZ test (Fig. **9**) [25]. Siddiqui *et al*. synthesized some heteroaryl semicarbazones and investigated them for anticonvulsant activity utilizing scPTZ and MES tests at 30, 100, and 300 mg/kg dose levels. Compounds **48** and **49** exhibited significant anticonvulsant activity at a 30 mg/kg dose level comparable to the standard drug phenytoin (Fig. **9**) [26].

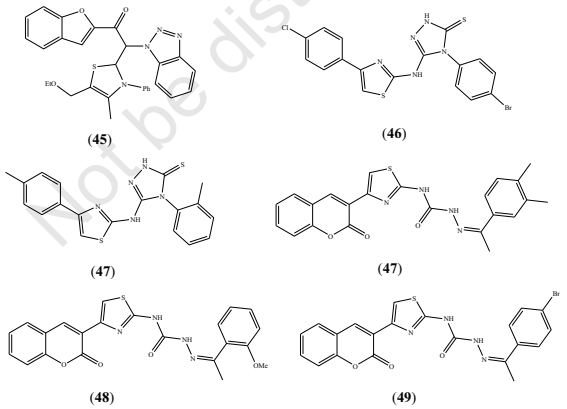


Fig. (9). Thiazole derivatives with anticonvulsant activity.

1.8. Other Activity

Nizatidine **50** and famotidine **51** are histamine H_2 receptor antagonists that inhibit stomach acid production (Fig. **10**). These drugs are commonly used in the treatment of peptic ulcer disease and gastroesophageal reflux disease [27, 28]. Pramipexole **52** is a medicine used to treat Parkinson's disease and restless legs syndrome. Arotinolol is a medication used in the treatment of high blood pressure (Fig. **10**) [29]. Sodelglitazar **53** is an inhibitor of peroxisome proliferator-activated receptor delta (PPARδ) (Fig. **10**) [30]. Thiazole derivative **54** with two aryl and one methyl substituents is a cyclooxygenase-2 inhibitor (Fig. **10**) [31]. Febuxostat **55** is a urate-lowering drug (Fig. **10)** [32]. Thiazole-based compounds have also been reported to have other bioactivities such as antitubercular [33] antimalarial [34].

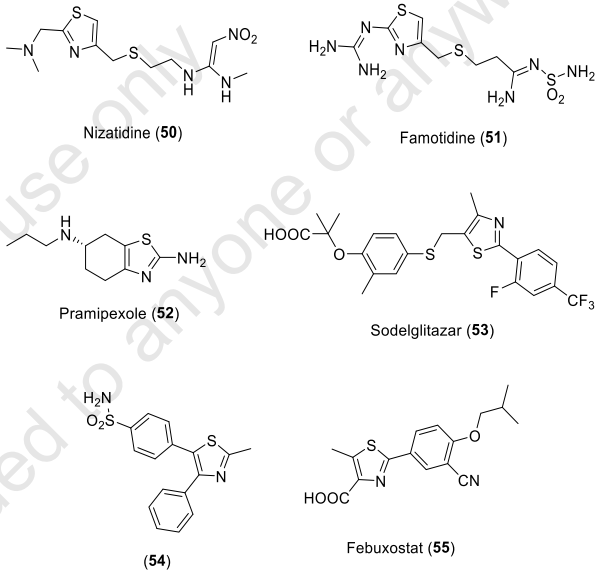


Fig. (10). Thiazole derivatives with other bioactivities.

1.9. Other Applications

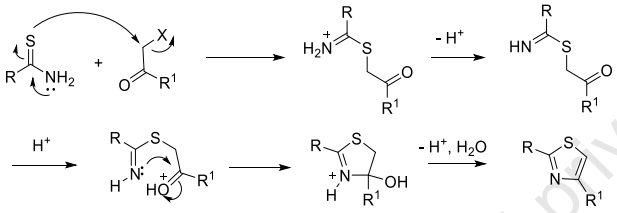
The biological activities of thiazole derivatives have also been described in some review articles [35-37]. Furthermore, the use of thiazole derivatives in other fields has also been well documented. In organic synthesis, drug synthesis, and synthesis of natural products, thiazole derivatives can be served as important intermediates or building blocks [38-44]. Thiazole-based compounds have well been applied in organic materials such as solar cells, organic semiconductors, chemosensors, fluorescent dyes, and liquid crystals [45-59]. The use of these heterocycles in cosmetics has also been documented [60, 61]. Some thiazole derivatives can be served as useful ligands [48, 62, 63].

With such broad applicability, increasing attention has been paid to synthesizing thiazole-containing compounds. The Hantzsch thiazole synthesis has still received great interest from chemists. Furthermore, numerous novel methods for the synthesis of thiazole-based compounds have been developed. In the literature, several thiazole synthesis review articles have been published. However, most of them are quite outdated [64, 65] or do not cover all aspects of thiazole synthesis [36, 66-73]. In addition, in these review articles,

reaction mechanisms are usually ignored. In this review, we give a brief description of the bioactivities of thiazole derivatives and a systematic overview of thiazole synthesis, which covers all aspects of thiazole synthesis studies dating back to 2012. We also try to describe reaction mechanisms as much as possible. The article might be useful for chemists who work in pharmaceutical, organic synthesis, and synthesis of natural products. Recently, we have reported reviews on the synthesis of furans, pyrroles, thiophenes, oxazoles, benzofurans, and benzothiophenes [74-78]. This article is a continuation of our investigation on the synthesis of aromatic five-membered ring heterocycles.

2. THE HANTZSCH THIAZOLE SYNTHESIS

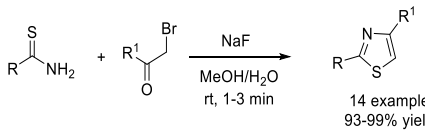
The Hantzsch thiazole synthesis is a reaction between α-haloketones and thioamides to form thiazole derivatives [79]. The general reaction mechanism of this reaction is outlined in Scheme **1**. This is one of the oldest and most straightforward to access thiazole derivatives. Various modifications of this method have been developed recently.



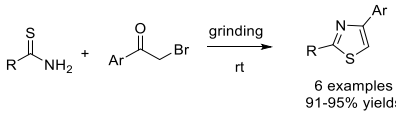
Scheme 1.

2.1. Reaction between Thioamide and α-Haloketones

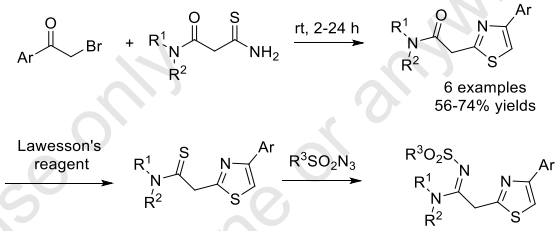
Banothu *et al*. introduced a simple, mild, and efficient method for the synthesis of 2,4-disubstituted 1,3-thiazoles by the reaction between phenacyl bromides/3-(2-bromoacetyl)-2*H*-chromen-2-one and thiourea/phenylthiourea catalyzed by sodium fluoride. Attractive features of the synthesis include shorter reaction times, easy work-up procedure, mild reaction conditions, and excellent yields of products (Scheme **2**) [80]. Heravi *et al*. described a simple and convenient protocol for the construction of 2, 4-disubstituted thiazoles *via* condensation reactions of α-halo carbonyl compounds with thiourea or thioacetamide. The synthesis was performed at room temperature under grinding conditions and led to products in good yields without using any solvent (Scheme **3**) [81]. Il'kin *et al*. obtained 2-thiazolyl acetamides in moderate yields through reactions of thioamides with bromoaceto-phenones under mild conditions, The products could be further transformed into 2-thiazoleacetic acid *N*-sulfonyl amidines (Scheme **4**) [82]. Zhai *et al*. demonstrated an efficient approach to access a series of ethyl (*Z*)-2-(2-substituted-thiazol-4-yl)pent-2-enoates from ethyl (*E*/*Z*)-2-(2-bromoacetyl)pent-2-enoate and thioureas or thioamides. A diverse range of products was achieved in good to excellent yields under mild reaction conditions (Scheme **5**) [83]. Asma *et al*. announced an efficient approach towards 2-(3-(aryl)-5-(4-(prop-2-ynyloxy) phenyl)-4,5-dihydropyrazol-1-yl)-4-(3-arylsydnone-4-yl) thiazoles. The Hanztzsch synthesis was performed at room temperature and furnished products with moderate yields (Scheme **6**) [84].



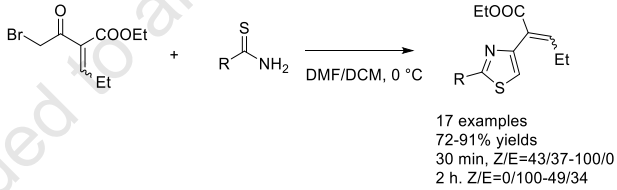
Scheme 2.



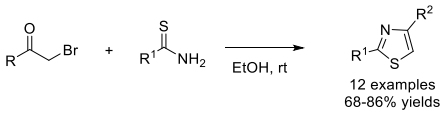
Scheme 3.



Scheme 4.



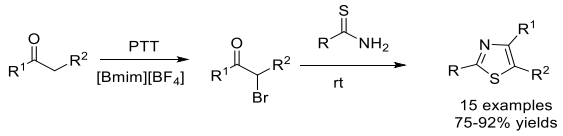
Scheme 5.



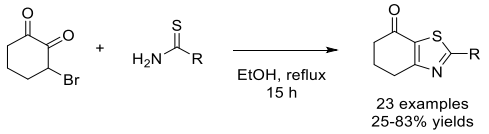
Scheme 6.

Muthyala *et al*. introduced a strategy for the construction of 2,4-disubstituted thiazoles from substituted ketones and thioamide or thiourea. In the first step, α-bromo ketones were generated from ketones and phenyl trimethyl ammonium tribromide *in situ*. A wide range of thiazole products was afforded in good to excellent yields (Scheme **7**) [85]. Guernon *et al*. reported the preparation of fused thiazoles starting from 3-bromocyclohexane-1,2-dione and thioamides. The Hanztzsch thiazole synthesis provided bicyclic thiazoles in reasonable to good yields with a wide substrate scope (Scheme **8**) [86]. Suntsova *et al*. established a protocol to access a series of fluorophores based on a thiazole core. Thiazole-2-acrylonitrile fluorophores were achieved in good to excellent yields without using a catalyst (Scheme **9**) [87]. Kumar *et al*. investigated a simple, efficient approach for the synthesis of diarylthiazoles from α-tosyloxy ketones with a variety of thioamides based on the Hanztzsch reaction. The synthesis featured some advantages such as the absence of

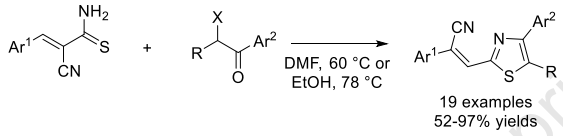
metal catalyst, the use of water as a solvent, and high efficiency (Scheme **10**) [88]. In an analogous study, Prakash *et al*. developed a method to synthesize 2-substituted 4-styrylthiazoles from the reaction of (*E*)-4-arylbut-3-en-2-ones with [(hydroxy(tosyloxy)iodo]benzene (HTIB) followed by treatment with thioureas or thioamides. Products were obtained in high yields with broad substrate scope (Scheme **11**) [89].



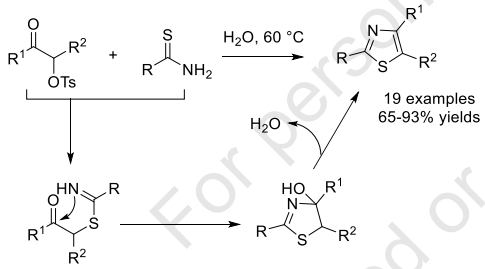
Scheme 7.



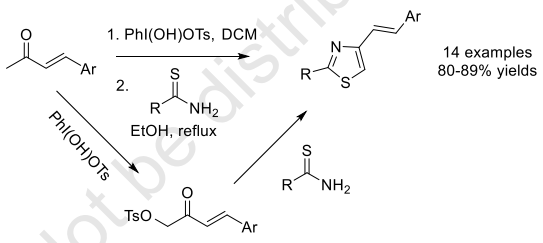
Scheme 8.



Scheme 9.

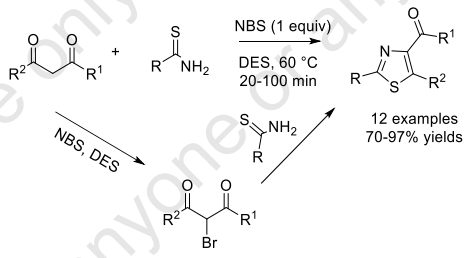


Scheme 10.

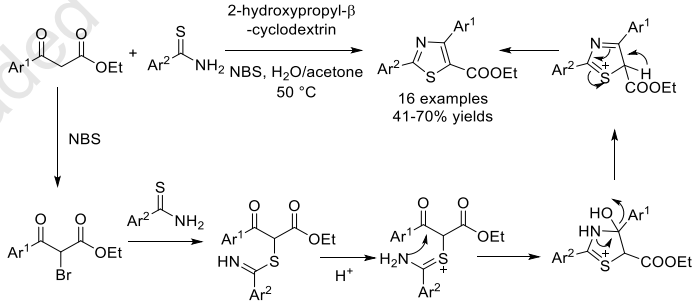


Scheme 11.

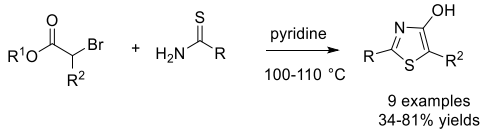
Azizi *et al.* accomplished the synthesis of thiazole by an efficient consecutive three-component reaction involving active methylene compounds, thioamides or thioreas, and NBS in a deep eutectic solvent. Various thiophene derivatives were produced in good to excellent yields in relatively short reaction times (Scheme **12**) [90]. Zhang *et al*. presented a novel strategy to access 2,4-diphenyl thiazoles from ethyl benzoyl acetate, NBS, and thiobenzamides. The synthesis involved a sequence of bromination of ethyl benzoyl acetate with NBS in the presence of 2-hydroxypropyl-β-cyclodextrin and a Hanztzsch cyclization. Attractive features of the synthesis include milder reaction conditions, good to excellent yields of products, relatively short reaction time, and simpler work-up procedure (Scheme **13**) [91]. Täuscher *et al*. disclosed a method to prepare 4-hydroxy-1,3-thiazoles from thioamides and α-halogeno ester. Various products were provided in reasonable yields under thermal conditions (Scheme **14**) [92]. Tomassetti *et al*. established an efficient approach towards 2,4-disubstituted-5-acylamino-1,3-thiazoles through a reaction between α-chloroglycinates and thiobenzamides. The synthesis was carried out under mild reaction conditions without using any catalyst and delivered products in moderate to excellent yields (Scheme **15**) [93].



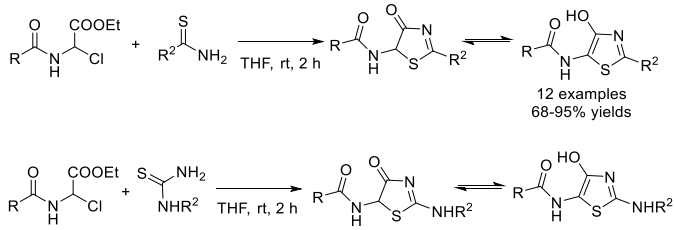
Scheme 12.



Scheme 13.

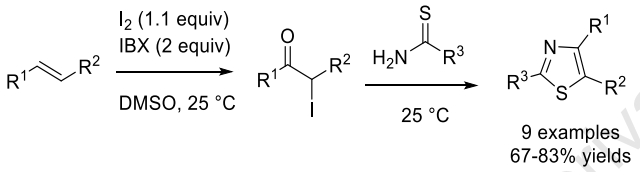


Scheme 14.

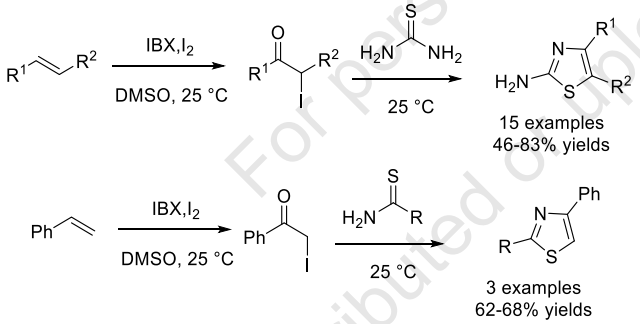


Scheme 15.

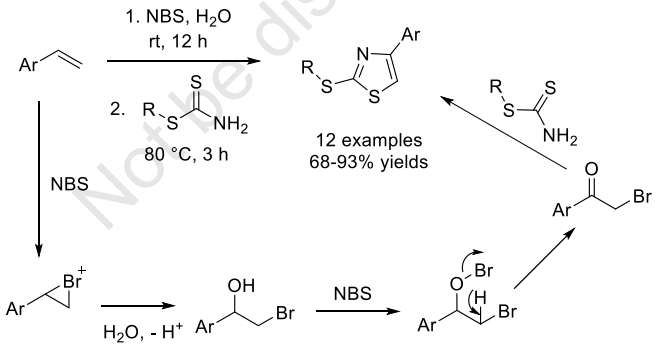
The Donohoe group described the preparation of thiazole from alkenes and thioamides. Initially, alkenes were transformed into α-iodo ketones by treatment with I_2 and IBX in DMSO. Subsequently, reactions between these intermediates with thioamide afforded the corresponding thiazoles. The synthesis was performed under mild conditions and gave products in high yields (Scheme **16**) [94]. In their subsequent study, this approach was applied for both thioamides and thiureas to synthesize thiazole derivatives in good yields under mild conditions (Scheme **17**) [95]. Moghaddam *et al*. introduced an efficient strategy to access thiazole heterocycles from styrenes and alkyl dithiocarbamates. Treatment of styrenes with NBS generated α-bromo ketones, which then were converted to thiazoles *via* the Hanztzsch cyclization with alkyl dithiocarbamates (Scheme **18**) [96]. Halimehjani *et al*. demonstrated a protocol for the synthesis of 4-substituted-2-(alkylsulfanyl)thiazoles from dithiocarbamates and *α*-halocarbonyl in high yields. The synthesis could be performed in one-pot for acetophenones and dithiocarbamates using I_2/CuO as the iodination reagent. Good yields of products were also observed (Scheme **19**) [97].



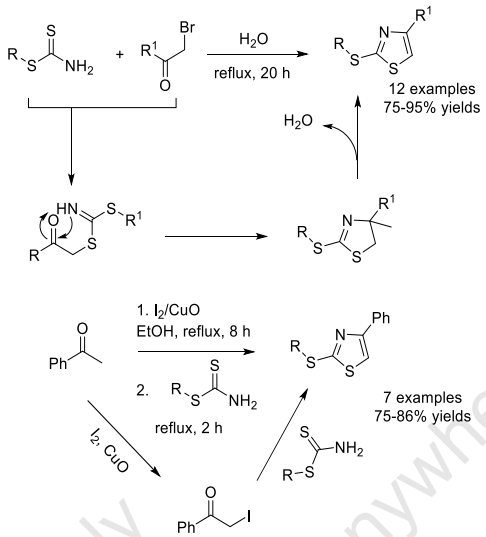
Scheme 16.



Scheme 17.

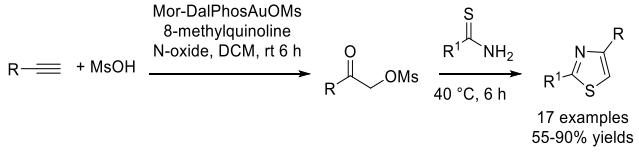


Scheme 18.

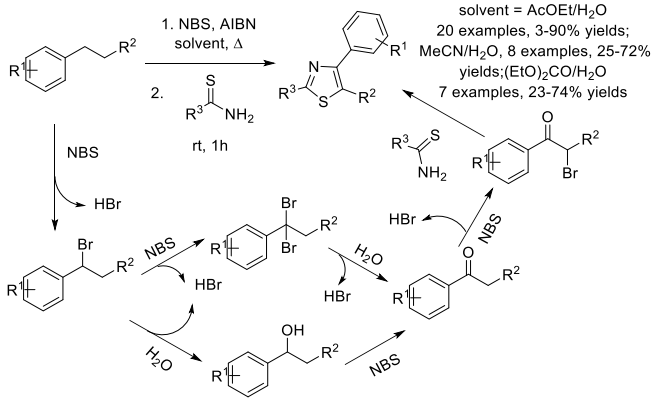


Scheme 19.

Wu *et al*. presented the synthesis of 2,4-disubstituted thiazoles from terminal alkynes, MsOH, and thioamides. Initially, terminal alkynes were transformed into methanesulfonyloxymethyl ketones using gold(I) complex catalyst with Mor-DalPhos as the *P*,*N*-bidentate ligand. Hanztzsch-type condensation of these ketones with thioamides afforded thiazole derivatives. The synthesis could be performed in a one-pot procedure and gram-scale for one substrate (Scheme **20**) [98]. Shibasaki and Togo announced the preparation of thiazoles from alkylarenes, *N*-bromo-succinimide, and arenethioamides or thiureas. Alkylarenes were converted to phenacyl bromides by treatment with NBS. Subsequently, Hanztzsch cyclization occurred to form the corresponding thiazoles. The one-pot synthesis was suitable for a wide range of substrates without using a metal catalyst (Scheme **21**) [99].

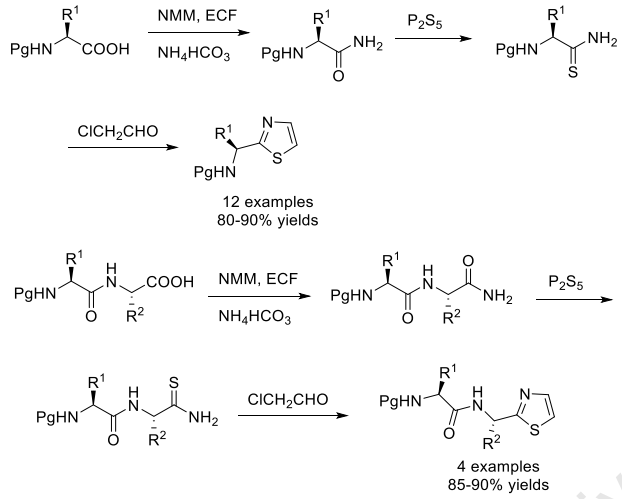


Scheme 20.

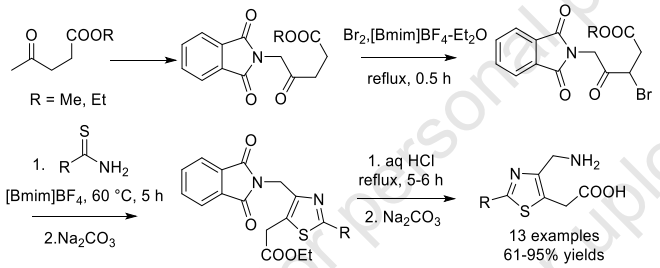


Scheme 21.

Lalithamba *et al*. designed a protocol to access thiazoles from the corresponding thioamides derived from protected amino acids. Products were obtained from protected amino acids in three steps in high yields (Scheme **22**) [100]. Zavozin *et al*. designed a multi-step protocol for the assembly of 2-(4-aminomethyl-thiazol-5-yl) acetic acid derivatives starting from γ-ketoesters. The synthesis was completed *via* a sequence of nucleophilic substitution, bromination, Hantzsch-type heterocyclization, and Gabriel-like deprotection reactions (Scheme **23**) [101].



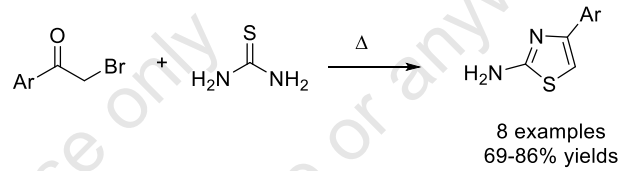
Scheme 22.



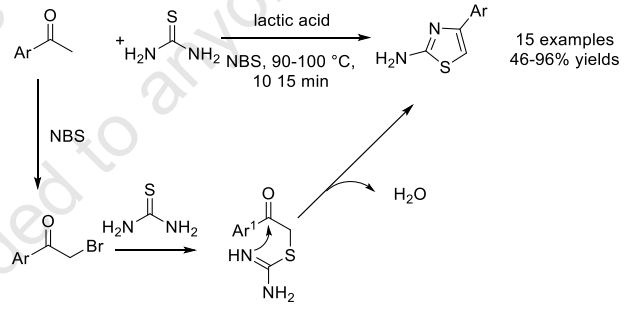
Scheme 23.

2.2. Reaction between Thiurea Derivatives and α-Haloketones

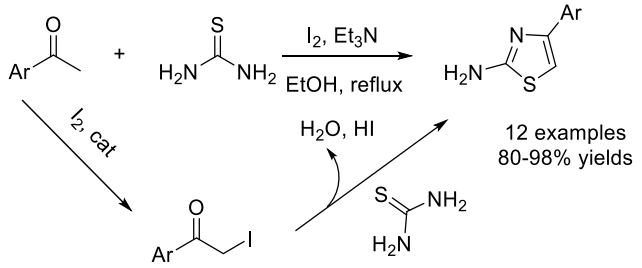
Facchinetti *et al.* completed a simple approach for the synthesis of 2-aminothiazoles based on the Hantzsch condensation without using any catalyst. Products were achieved in high yields under solvent-free conditions (Scheme **24**) [102]. Bodireddy *et al*. reported an environ-mentally benign strategy to prepare 2-aminothiazole derivatives from acetophenones and thiurea. The synthesis proceeded *via in situ* regioselective α-bromination using *N*-bromosuccinimide followed by cyclization with thiourea at 90-100°C. The major attractive features of the synthesis include short reaction times, easy work-up, good yield of products, scalability, inexpensive and biodegradable catalyst, and readily available starting materials (Scheme **25**) [103]. In an analogous study, Abedi-Jazini *et al*. examined the modified Hantzsch thiazole synthesis from thiurea and α-iodoaceto-phenones, which were generated from acetophenones and iodine catalyzed by triethylamine (Scheme **26**) [104]. The Safari group prepared asparagine functionalized aluminum oxide nanoparticles (Asp-Al_2O_3) and applied this material as the catalyst for the rapid synthesis of 2-aminothiazoles from acetophenones, iodine, and thiurea based on Hantzsch cyclization. Products were furnished in excellent yields, and the nano catalyst could be recycled for five runs without a significant decrease in activity (Scheme **27**) [105]. Later, the group performed a one-pot synthesis of 2-aminothiazoles *via* the reaction of thiourea with methylcarbonyls in the presence of iodine as an oxidant reagent. The synthesis was based on the Hantzsch reaction of thiourea and α-iodo carbonyls, which were generated *in situ* from carbonyl compounds and iodine catalyzed by asparagine. The main advantages of the synthesis include operational simplicity, easy work-up procedure, economical and biodegradable catalyst, and high yields of the products (Scheme **28**) [106].



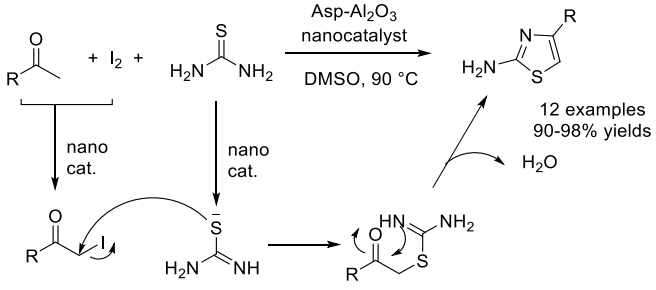
Scheme 24.



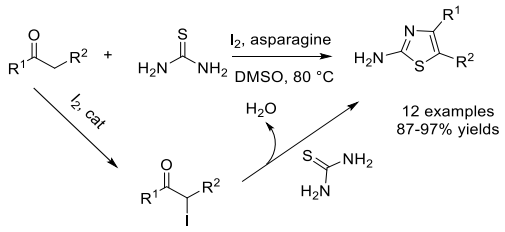
Scheme 25.



Scheme 26.

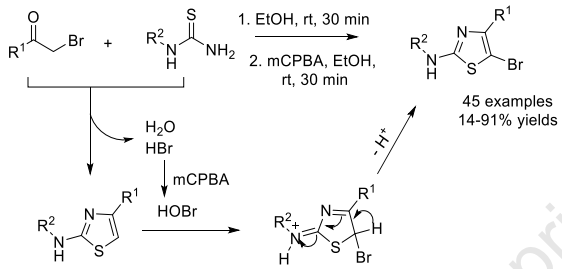


Scheme 27.

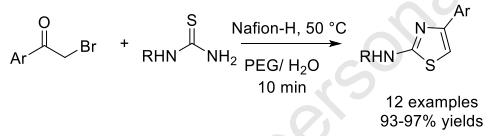


Scheme 28.

Prevost *et al*. investigated a protocol to access highly functionalized 5-bromo-2-amino-1,3-thiazoles from α-bromomethyl-ketones and thiosemicarbazides. A diverse range of products was obtained in reasonable yields under mild conditions (Scheme **29**) [107]. Kidwai *et al*. developed a simple and efficient approach for the synthesis of 2-amino-thiazoles from α-bromomethyl-ketones and thiosemi-carbazides. The synthesis featured some advantages such as short reaction time, simple work-up, reusability of the catalyst, and high yields of products (Scheme **30**) [108].

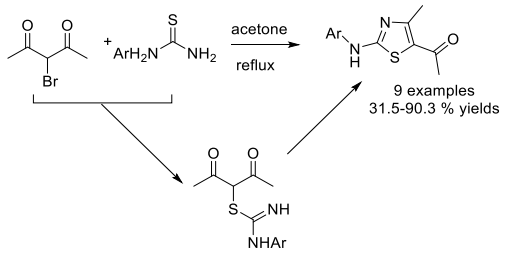


Scheme 29.

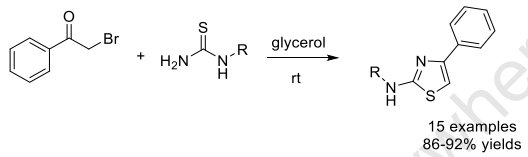


Scheme 30.

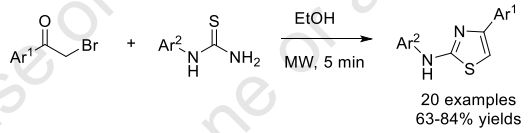
Shi *et al*. discovered a method towards 5-acetyl-4-methyl-2-(substituted anilino) thiazoles by the condensation of *N*-aryl thioureas with 3-bromo-acetylacetone. The synthesis was performed without using any catalyst and gave products in short times (Scheme **31**) [109]. Narsaiah *et al*. disclosed a protocol to prepare thiazole derivatives by the Hantzsch-type condensation between α-bromoketones and thiourea/ thioa-mides. Attractive features of the synthesis include catalyst-free and mild conditions, relatively short reaction times, recyclability of the solvent, and high efficiency (Scheme **32**) [110]. Sun *et al*. examined an approach to construct 4-diaryl-1,3-thiazole-2-amines from α-bromoke-tones and thiurea derivatives under microwave irradiation. A diverse range of products was obtained in moderate to good yields in a short reaction time without using any catalyst (Scheme **33**) [111]. Deepti *et al*. investigated a method for the preparation of 2-aminothiazole derivatives by the reaction of α-bromoketones and thioamides. The advantageous features of the synthesis include shorter reaction times, simple experimental procedures, and the absence of catalyst and solvent (Scheme **34**) [112].



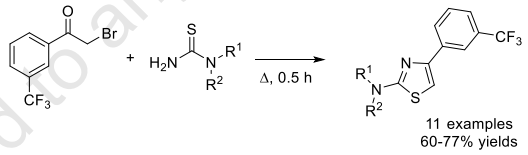
Scheme 31.



Scheme 32.

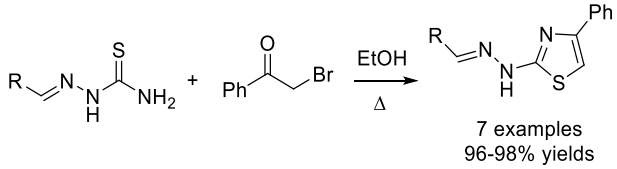


Scheme 33.

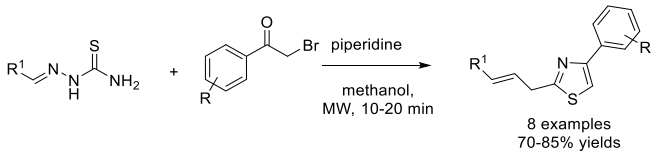


Scheme 34.

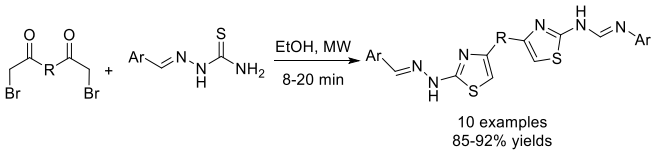
Hassan *et al*. described a facile strategy for the preparation of di- and trisubstituted-1,3-thiazoles starting from 1-aryl-2-bromoethanones and 2-(1-substitutedmethylidene) hydrazine-carbothioamides and cycloalkylidene-*N*-phenyl hydrazine-ecarbo-thioamides. The method featured some advantages such as short reaction time, absence of catalyst, and high yields of products (Scheme **35**) [113]. Namera *et al*. reported the synthesis of thiazole derivatives by the cyclocondensation reaction between α-bromoketones and thiurea derivatives under microwave irradiation. Products were achieved in good yields in short times with a simple work-up procedure (Scheme **36**) [114]. Baba *et al*. completed the preparation of thiazole-substituted dibenzofurans starting from dibenzofuran derivatives and substituted thiosemicarbazones under micro-wave irradiation. The new bioactive thiazole derivatives were produced in high yields in short times (Scheme **37**) [115].



Scheme 35.

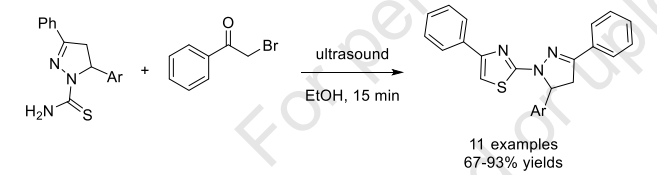


Scheme 36.

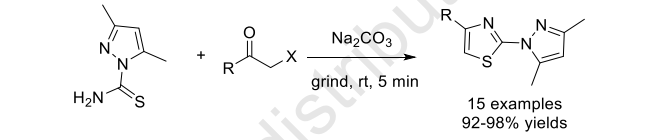


Scheme 37.

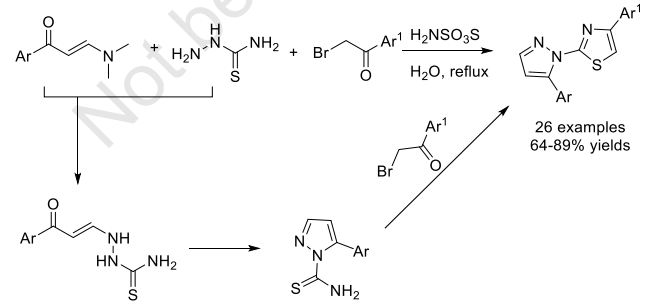
Venzke *et al*. designed a rapid protocol for the synthesis of a series of 2-(3,5-diaryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazoles under ultrasonic irradiation. The sono-chemical synthesis delivered some attractive features such as simple work-up, short reaction time, catalyst-free conditions, and high yields of products (Scheme **38**) [116]. In a similar report, Aggarwal *et al*. described an efficient and facile approach for the construction of 4-substituted-2-(3,5-dimethylpyrazol-1-yl)thiazoles by grinding an equimolar mixture of *α*-haloketones with 3,5-dimethylpyrazol-1-thiocarboxamide. Advantages of the synthesis include short reaction time, environmentally benign conditions, broad substrate scope, and excellent yields of products (Scheme **39**) [117]. Sridevi *et al*. discovered an efficient protocol to synthesize pyrazolyl-thiazole derivatives starting from (*E*)-*N,N*-dimethyl-3-phenylprop-1-en-1-amines, substituted phen-acyl bromides, and 2-thiosemicarbazide. The solvent-free synthesis was suitable for a diverse range of substrates and furnished products in moderate to excellent yields (Scheme **40**) [118].



Scheme 38.

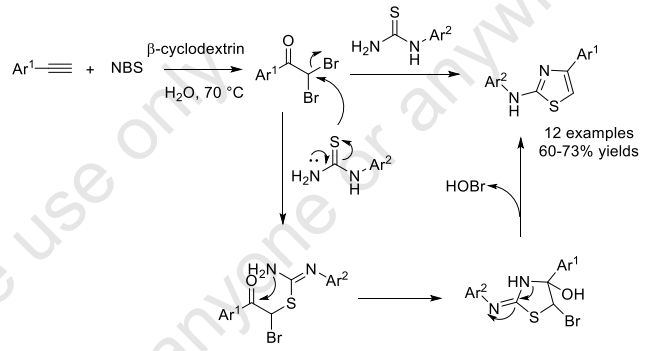


Scheme 39.

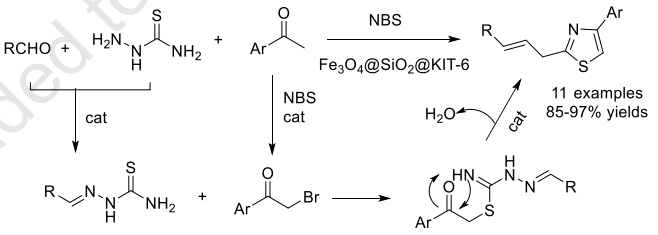


Scheme 40.

Madhav *et al*. demonstrated a protocol towards thiazoles selenazoles from alkynes and thiurea or its derivatives *via* the formation of 2,2-dibromo-1-phenylethanone. The one-pot synthesis was catalyzed by β-cyclodextrin and provided products in good yields (Scheme **41**) [119]. Nikpassand *et al*. presented the synthesis of KIT-6 mesoporous silica-coated magnetite nanoparticles and applied this material as the catalyst for the synthesis of a series of 2-hydrazonyl-4-phenylthiazoles from aldehydes, acetophenes, and thiosemicarbazide in aqueous media. The one-pot thiazole synthesis offers some advantages such as high efficiency, simple procedure, mild reaction conditions, and relatively short reaction time. Furthermore, the catalyst could be recycled for six runs without significant decrease in reaction yield (Scheme **42**) [120].

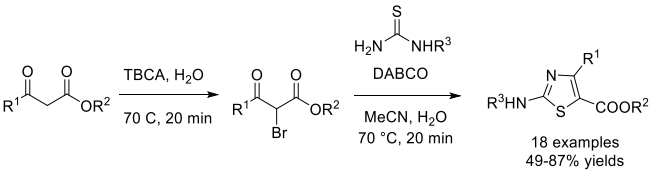


Scheme 41.

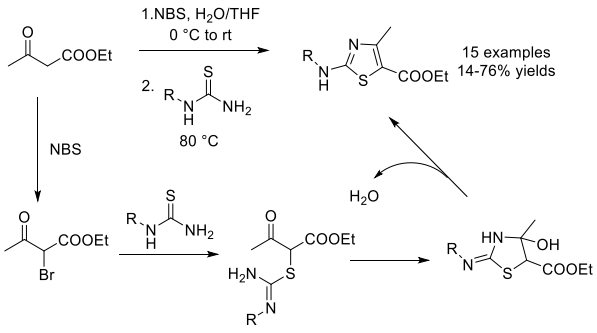


Scheme 42.

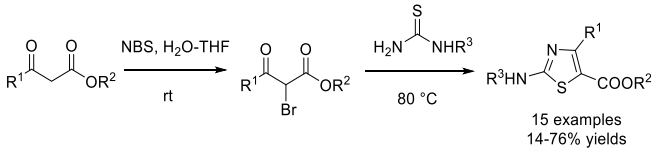
De Andrade group introduced a simple strategy for the construction of thiazole derivatives in one pot from β-ketoesters and thiurea derivatives. The first step involved brommonation of the β-ketoesters by tribromoisocyanuric (TBCA). A library of thiazoles was furnished in reasonable to good yields using DABCO as a catalyst (Scheme **43**) [121]. Later, the group investigated an approach for the assembly of 4-aryl-2-aminothiazoles from styrenes, thioureas, and TBCA. Thiazole derivatives were produced in moderate yields in one pot (Scheme **44**) [122]. Meng *et al*. developed a practical one-pot protocol for the preparation of a series of 2-sustituted-4-methylthiazole-5-carboxylates from acetoacetate, *N*-bromo-succinimide, and thiourea or its derivatives. Products were obtained in reasonable yields under mild conditions (Scheme **45**) [123].



Scheme 43.

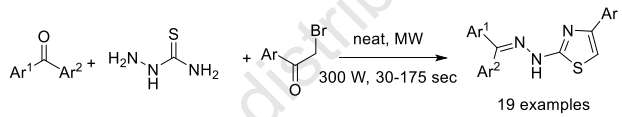


Scheme 44.

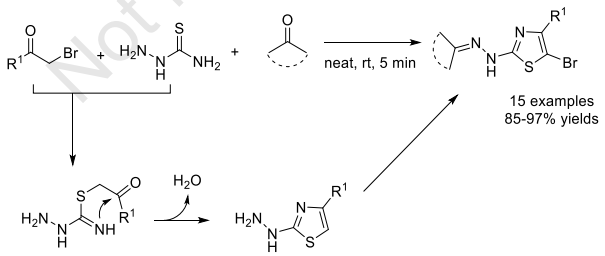


Scheme 45.

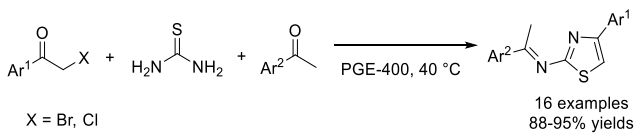
Chinnaraja *et al*. established a rapid synthesis of hydrazinyl thiazoles under solvent and catalyst-free conditions. A diverse range of products was afforded from aryl ketones, thiosemicarbazide, and α-haloketones in moderate to good yields under microwave irradiation (Scheme **46**) [124]. Sujatha *et al*. examined an expeditious method for the construction of 2,4-disubstituted thiazoles from cyclic ketones, thiosemicarbazide, and phenacyl bromides or 3-(2-bromoacetyl)-2*H*-chromen-2-ones in one pot. The protocol exhibited some advantages such as mild reaction conditions, good to excellent yields, solvent-free conditions, and short reaction time (Scheme **47**) [125]. Dawane *et al*. reported a convenient procedure for the preparation of thiazole derivatives from α-haloketone, thiourea, and substituted acetophenones using polyethylene glycol-400 as a solvent. The synthesis was performed under mild reaction conditions resulting in thiazoles in excellent yields with broad substrate scope. The solvent could be recovered and reused for five runs without considerable loss of its activity (Scheme **48**) [126]. In an analogous report, Raut and Bhosale employed polyethylene glycol-300 as a catalyst and a solvent for this condensation reaction. Products were furnished in very high yields with easy work-up and isolation of products (Scheme **49**) [127].



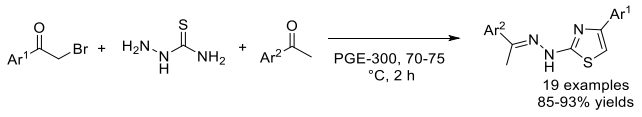
Scheme 46.



Scheme 47.

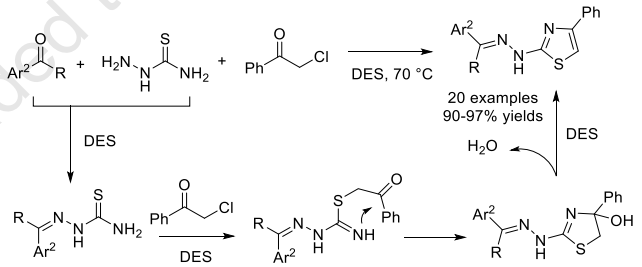


Scheme 48.

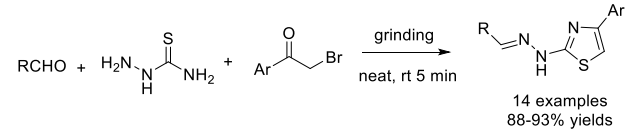


Scheme 49.

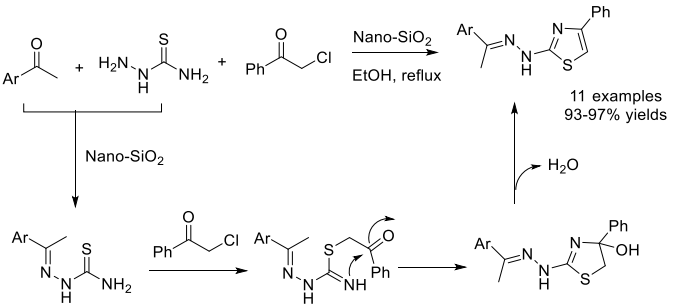
Kaldareh *et al*. accomplished the one-pot synthesis of hydrazinyl-4-phenyl-1,3-thiazoles starting from ketones, phenacyl chloride, and thiosemicarbazide using choline chloride/ urea as a deep eutectic solvent. Excellent yields of products, relatively short reaction times, and broad substrate scope are the main advantages of this method (Scheme **50**) [128]. Ding *et al*. demonstrated a facile one-pot procedure to access 2,4-disubstituted thiazoles from aldehydes, α-bromoketones, and thiosemicarbazide by grinding. The synthesis offered some merits such as short reaction time, absence of catalysts or solvents, high efficiency, simple work-up, and mild reaction conditions (Scheme **51**) [129]. Gholami and Mokhtary disclosed a one-pot strategy to prepare 4-phenyl-hydrazinyl thiazole derivatives by reactions of ketones, phenacyl chloride, and thiosemicarbazide. The nano-SiO_2-catalyzed synthesis gave products excellent yields in short reaction times (Scheme **52**) [130].



Scheme 50.



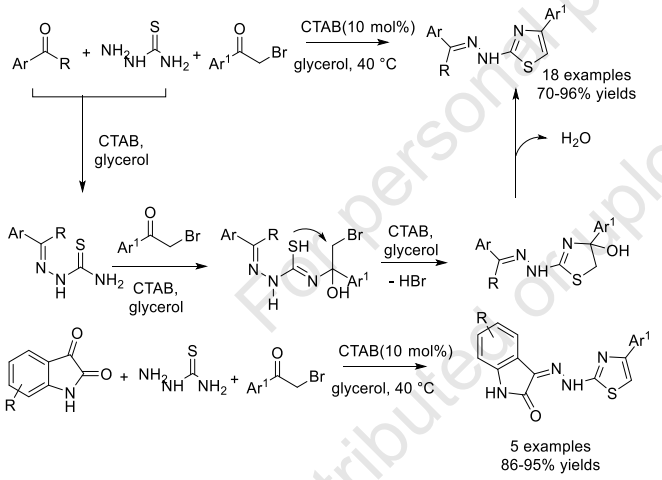
Scheme 51.



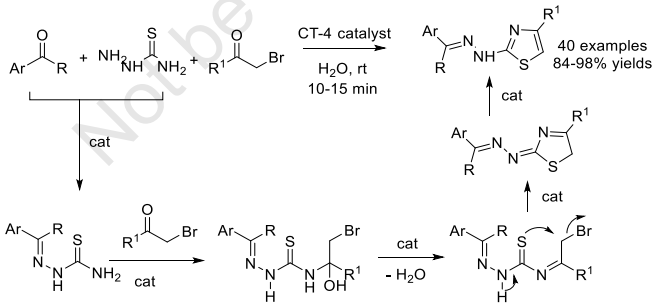
Scheme 52.

Tiwari *et al*. designed a one-pot, multi-component protocol towards 2,4-disubstituted hydrazinyl-thiazoles from

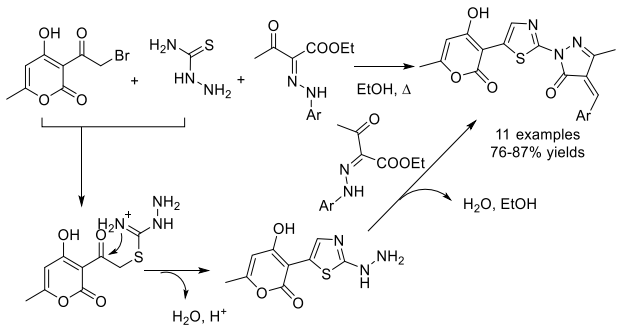
ketones, phenacyl bromide, and thiosemicarbazide catalyzed by micellar in glycerol. Mild reaction conditions, broad substrate scope, simple operation, short reaction times, easy workup procedures, and high yields are the advantages of the method. Furthermore, the synthesis could be expanded to a gram-scale, and the solvent could be recycled five times without affecting reaction yield. Products were also obtained in high yields when isatin was used (Scheme **53**) [131]. Reddy *et al*. informed the construction of a library of hydrazinyl-thiazoles *via* a three-component reaction of aldehydes/ketones with thiosemicarbazide and phenacyl bromides using copper oxide nanoparticles dispersed on titanium dioxide as a catalyst. The synthesis delivered several attractive features such as short reaction times, the use of H_2O as a solvent, mild reaction conditions, and high efficiency. Moreover, the developed catalyst can be recovered and reused 5 times without a significant decrease in reaction yield (Scheme **54**) [132]. Penta and Vedula introduced a convenient one-pot method for the assembly of thiazolyl-pyrazolones by reaction of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*pyran-2-one with thiosemicarbazide and ethyl 2-(2-arylhydrazono)-3-oxobutanoates. Various 4-(2-arylhydrazono)-1-(4-(4-hydroxy -6-methyl-2-oxo-2*H*-pyran-3-yl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-ones were isolated in good yields (Scheme **55**) [133]. Xiabing *et al*. established a one-pot three-compo-nent protocol for the preparation of thiazole derivatives from aldehyde/ketones, thiosemicarbazide, and chlorinated β-keto ester. The AcONa-catalyzed reaction furnished products in good yields (Scheme **56**) [134].



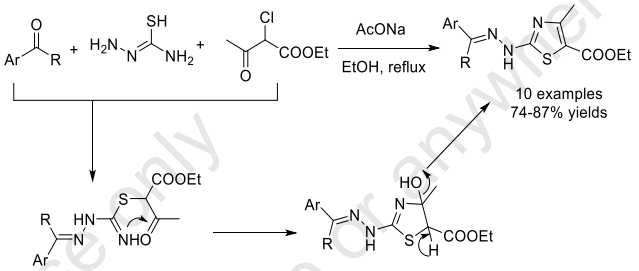
Scheme 53.



Scheme 54.

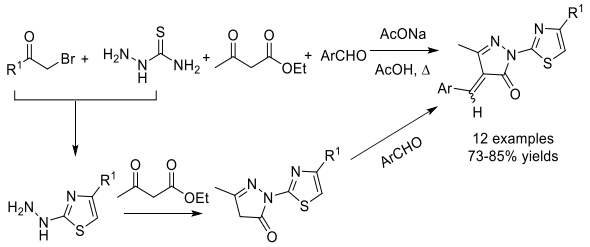


Scheme 55.

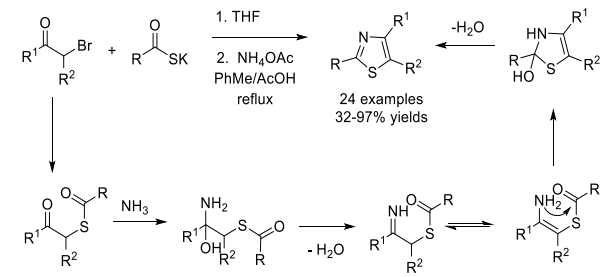


Scheme 56.

Venkata and Ra discovered a novel, one-pot, multi-component approach for the synthesis of 4-arylidene-3-methyl-1-(4-arylthiazol-2-yl)-1*H*-pyrazol-5(4*H*)-ones by reaction of phenacyl bromides, thiosemicarbazide, ethylaceto-acetate, and aryl aldehydes. Various products were obtained in good yields in short reaction times (Scheme **57**) [135]. Venkateswararao *et al*. developed a one-pot sequential protocol for the assembly of 2,4-di- and 2,4,5-trisubstituted thiazoles from α-boromoketones, thio-acid salt, and ammo-nium acetate. The synthesis involved the formation of a β-keto-thioester intermediate from the nucleophilic substitution of α-bromoketones with thioacid potassium salts, which were converted to imine intermediates by treatment with ammonium acetate and acetic acid and eventually thiazoles by cyclization (Scheme **58**) [136].



Scheme 57.

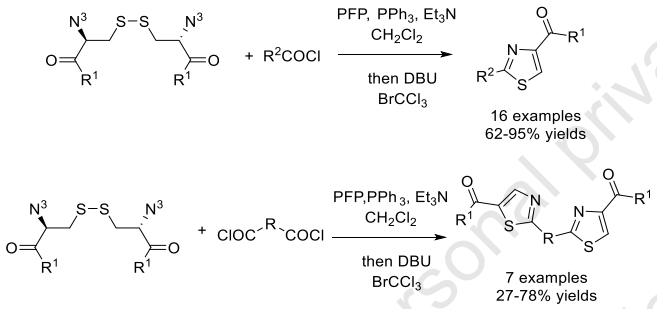


Scheme 58.

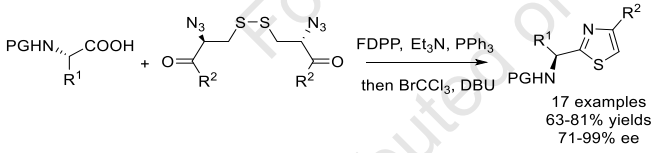
3. NON-ESTABLISHED METHODS FOR THIAZOLE SYNTHESIS

3.1 Thiazole Synthesis *via* Other Two-component Reactions

Liu *et al*. reported a facile one-pot synthesis of 2,4-disubstituted mono- and di-thiazoles directly by reaction of acid chlorides with β-azido disulfides. The synthesis involved a sequence of phosphine-promoted disulfide bond cleavage/ thiocarbonylation with acyl chloride/intramolecular Staudinger reduction/aza-Wittig reaction of the generated vicinal azido thiolester/ dehydrogenation reaction. In most cases, products were furnished in good yields, and the synthesis could be performed efficiently in gram-scale (Scheme **59**) [137]. Liu *et al*. examined an effective one-pot protocol for the enantiomerical synthesis of thiazole-containing amino acid. A sequence of disulfide cleavage / thiocarbonylation / intramolecular Staudinger reduction / aza-Wittig / oxidation reaction was proposed to occur. Mild reaction conditions, broad substrate scope, good yields of products, and high optical purities are the main advantages of the synthesis (Scheme **60**) [138].

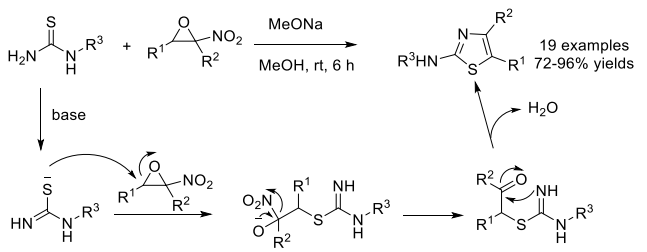


Scheme 59.

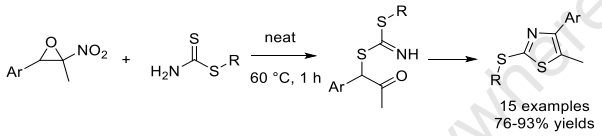


Scheme 60.

Zhao *et al*. investigated an efficient approach to access 2,4,5-trisubstituted thiazoles by reaction of α-nitroepoxides and thioureas. A wide range of products was afforded in high yields under mild reaction conditions (Scheme **61**) [139]. Halimehjani and Nosood described a facile and efficient protocol for the assembly of substituted thiazole-2(3*H*)-thiones from nitroepoxides and thioureas. The synthesis featured some attractive features such as catalyst-free and solvent-free conditions, mild reaction conditions, short reaction times, and good to excellent product yields (Scheme **62**) [140].

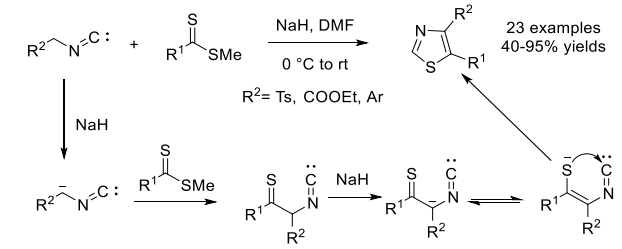


Scheme 61.

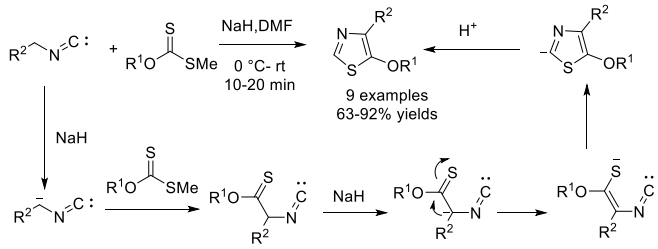


Scheme 62.

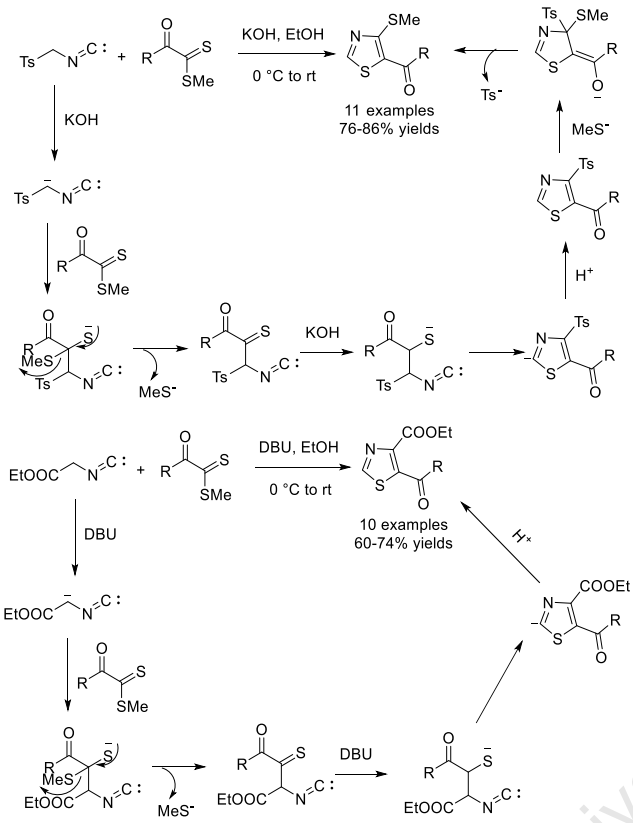
Lingaraju *et al*. accomplished the synthesis of 4,5-disubstituted thiazoles *via* base-induced cyclization of active methylene isocyanides with aryl carbodithioates. A library of products was obtained in reasonable to excellent yields under mild reaction conditions (Scheme **63**) [141]. The Rajeev group completed the synthesis of 5-alkoxy-4-tosylthiazoles by sodium hydride-induced cyclization of 1-[(isocyanomethyl) sulfonyl]-4-methylbenzene or ethyl isocyanoacetate with various xanthate esters. The method gave products in moderate to excellent yields under mild reaction conditions (Scheme **64**) [142]. Later, this group demonstrated the preparation of 4-methylthio-5-acylthiazoles and 4-ethoxycarbonyl-5-acylthiazoles by the reaction of α-oxodithioesters with tosylmethyl isocyanide or ethyl isocyanoacetate. The DBU-promoted cyclization took place smoothly, giving products good yields (Scheme **65**) [143].



Scheme 63.

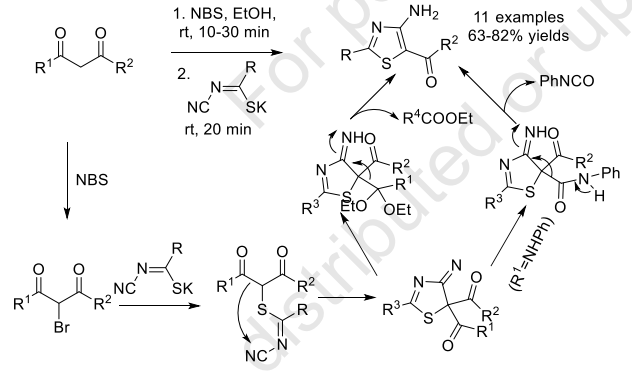


Scheme 64.



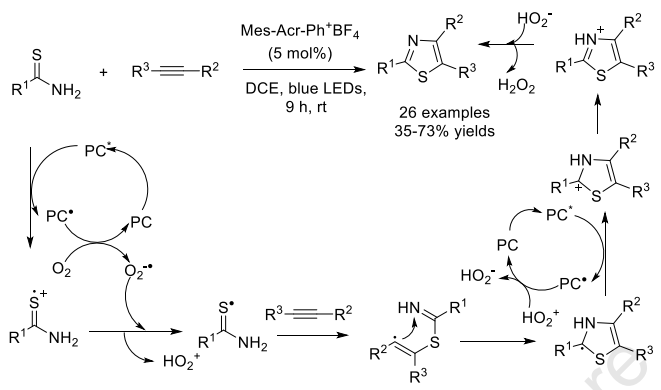
Scheme 65.

Luo *et al*. disclosed a method towards multi functionalized thiazoles from dicarbonyl compounds and mercaptonitrile salts by an NBS-mediated sequential reaction. The synthesis offered some advantages such as mild reaction conditions, short reaction time, simple operation, broad substrate scope, and good product yields (Scheme **66**) [144].



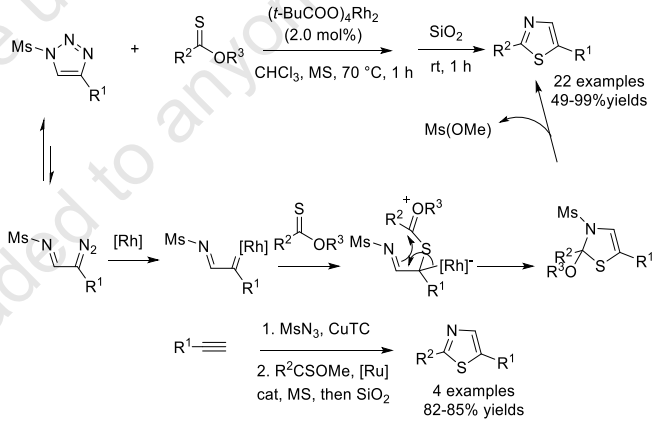
Scheme 66.

Huang *et al*. explored a visible-light-induced cascade cyclization of thioamides with alkynes for the assembly of thiazoles. The reaction might involve the cascade reaction of thioamide *via* the single electron transfer process promoted by photocatalysis. A diverse range of products was provided in reasonable to good yields under mild conditions (Scheme **67**) [145].



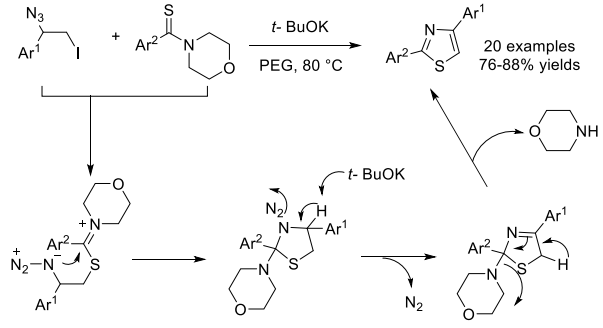
Scheme 67.

Miura *et al*. discovered an efficient strategy to prepare 2,5-disubstituted thiazoles from 1,2,3-triazoles and thionoesters. 1,2,3-triazoles react with thionoesters in the presence of a rhodium (II) catalyst to generate 3-sulfonyl-4-thiazolines, which then undergo elimination of the sulfonyl group to give thiazoles. The synthesis could be applied for terminal alkynes, sulfonyl azides, and thionoesters to prepare thiazoles in one pot (Scheme **68**) [146].

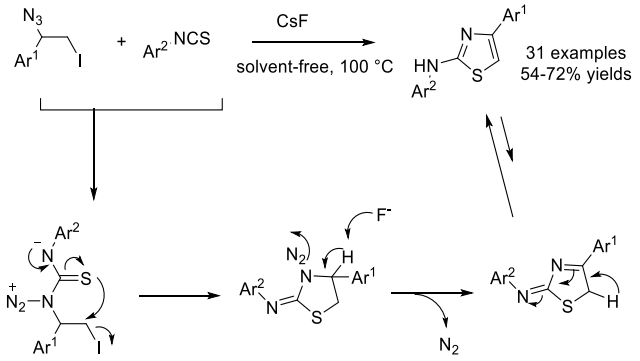


Scheme 68.

Majnooni *et al*. developed an efficient approach for the synthesis of thiazole derivatives from aryliodoazides catalyzed by the base. Treatment of aryliodoazides with morpholino- (aryl)methanethiones in PGE afforded 1,3-thiazoles in good yields, while reaction between these substrates and aromatic isothiocyanates under solvent-free conditions provided 2-aminothiazoles (Scheme **69**) [147].

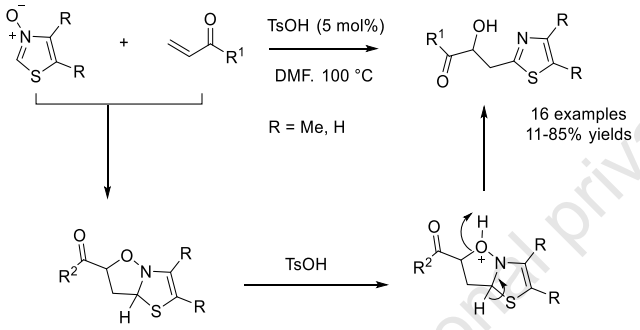


(Scheme 69) Contd....



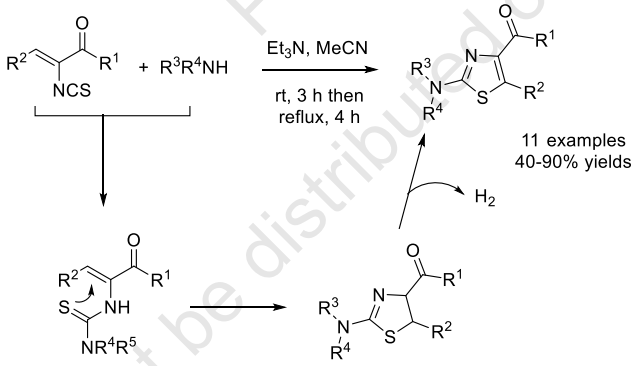
Scheme 69.

Li *et al.* introduced a strategy to synthesize thiazole-substituted α-hydroxy carbonyls from thiazole *N*-oxides and vinyl ketones. The synthesis proceeded *via* a 1,3- dipolar cycloaddition of thiazole *N*-oxides with olefins, followed by a ring-opening reaction. In most cases, products were achieved in moderate to good yields under thermal conditions (Scheme **70**) [148].



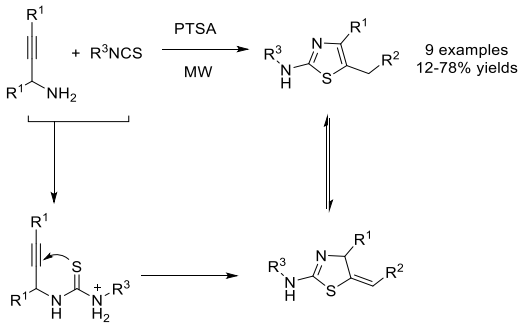
Scheme 70.

Xie *et al*. designed an approach to access 2,4,5-trisubstituted thiazoles from isothiocyanate with aliphatic secondary amines using Et_3N as a catalyst. In most cases, products were isolated in good yields (Scheme **71**) [149].



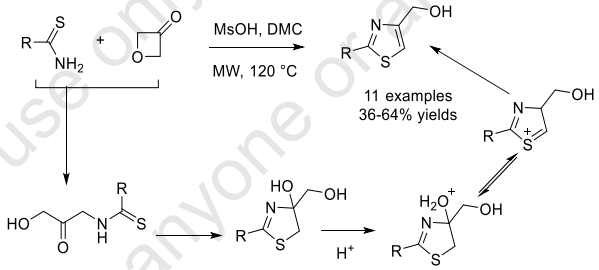
Scheme 71.

Scalacci *et al*. investigated a simple and versatile microwave-assisted protocol for the synthesis of 2-aminothiazoles by the reaction between propargyl amines and isothiocyanates. The synthesis was catalyzed by PTSA and completed in a short reaction time (Scheme **72**) [150].



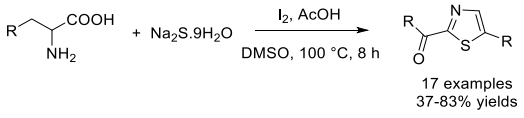
Scheme 72.

Orr *et al*. established a protocol to prepare (hydroxylmethyl)thiazoles from 3-oxetanone and primary amides. The synthesis was performed under microwave irradiation and delivered products in moderate to good yields (Scheme **73**) [151].



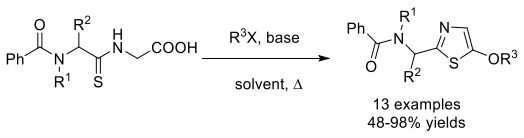
Scheme 73.

Cheng *et al*. described a strategy to prepare 2,5-disubstituted thiazoles by the reaction of amino acids with $Na_2S·9H_2O$ promoted by iodine. The synthesis might involve a sequence of decarboxylation/deamination/S insertion/cyclization/ grad-ient oxidation processes. The synthesis featured some advantages such as easily available starting material, broad substrate, and satisfactory yields of products (Scheme **74**) [152].



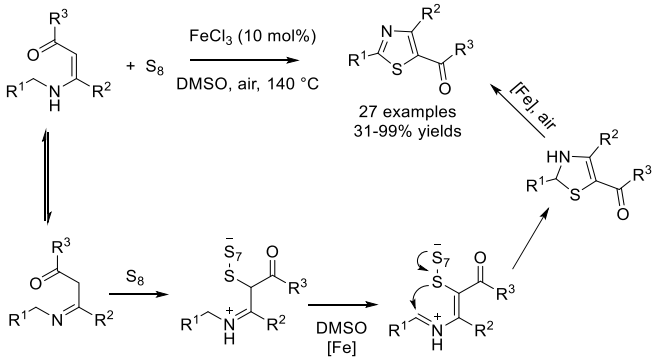
Scheme 74.

Kazmaiere *et al*. examined a procedure for the assembly of 5-substituted thiazoles from thiopeptides and acyl halides. The synthesis was suitable for a diverse range of substrates and afforded products in moderate to excellent yields (Scheme **75**) [153].



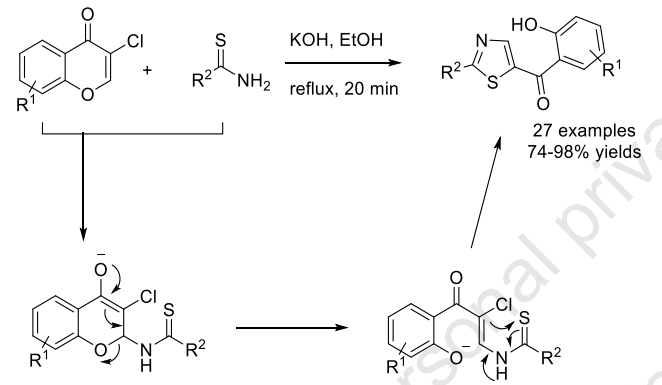
Scheme 75.

Wu *et al*. presented an efficient strategy towards thiazoles starting from enamines and elemental sulfur through the C-H functionalization/C-S bond formation. Thiazole derivatives were generated in moderate to excellent yields under thermal conditions for a broad range of enamines (Scheme **76**) [154].



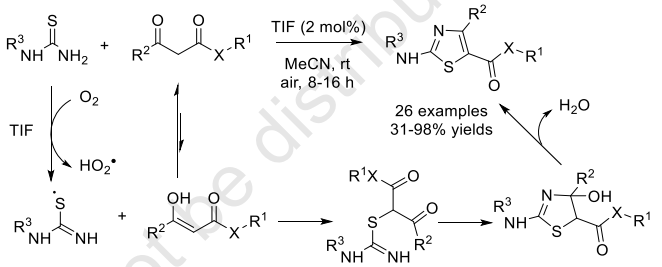
Scheme 76.

Dai *et al*. demonstrated a facile and efficient approach to construct substituted thiazoles by a cascade reaction of chromone derivatives and thioamides. The synthesis might proceed *via* a sequence of Michael addition and intramolecular cyclization. Broad scope, short reaction time, and high product yields are the main attractive features of the synthesis (Scheme **77**) [155].



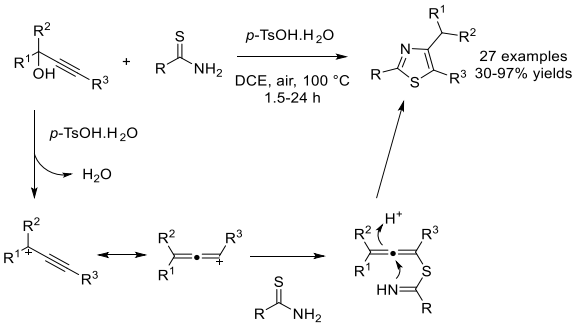
Scheme 77.

Roslan *et al*. accomplished the synthesis of aminothiazoles from various 1,3-dicarbonyls and thioureas under green LEDs irradiation catalyzed by tetraiodofluorescein (TIF). A diverse range of products was provided in reasonable to excellent yields with excellent atom economy under mild conditions (Scheme **78**) [156].



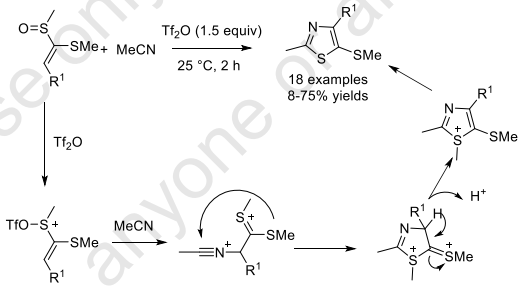
Scheme 78.

Zhang *et al*. reported an efficient method to access 2,4-di- and trisubstituted thiazoles by cyclization of trisubstituted propargylic alcohols with thioamides catalyzed by *p*-TsOH.3H_2O. A wide array of thiazole derivatives was furnished in moderate to excellent product yields without using any metal catalyst (Scheme **79**) [157].



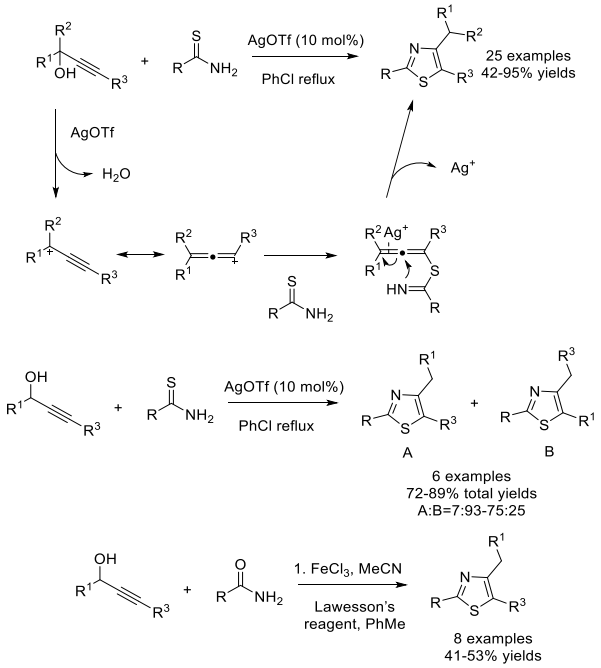
Scheme 79.

Hori *et al*. completed the preparation of 5- (methylsulfanyl)thiazoles from alkenyl sulfoxides and nitriles *via* Pummerer-based annulation reaction. Most of the products were isolated in moderate yields under mild reaction conditions (Scheme **80**) [158].



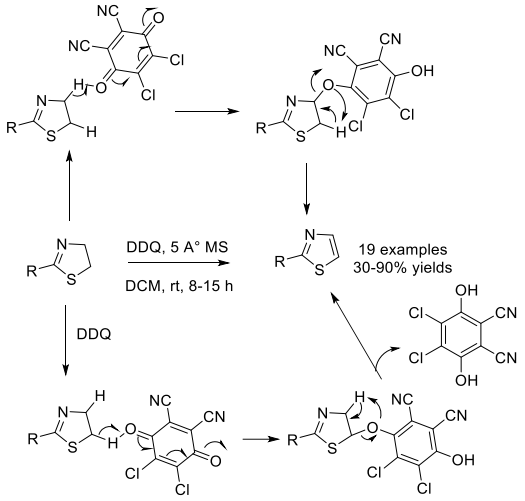
Scheme 80.

Gao *et al*. announced the construction of three different substituted thiazoles from propargylic alcohols and thioamides. The reaction might involve the formation of an allenyl isomer or propargylic cation intermediate. A diverse library of products was furnished in moderate to good yields using AgOTf or $FeCl_3$ as a catalyst (Scheme **81**) [159].



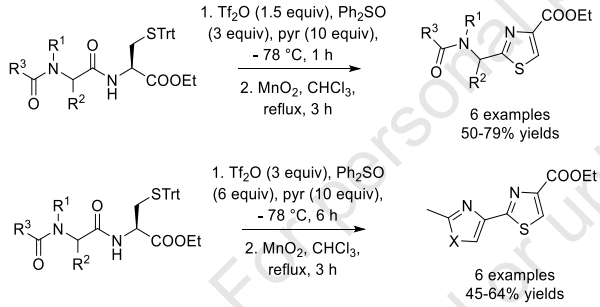
Scheme 81.

Li *et al*. performed the synthesis of 2-thiazoles by the oxidation of 2-thiazolines without substituents at the C4 and C5 positions by DDQ. A wide range of 2-thiazoles was produced in moderate to good yields under mild conditions (Scheme **82**) [160].



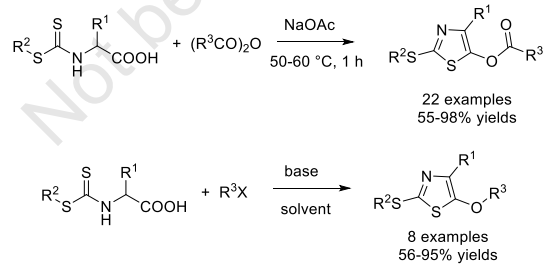
Scheme 82.

Vishwanatha *et al*. developed a procedure for the short synthesis of thiazole and bis-oxazole/thiazole deri-vatives from Cys(Trt) amides and diphenyl sulfoxide. Products were obtained in moderate to good yields using Tf_2O as a catalyst (Scheme **83**) [161].



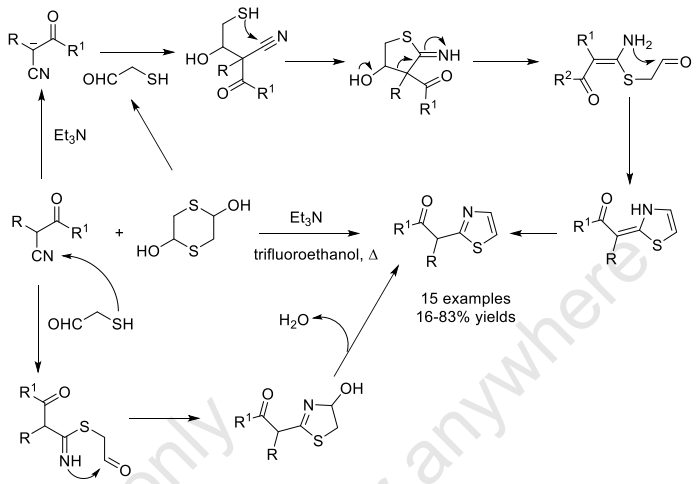
Scheme 83.

Halimehjani *et al*. introduced an efficient protocol for the preparation of a diverse array of novel di and tri-substituted thiazoles by the condensation reaction of amino acid-based dithiocarbamates with anhydrides, acyl halides, and benzene sulfonyl chloride. Products were achieved in moderate to excellent yields under mild reaction conditions with good functional group tolerance (Scheme **84**) [162].



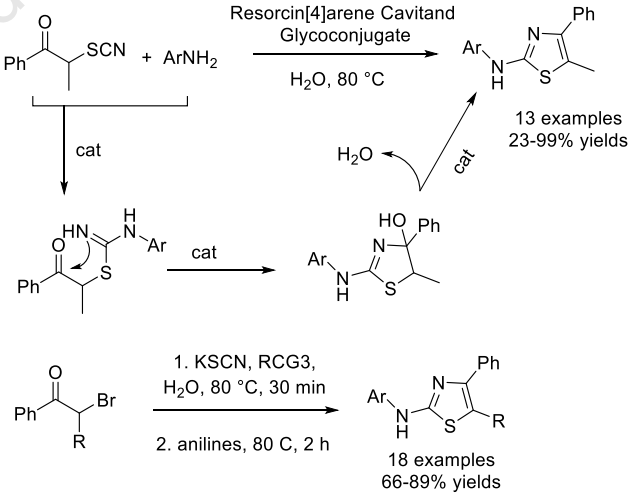
Scheme 84.

Mallia *et al*. designed an efficient method for the assembly of thiazoles from nitriles and 1,4-dithiane-2,5-diol based on the Gewald reaction (Scheme **85**) [163].



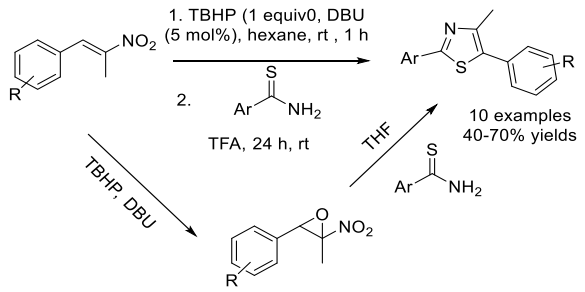
Scheme 85.

Husain and Bisht discovered a procedure for the preparation of 2-amino-1,3-thiazoles from α-thiocyanato ketones and anilines in water. The synthesis employed resorcin[4]arene cavit and glycoconjugates as catalysts and delivered products at reasonable to high yields. The catalyst could be reused five times without considerable loss in activity. The synthesis could be applied for phenacyl bromides in the one-pot procedure (Scheme **86**) [164].



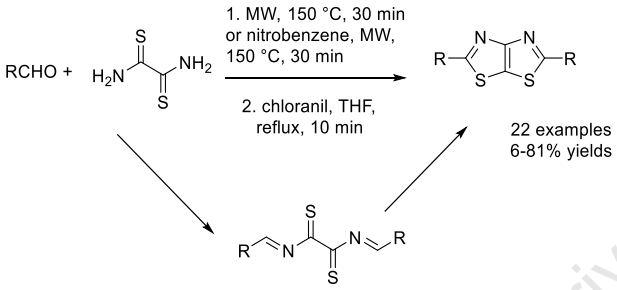
Scheme 86.

Wei *et al.* established a facile one-pot, two-step procedure for the assembly of 1,3-thiazole derivatives from nitro-olefins and thioamides. α-nitro-epoxides were generated by treating α-nitro-olefins with the t-BuOOH/DBU system, which were then converted to thiazoles by reacting with thioamides. Various products were obtained under mild reaction conditions (Scheme **87**) [165].



Scheme 87.

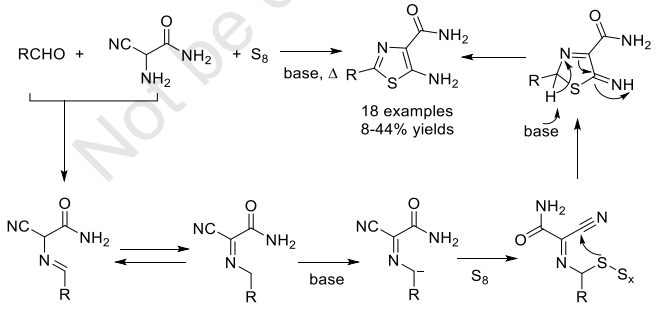
A rapid and simple approach for the preparation of thiazolo[5,4-*d*]thiazoles from the condensation reaction of dithioxoamide with aromatic aldehydes, followed by oxidetion, was investigated by Dessì *et al*. A diverse range of products was afforded in moderate yields (for most substrates) under microwave irradiation (Scheme **88**) [166].



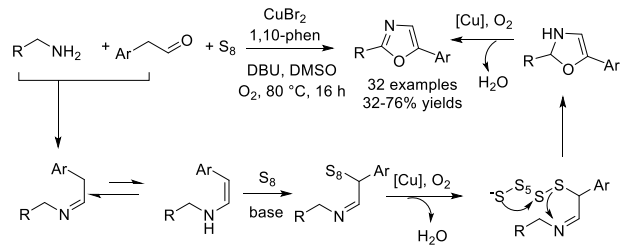
Scheme 88.

3.2. Thiazole Synthesis *via* Multi-component Reactions

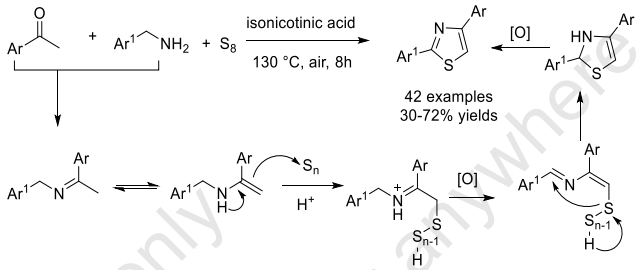
Childers *et al*. disclosed a method to access substituted 5-amino-4-carboxamidthiazoles by the condensation of aldehydes with 2-amino-2- cyanoacetamide in the presence of elemental sulfur and base (Scheme **89**) [167]. A novel and practical Cu-catalyzed aerobic oxidative strategy for the synthesis of thiazoles from aldehydes, amines, and element sulfur through a novel multiple Csp^3-H bond cleavage processes was presented by Wang *et al*. A library of products was provided in moderate yields under thermal conditions (Scheme **90**) [168]. In a similar study, Ni *et al*. illustrated the synthesis of disubstituted thiazoles from benzylamines, acetophenones, and sulfur powder. One C–N bond and multi C–S bonds were selectively formed in one pot. A vast number of thiazole derivatives were produced in moderate yields by the Bronsted acid-promoted sulfuration/annulation reaction (Scheme **91**) [169].



Scheme 89.

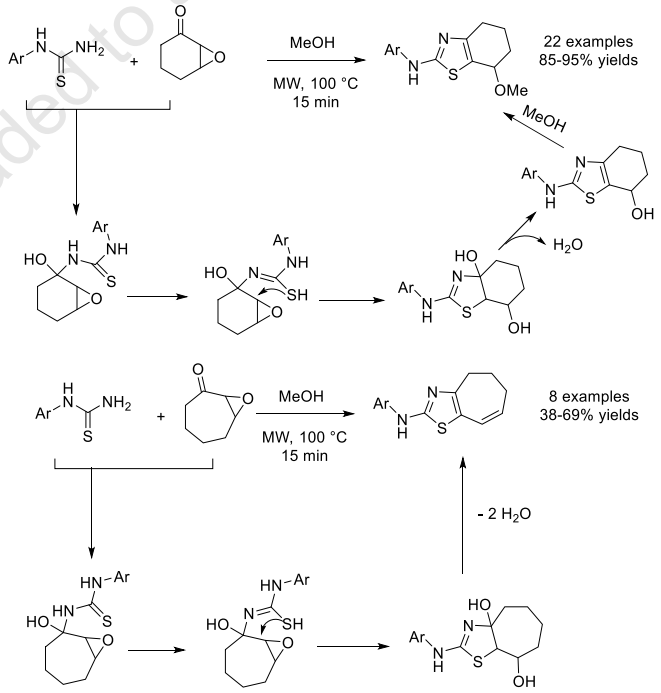


Scheme 90.



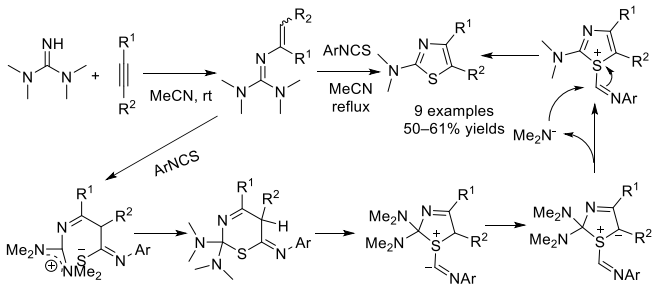
Scheme 91.

Liu *et al*. examined a new methodology for the construction of fused bicyclic 2-aminothiazolyl compounds by the cyclocondensation reaction of aromatic thioureas with α,β-epoxy cycloketones. The microwave-assisted synthesis was performed without using any catalyst and afforded products in high yields in a short time (Scheme **92**) [170].



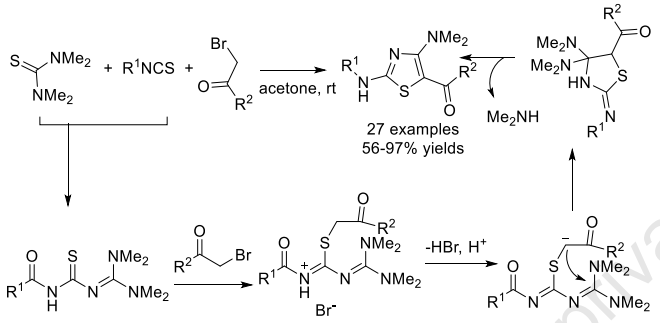
Scheme 92.

Yavari *et al*. described the synthesis of 2-(dimethylamino)-1,3-thiazole derivatives *via* the reaction of dialkyl 2-{[bis(dimethylamino)methylene]amino}maleates with isothiocyanates. The dialkyl 2-{[bis(dimethylamino) methylene]amino} maleate substrates were generated from 1,1,3,3-tetramethylguanidine and acetylenic esters under mild reaction conditions (Scheme **93**) [171].



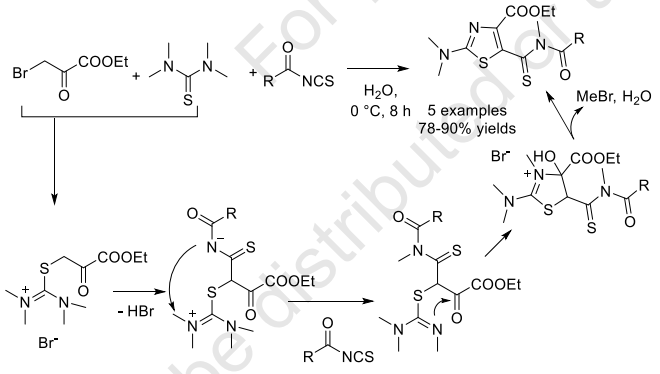
Scheme 93.

Yavari *et al*. reported a convenient one-pot route for the preparation of functionalized 2,4-diaminothiazoles from tetramethylguanidine, isothiocyanates, and *α*-bromoketones. A library of products was furnished in moderate to excellent yields under mild reaction conditions without using any catalyst (Scheme **94**) [172].



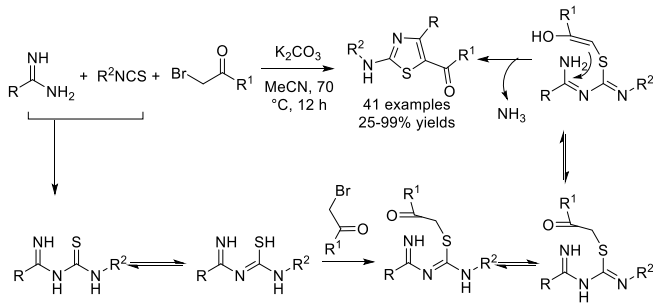
Scheme 94.

Joybari and Hossaini illustrated the synthesis of 1,3-thiazole derivatives through a three-component reaction isothiocyanate, tetramethyl thiourea, and ethyl bromopyruvate. Products were achieved in good to excellent yields under mild conditions in the one-pot procedure (Scheme **95**) [173].



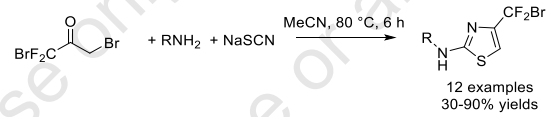
Scheme 95.

Guo *et al*. developed a base-promoted and metal-/oxidant-free one-pot three-component tandem annulation of amidines, aryl/alkyl isothiocyanates, and α-bromoesters/ketones for the assembly of 2,4,5-trisubstituted thiazoles. The synthesis offered some advantages, such as simple operation, broad substrate scope, mild reaction conditions, and good product yields (Scheme **96**) [174].



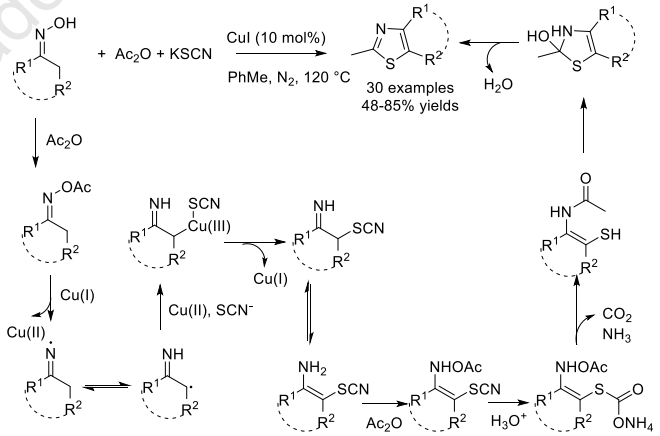
Scheme 96.

Colella *et al*. introduced a protocol for the assembly of 4-CF_2Br-substituted 2-aminothiazoles from 1,3-dibromo-1,1-difluoro-2-propanones, aromatic amines, and sodium thiocyanate. Various thiazole-based compounds were provided in high yields in most cases under thermal conditions (Scheme **97**) [175].



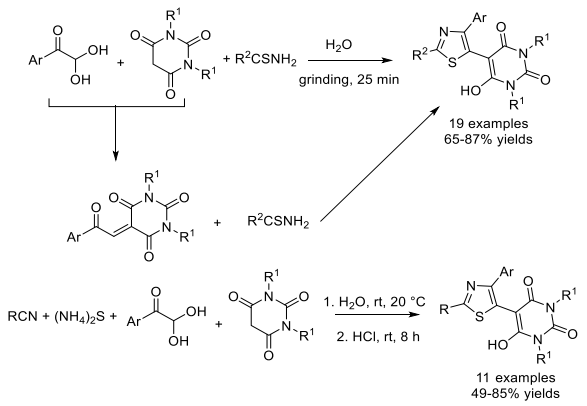
Scheme 97.

Tang *et al*. discovered a copper-catalyzed [3+1+1]-type condensation approach for the synthesis of thiazoles from oximes, anhydrides, and potassium thiocyanate. The synthesis proceeded *via* N-O/C-S bond cleavages and new C-S/C-N bond formations, along with the activation of vinyl sp^2 C-H bond. A wide array of products was furnished in moderate to good yields with operational simplicity (Scheme **98**) [176].



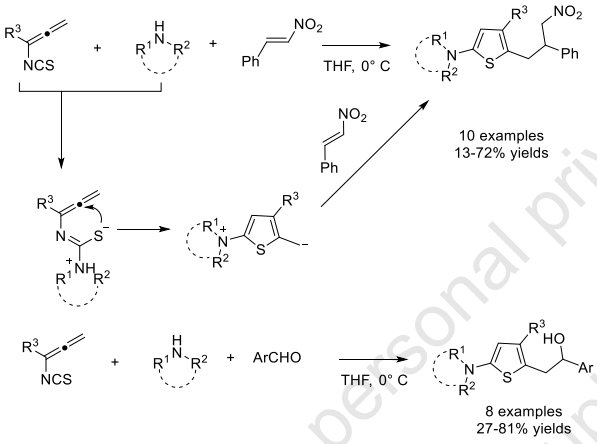
Scheme 98.

Mahata *et al*. demonstrated an efficient approach to access diphenyl-1,3-thiazole linked barbituric acid hybrids by the three-component reaction between arylglyoxal, barbituric acid with aryl thioamides under liquid assisted grinding. The methods delivered some merits such as environmentally benign reaction conditions, broad substrate scope, good yields of the products, easy purification of products, and short reaction time. The synthesis was also conveniently applied for the three-component reaction of arylglyoxal, barbituric acid, nitriles, and ammonium sulfide to produce thiazoles bearing barbituric acid moiety in moderate to good yields (Scheme **99**) [177].



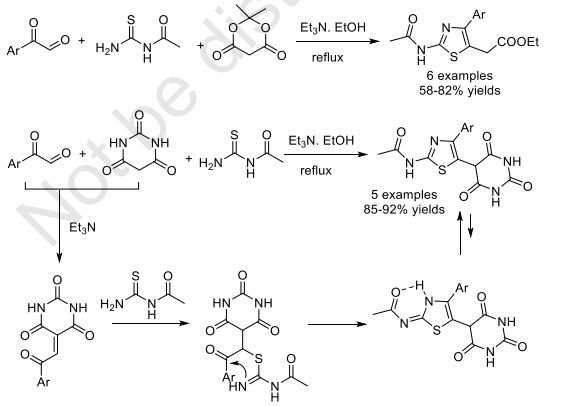
Scheme 99.

Richter *et al*. investigated a strategy to access thiazoles by the three-component reaction of allenyl isothiocyanates, amines, and β-nitro styrene or aldehydes. The one-pot, three-component reaction took place smoothly under mild conditions and gave 2-amino-1,3-thiazole derivatives in reasonable to good yields (Scheme **100**) [178].



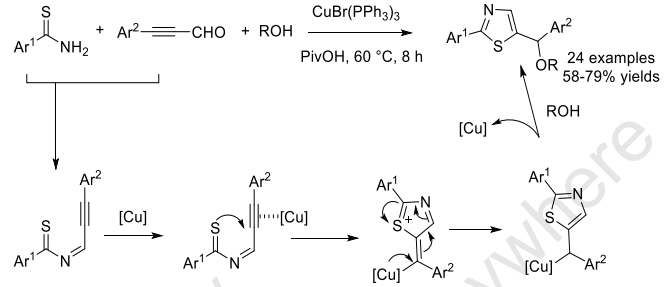
Scheme 100.

Alizadeh-Bami *et al*. established an efficient protocol for the construction of 2-acetamido-4-arylthiazol- 5-yl derivatives *via* a novel one-pot three-component reaction of arylglyoxals, 1,3-dicarbonyl compounds, and acetylthiourea. Salient features of the method include mild reaction conditions, short reaction time, simple operation, and good product yields (Scheme **101**) [179].



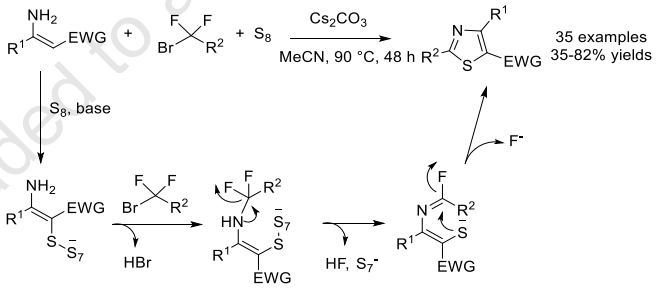
Scheme 101.

Wang *et al*. disclosed a novel and straightforward approach for the preparation of functionalized thiazoles by copper(I)-catalyzed three-component reaction of thioamides, ynals, and alcohols. In this synthesis, new C-S, C-N, and C-O bonds were formed in one pot by a domino process with broad substrate scope. A library of products was achieved in moderate to good yields (Scheme **102**) [180].



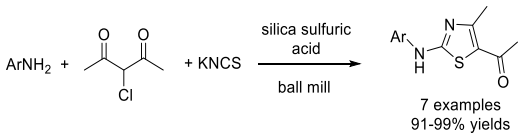
Scheme 102.

Ma *et al*. examined a three-component route for the assembly of thiazoles from enaminoesters, fluorodibromoiamides/ester, and elemental sulfur. The [3+1+1] cyclization reaction offered the cleavage of one C-Br bond and two C-F bonds along with the formation of new C-S, C-N, as well as N-S bonds in one pot. A diverse series of products was furnished in reasonable to good yields (Scheme **103**) [181].



Scheme 103.

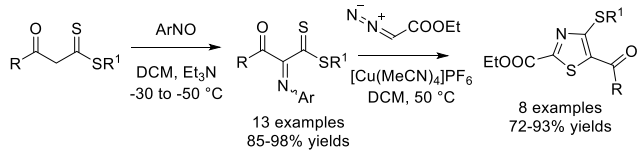
Al-Bogami *et al*. designed a mechanochemical synthesis of 5-acetylthiazole derivatives by the three-component of aryl amines, potassiumthiocyanate, and 3-chloro penta-1,3-dione. The synthesis used silica sulfuric acid as a catalyst and was performed under solvent-free conditions. In addition, the catalyst could be recycled up to five runs without significant loss of its catalytic activity. Products were obtained in excellent yields under mild conditions (Scheme **104**) [182].



Scheme 104.

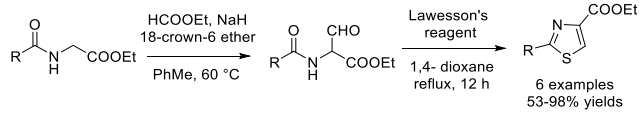
Srivastava *et al*. introduced a practical protocol towards fully substituted thiazoles by [4 + 1] heterocyclization of α-(*N*-hydroxy/aryl)imino-β-oxodithioesters with *in situ* generated Cu-carbenoids of diazocarbonyls. The α-(*N*-hydroxy/aryl)imino-β-oxodithioesters were generated in high yields from β-oxodithioesters and nitrous acid/nitrosoarenes. The synthesis undergoes a sequential N–O/C–N bonds cleavage

followed by cascade C–N/C–S bonds formation in one pot (Scheme **105**) [183].



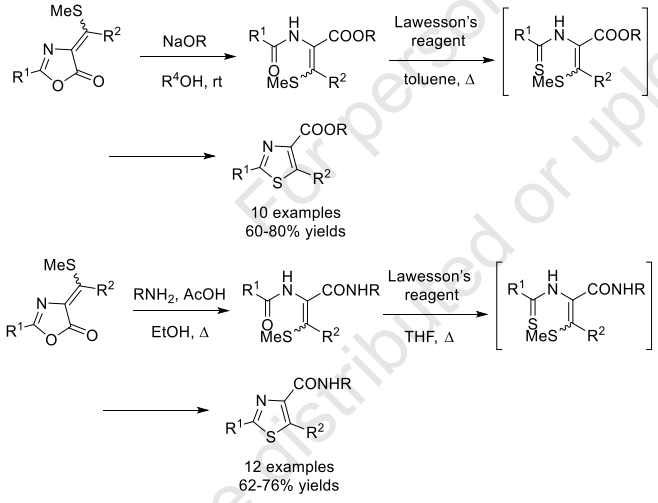
Scheme 105.

Khose *et al*. discovered a novel method to prepare thiazoles from glycine ethyl ester hydrochloride, ethyl formate, and Lawesson's reagent. C-formylation of glycine ester by ethyl formate generated α-formyl esters, which were then transformed into thiazole derivatives by treatment with Lawesson's reagent. The two-step synthesis gave products moderate to excellent yields (Scheme **106**) [184].



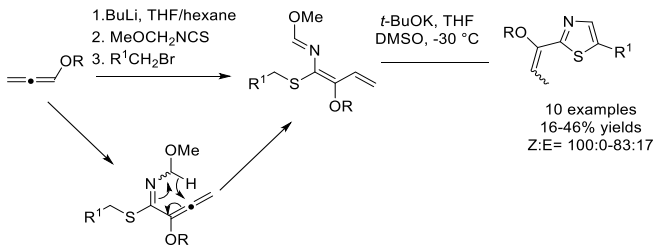
Scheme 106.

Kumar *et al*. developed an efficient strategy access 2-phenyl/(2-thienyl)-5-(het)aryl/(methylthio)-4-functionalized thiazoles from 5-oxazolones *via* one-step thionation-cyclization. Initially, nucleophilic ring-opening of 2-phenyl/(2-thienyl)-4-[bis(methylthio)/(methylthio)(het) aryl-methylene]-5-oxazolones with alkoxides generated enamide intermediates, which were then converted to thiazole products in good yields by treatment with Lawesson's reagent (Scheme **107**) [185].



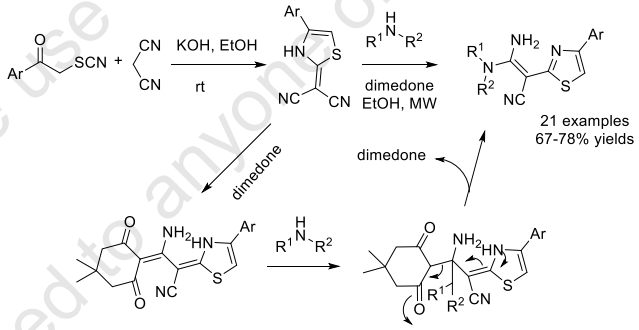
Scheme 107.

Nedolya *et al*. accomplished the synthesis of 5-ethynyl-2-vinyl- and 2,5-divinyl-1,3-thiazoles from allenyl ether, methoxymethyl isothiocyanate, and bromides. In the first step, 2-aza-1,3,5-trienes {methyl *N*-[2-alkoxy-1-(prop-2-ynylsulfanyl)buta-1,3-dienyl]- and methyl *N*-[1-(allylsulfanyl)-2-alkoxybuta-1,3-dienyl]iminoformates} were obtained from lithiated alkoxyallenes, methoxymethyl isothiocyanate, and propargyl or allyl bromide. Base-catalyzed cyclization of these intermediates provided thiazole products (Scheme **108**) [186].



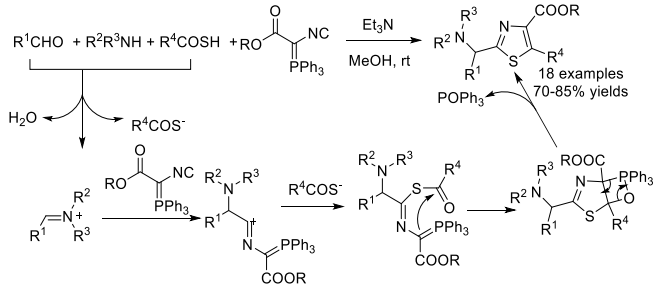
Scheme 108.

Zhu *et al*. completed an efficient methodology for the synthesis of highly functionalized thiazol-2-yl substituted *E*-acrylonitrile derivatives from *α*-thiocyanate ketones, malononitrile, and amines. The *α*-thiocyanate ketones react with malononitrile to provide thiazol-2-ylidenemalononitrile intermediates, which then were subjected to various amines in the presence of dimedone under microwave irradiation to yield the final thiazol-2-yl substituted acrylonitrile derivatives. Products were furnished in good yields for a diverse array of substrates (Scheme **109**) [187].



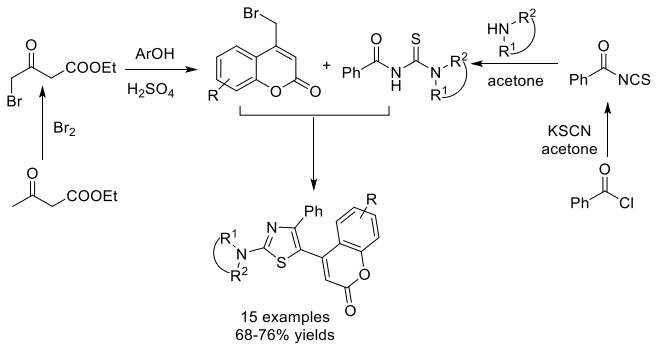
Scheme 109.

Guan *et al*. illustrated a new one-pot four-component protocol for the assembly of polysubstituted thiazoles by a cascade Ugi/Wittig cyclization of isocyano (triphenylphosphoranylidene)acetates, aldehydes, amines, and thiocarboxylic acids. A diverse series of products was achieved in good yields under mild reaction conditions (Scheme **110**) [188].



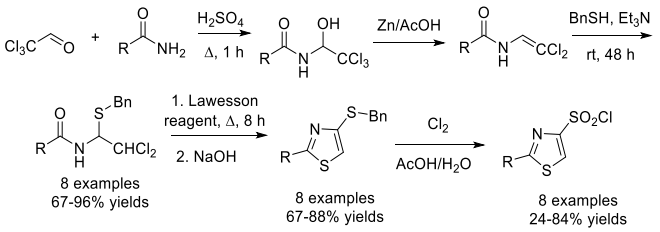
Scheme 110.

Kumbar *et al*. investigated a methodology to access substituted thiazoles containing coumarins from ethyl acetoacetate, phenols, aroyl chloride, amines, and potassium thiocyanate. The synthesis proceeded *via* intramolecular Knoevenagel condensation-cyclization reaction using triethylamine (TEA) as a base under microwave irradiation (Scheme **111**) [189].



Scheme 111.

Demydchuk *et al*. established a procedure for the synthesis of thiazole-4-sulfonyl chlorides starting from chloralamide and thioamides (Scheme **112**) [190].



Scheme 112.

CONCLUSION

In conclusion, this article gives a systematic overview of the synthesis and a brief description of the biological application of thiazole derivatives by summarizing recent studies. Among the established methods for the synthesis of thiazoles, the Hantcsch method still has received great attention from chemists. Besides, a great number of new synthetic methods have been developed recently. In addition, many methods with high efficiency or employing environmentally benign procedures have been developed. Undoubtedly, more facile and efficient approaches to prepare thiazole will appear in the near future. Application of thiazole synthesis to natural product synthesis and drug synthesis is probably the next challenge in the field. This review article summarizes updated articles, deals with a great number of studies, covers all aspects of thiazole synthesis and describes reactions pathways in most studies.

LIST OF ABBREVIATIONS

Ac	=	Acetyl
AIBN	=	Azobisisobutyronitrile
AP-1	=	Activator protein 1
Ar	=	Aryl
Bmim	=	1-Butyl-3-methylimidazolium
Bu	=	Butyl
CTAB	=	Cetrimonium bromide
DABCO	=	(1,4-diazabicyclo[2.2.2]octane
DBU	=	1,8 Diazabicyclo[2.2.2]octane
DCE	=	1,2-Dichloroethane
DCM	=	Dichloromethane
DDQ	=	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DES	=	Deep eutectic solvent
DMF	=	*N,N*- Dimethylformamide
DMSO	=	Dimethyl sulfoxide
ECF	=	Ethyl chloroformate
Et	=	Ethyl
FDA	=	Food and Drug Administration
FDPP	=	Pentafluorophenyl diphenylphosphinate
IBX	=	2-Iodoxybenzoic acid
LDA	=	Lithiumdiisopropyl amide
Me	=	Methyl
m-CPBA	=	*m*- chloroperbenzoic acid
MES	=	Mouse embryonic stem
Mor-DalPhos	=	Di(1-adamantyl)-2-morpholinophosphine
Ms	=	Mesyl
MW	=	Microwave
NBS	=	*N*-Bromosuccinimide
NF-Kb	=	Nuclear factor kappa B
NMM	=	*N*-Methylmorpholine
PEG	=	Polyethyleneglycol
Ph	=	Phenyl
PFP	=	Pentafluorophenyl esters
PTSA	=	p-Toluenesulfonic acid
PTT	=	phenyl trimethylammoniumtribromide
Pyr	=	pyridine
Rt	=	Room temperature
TBCA	=	Tribromoisocyanuric acid
t- Bu	=	*tert*- Butyl
TBHP	=	*tert*-Butyl hydroperoxide
TBHP	=	*tert*-butyl hydroperoxide
THF	=	Tetrahydrofuran
Ts	=	Tosyl

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

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CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest.

ACKNOWLEDGEMENTS

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