Send Orders for Reprints to reprints@benthamscience.net

Mini-Reviews in Organic Chemistry, 2022, *19*, 1-15

MINI-REVIEW ARTICLE

Recent Advances in the Synthesis of Thiazole Ring: Mini Review

Inas G. Shahin[1], Khaled O. Mohamed[2], Azza T. Taher[2,3], Abdelrahman S. Mayhoub[4,5] and Asmaa E. Kassab[2,*]

[1]*Department of Organic Chemistry, Faculty of Pharmacy, October University for Modern Sciences and Arts, Giza, 11787, Egypt;* [2]*Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Cairo University, Cairo, 11562, Egypt;* [3]*Department of Pharmaceutical Organic Chemistry, College of Pharmacy, October 6 University, 6-October, Giza, Egypt;* [4]*Department of Pharmaceutical Organic Chemistry, College of Pharmacy, Al- Azhar University, Cairo, 11884, Egypt;* [5]*University of Science and Technology, Nanoscience Program, Zewail City of Science and Technology, October Gardens, 6th October, Giza, 12578, Egypt*

ARTICLE HISTORY

Received: January 10, 2022
Revised: February 01, 2022
Accepted: February 28, 2022

DOI:
10.2174/1570193X19666220413104255

Abstract: The thiazole scaffold is an essential structural foundation in a plethora of pharmaceutical products having an extensive array of biological activities. Consequently, its synthesis has been extensively discussed in the literature. In this mini review, we have summarized the recent advances in thiazole synthesis, covering articles published between 2002 and 2021. We have reviewed and discussed various recent and novel routes for synthesizing compounds containing thiazole rings from various starting materials such as thiourea, thioamide, or thiosemicarbazone. Additionally, we have illustrated environmentally benign methods for thiazole synthesis. We hope that this review can help other researchers efficiently synthesize the thiazole ring.

Keywords: Thiazole, thiourea, thioamide, thiosemicarbazone, green.

1. INTRODUCTION

The thiazole ring is a fundamental structural component for an extensive range of biologically active compounds, including anticonvulsants [1], anticancer [2], antiviral [3], antibacterial agents [4-6], antifungal [7], anti-inflammatory [8], analgesic [9], and antidiabetic agents [10].

Since 1887, when Hantzsch and Weber first synthesized the thiazole ring by condensation of α-haloketones (or aldehydes) and thioamides, there have been numerous reported methods with variations in the key starting compounds. This is mainly due to some of its shortcomings, such as toxic solvents, long reaction times, low yields, and drastic reaction conditions. In spite of this, due to its biological significance, there has been extensive attention to the development of synthetic routes for the synthesis of compounds containing thiazolyl derivatives [11, 12]. Based on their extensive application and drug design fundamentals, hydrazine compounds would possess stronger bioactive properties if a thiazole ring was introduced [13, 14].

Consequently, instead of thiourea, other thio-ketone derivatives were condensed with α-haloketones such as thioamides [15,16], dithiocarbamates [17], and thiosemicarbazones [12, 18].

Therefore, a brief survey of the synthesis of thiazole rings will be explored from the above findings and facts.

*Address correspondence to this author at the Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt; Tel: 002023639307; Fax: 002023635140;
E-mail: asmaa.kassab@pharma.cu.edu.eg

2. NEW APPROACHES IN THIAZOLE SYNTHESIS

Many of the synthetic methods of thiazole rings involve the 'Hantzsch synthesis' method due to its simplicity, which in turn can introduce many functional groups and is used widely at present [19-21]. Nevertheless, due to its shortcomings that involve drastic reaction conditions, expensive catalysts, slow reaction rates, complicated postprocessing, and toxic solvents, the discovery of novel methods that employ ecofriendly solvents, lower reaction time, and easier product separation procedures has been an important research direction and a hot topic [22-24].

There are three main approaches to the synthesis of the thiazole ring. The most extensive methods can be summarized in the reaction of a carbonyl compound with thiourea, thioamide, or thiosemicarbazone precursors.

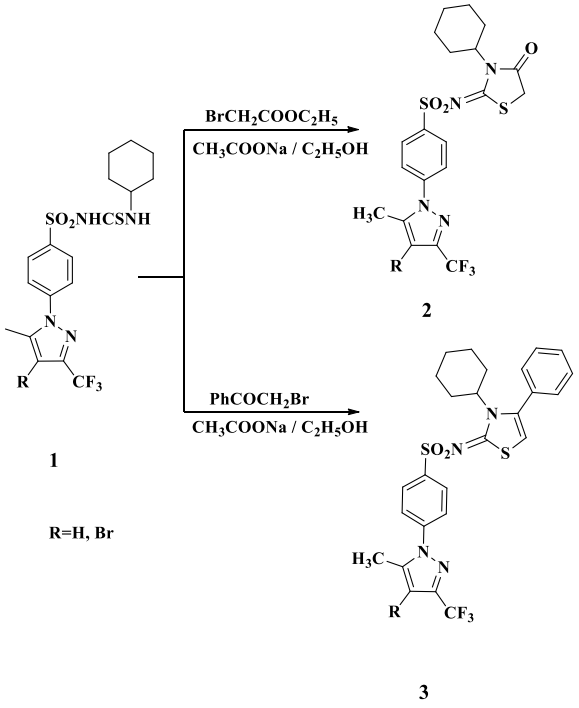
2.1. Synthesis of Thiazole Ring from Thiourea or its Derivatives

A search in the literature revealed a myriad of thiazole cyclisation methods. Therefore, in 2011, imine thiazole derivatives **2** and **3** were prepared by refluxing the thiourea derivative **1** with ethyl bromoacetate or phenacyl bromide, respectively, in the presence of anhydrous sodium acetate using absolute ethanol as a solvent (Scheme **1**) [25].

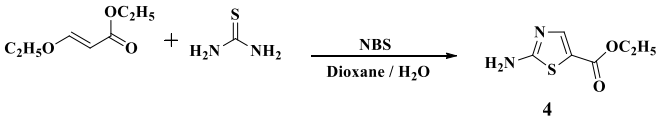
Researchers adopted new methods for thiazole synthesis with different precursors or different reaction conditions from those of Hantzsch. In 2010, Chen *et al.*[26], reacted ethyl-β-ethoxyacrylate with thiourea in the presence of *N*-

1570-193X/22 $65.00+.00

bromosuccinimide (NBS) to afford ethyl 2-aminothiazole-5-carboxylate **4** (Scheme **2**).

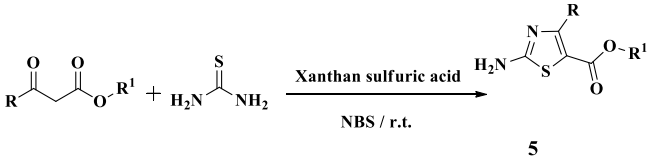


Scheme 1. Synthesis of thiazole derivatives **2** and **3**.



Scheme 2. Synthesis of thiazole derivative **4**.

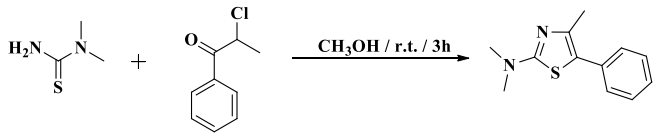
Another approach required the mixing of β-ketoesters with thiourea in the presence of Xanthan, sulfuric acid, and NBS as a catalyst at room temperature to produce the 2-aminothiazoles **5** (Scheme **3**) [27].



Scheme 3. Synthesis of thiazole derivative **5**.

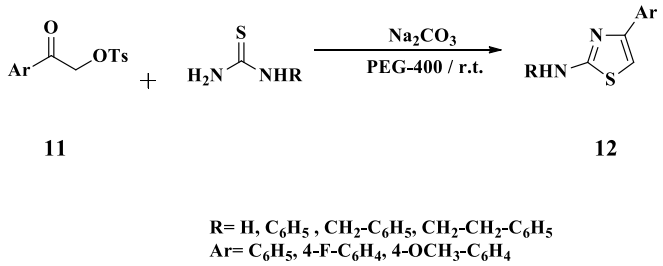
To produce thiazole derivatives from unconventional precursors like propargylamine, this investigation initially prepared *N*-propynyl-*N*'-benzoylthiourea **6**, which was prepared from benzoyl chloride, NH_4SCN, and propargylamine. Cyclisation of thiazolidine **7** takes place by treating compound **6** with KOH in ethanol at room temperature, resulting in the formation of the thiazolate **8** by refluxing with DMSO (Scheme **4**) [28].

A search in the literature revealed that this method simply adopts the cyclisation of a thiourea derivative and chloroketone **9** at room temperature into the respective substituted thiazole ring **10** (Scheme **5**) [29].



Scheme 5. Synthesis of thiazole derivative **10**.

In continuous efforts to improve the reaction conditions and product yields, Lin *et al*. discovered an efficient method for the cyclo-condensation of several α-tosyloxyketones **11** with thiourea derivatives. The reaction was conducted in polyethylene glycol-400 (PEG-400) at room temperature with the aid of sodium carbonate and required only 1 h, affording a highly satisfactory yield (85-94%) of 2-aminoarylthiazole derivatives **12** (Scheme **6**) [30].

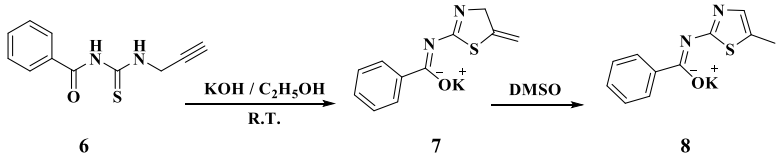


Scheme 6. Synthesis of thiazole derivative **12**.

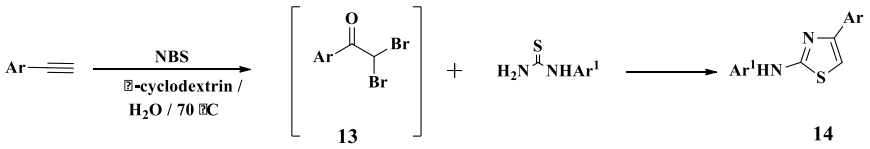
Madhav *et al.* [31] described a novel method of phenylthiazole synthesis where arylacetylene was employed as a precursor. In this study, the thiazole derivatives **14** were obtained through a one-pot, eco-friendly procedure, in a single step in which arylacetylene derivatives bind to NBS to give dibromo intermediates **13**, which react *in situ* with thiourea compounds to furnish the desired thiazole derivatives **14** (Scheme **7**).

A series of one-pot reactions resulted in an array of thiazole cyclo-condensation products. Zhu *et al.* [32] managed to obtain 2-aminothiazoles **15** from easily available aromatic ketones and thiourea assisted by I_2/CuO in absolute ethanol (Scheme **8**).

Similarly, another research adopted an analogous procedure while using iodine, toluene sulphonic acid(TsOH), and dimethyl sulphoxide DMSO for halogenation followed by



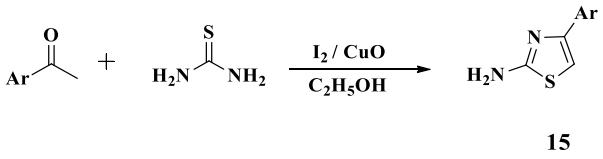
Scheme 4. Synthesis of thiazole derivative **8**.



Ar= C_6H_5, 2-F-C_6H_4, 4-F-C_6H_4, 2-CH_3-C_6H_4, 4-CH_3-C_6H_4
Ar^1= H, 4-Cl-C_6H_4, 4-CN-C_6H_4, 4-F-C_6H_4

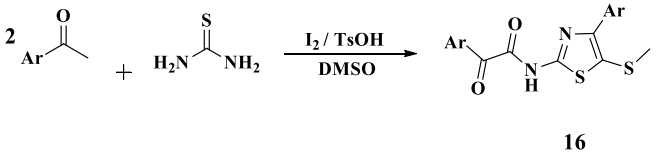
Scheme 7. Synthesis of thiazole derivative **14**.

cyclocondensation of various aromatic ketones and thiourea in a ratio of 2:1, respectively, to obtain **16** (Scheme **9**) [33].



Ar= C_6H_5, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-Cl-C_6H_4, 2,4-$(OCH_3)_2$-C_6H_3

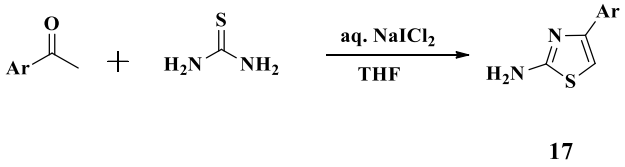
Scheme 8. Synthesis of thiazole derivative **15**.



Ar= C_6H_5, 4-CH_3-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4

Scheme 9. Synthesis of thiazole derivative **16**.

Furthermore, in another study, the thiazole target compounds **17** were synthesized *via* refluxing thiourea with aromatic ketones and sodium dichloroiodate ($NaICl_2$) in THF (Scheme **10**) [21].

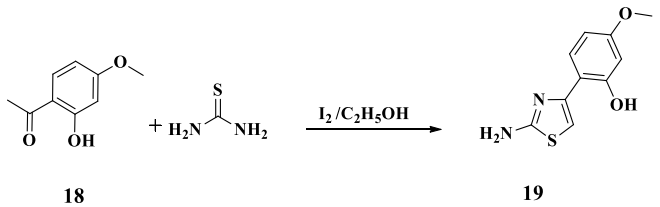


R= C_6H_5, 4-CH_3-C_6H_4, 4-NH_2-C_6H_4, 4-OCH_3-C_6H_4,

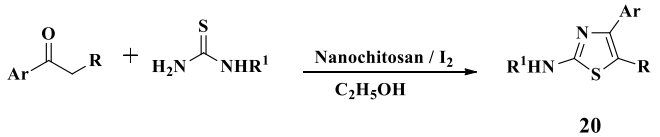
Scheme 10. Synthesis of thiazole derivative **17**.

Another one-pot method of synthesizing substituted thiazoles was reported in 2016 by Tsai and coworkers [34]. They constructed a reaction between 2-hydroxy-4-methoxyacetophenone (paeonol) (**18**) and thiourea along with iodine in ethanol, leading to the formation of 2,4-disubstituted thiazole derivative **19** through condensation followed by cyclisation reaction (Scheme **11**).

Furthermore, a one-pot method of synthesis of 2-aminothiazoles **20** was devised in 2016, where nanochitosan is used as a green catalyst in the presence of iodine. The best results of this method were obtained when the carbonyl compounds were refluxed with thiourea derivatives in ethanol in the presence of the catalyst to produce **20** (Scheme **12**) [35].



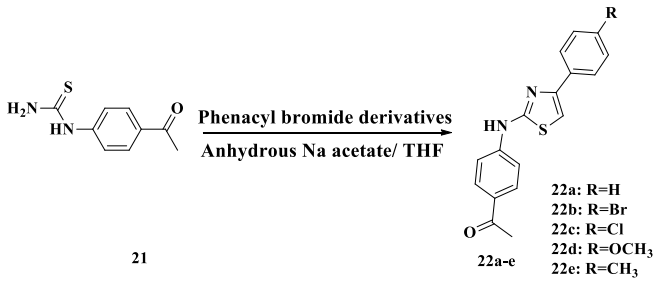
Scheme 11. Synthesis of thiazole derivative **19**.



R= H, $COCH_3$, $COOCH_3$, $COOC_2H_5$
R^1= H, CH_3
Ar= C_6H_5, 4-OH-C_6H_4, 4Cl-C_6H_4, 4-Br-C_6H_4

Scheme 12. Synthesis of thiazole derivative **20**.

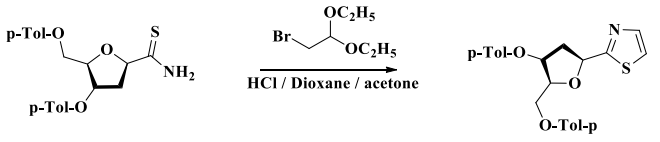
In 2020, the base-promoted cyclisation of compound **21** with phenacyl bromide in tetrahydrofuran produced the thiazole derivative **22** (Scheme **13**) [36].



Scheme 13. Synthesis of thiazole derivative **22**.

2.2. Synthesis of Thiazole Ring from Thioamide Derivatives

Miller *et al.* [37] prepared 2-substituted thiazole **24** *via* refluxing the appropriate thioamide **23** and bromoacetaldehyde diethyl acetal with catalytic amounts of 4M HCl/Dioxane in acetone (Scheme **14**).



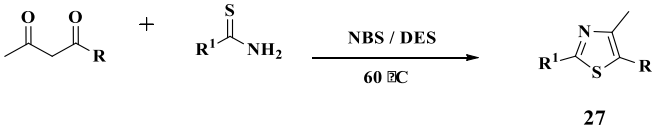
Scheme 14. Synthesis of thiazole derivative **24**.

In 2012, a group of scientists conducted a reaction to furnish 2-methyl-4-[(trimethylsilyl)ethynyl]thiazole (**26**) by treatment of 1-chloro-4-(trimethylsilyl)but-3-yn-2-one (**25**) with thioacetamide in DMF at room temperature (Scheme **15**) [38].

25 **26**

Scheme 15. Synthesis of thiazole derivative **26**.

In an attempt to avoid the use of common organic solvents in reactions and separations, due to their destructive and flammable properties, deep eutectic solvents (DES) were employed as environmentally friendly reaction media. This research focuses on the use of choline-chloride-urea as a DES in a one-pot reaction of 1,3 diketones, thioamide derivatives, and NBS at a temperature of 60 ºC to furnish the corresponding thiazole derivatives **27** (Scheme **16**) [39].

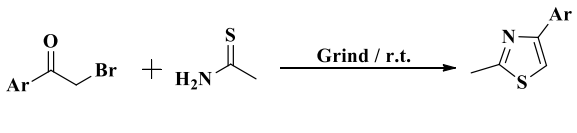


27

R= CH_3, OCH_3, OC_2H_5, CF_3
R^1= CH_3, C_6H_5

Scheme 16. Synthesis of thiazole derivative **27**.

A very efficient method of synthesis was provided by Heravi *et al.*, and the reaction was conducted at room temperature by grinding the suitable phenacyl bromide with thioacetamide to produce the designated 2,4-disubstituted thiazoles **28** (Scheme **17**) [40].

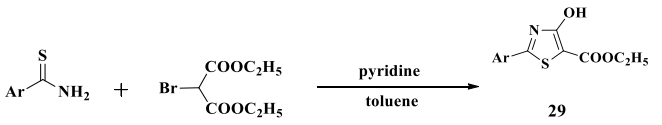


28

Ar= C_6H_5, 4-OCH_3-C_6H_4, 4-Cl-C_6H_4

Scheme 17. Synthesis of thiazole derivative **28**.

In their conquest to synthesise several thiazole derivatives, Jeankumar *et al.* [41] forged the condensation of thioamide derivatives with diethyl bromomalonate with the help of pyridine and toluene as solvent, followed by cyclisation, which afforded 4-hydroxythiazoles **29** (Scheme **18**).

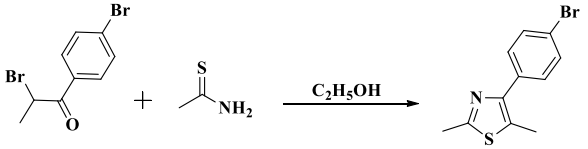


29

Ar= C_6H_5, 2-pyridyl, 4-pyridyl

Scheme 18. Synthesis of thiazole derivative **29**.

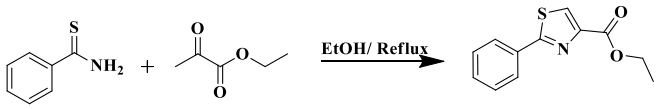
The synthesis of trisubstituted thiazole derivative **30** was achieved through the condensation cyclisation processes of 2-bromo-1-(4-bromophenyl)propan-1-one with thioacetamide to produce the targeted compound (Scheme **19**) [42].



30

Scheme 19. Synthesis of thiazole derivative **30**.

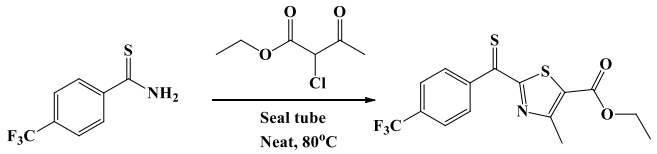
In 2020, Fan *et al.* managed to synthesize the crucial intermediate in their research, phenyl thiazole **31,** through the simple condensation of thiobenzamide with ethyl bromopyruvate in ethanol (Scheme **20**) [43].



31

Scheme 20. Synthesis of thiazole derivative **31**.

One year later, the thiazole ring was formed *via* reacting 4-(trifluoro)thiobenzamide with 2-chloroacetylacetate to get ethyl 4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carboxylate **32** (Scheme **21**) [44].



32

Scheme 21. Synthesis of thiazole derivative **32**.

2.3. Synthesis of thiazole Ring from Thiosemicarbazone

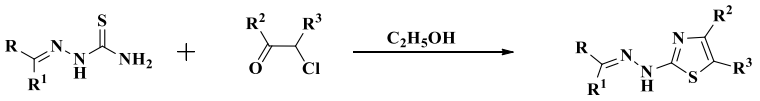
In 2013, Makam *et al.* [45] employed thiosemicarbazones **33** with aliphatic α-chloroketones in ethanol as a solvent to afford the desired hydrazinyl thiazole **34** (Scheme **22**).

In 2013, a trial to synthesise the title thiazole compound **37** through the reaction of intermediate **35** with aryl thiosemicarbazones **36** resulted in a good yield (63-86%) using ethanol as a solvent under reflux conditions at 60 °C (Scheme **23**) [14].

Aggarwal *et al.* [46] managed to produce arylthiazole derivative **39** by grinding α-haloketones with 3,5-dimethylpyrazol-1-thiocarboxamide (**38**) enhanced by sodium carbonate in solvent-free conditions (Scheme **24**).

In 2016, Gomes *et al.* [47] conducted the synthesis of 1,3 thiazoles through the reaction of thiosemicarbazones **40** with various α-halo aromatic ketone derivatives in 2-propanol at room temperature to furnish the respective thiazole derivatives **41** (Scheme **25**).

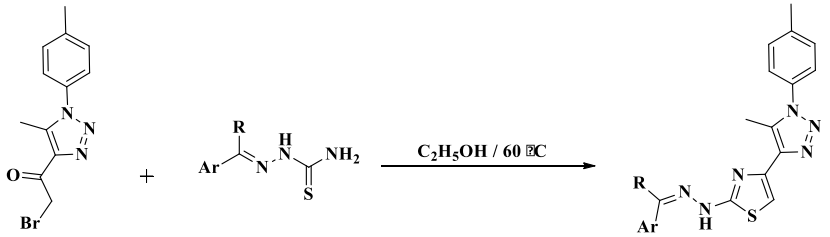
Demirici S. [48] reported the synthesis of 1,3-thiazole derivative **43** *via* the cyclisation of the thiosemicarbazone derivative **42** through its condensation with 2-bromo-1-(4-



33 **34**

R= C_6H_5, 3-OCH_3-C_6H_4 , 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4
R^1= H, CH_3
R^2= CH_3, $CH_2COOC_2H_5$
R^3= H, $COCH_3$, $COOC_2H_5$

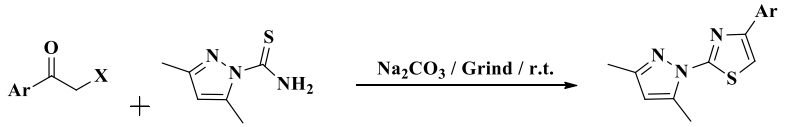
Scheme 22. Synthesis of thiazole derivative **34**.



35 **36** **37**

R= H, CH_3
Ar= C_6H_5, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4

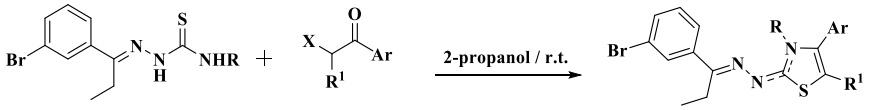
Scheme 23. Synthesis of thiazole derivative **37**.



38 **39**

X= Br, I
Ar= C_6H_5, 4-CH_3-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 4-Br-C_6H_4

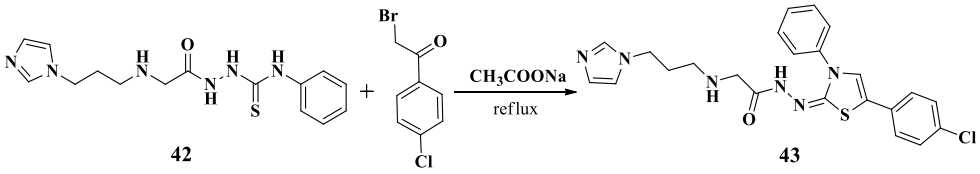
Scheme 24. Synthesis of thiazole derivative **39**.



40 **41**

X=Br, Cl
R= H, CH_3, C_6H_5
R^1= H, CH_3
Ar= C_6H_5, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-NO_2-C_6H_4, 4-Br-C_6H_4

Scheme 25. Synthesis of thiazole derivative **41**.



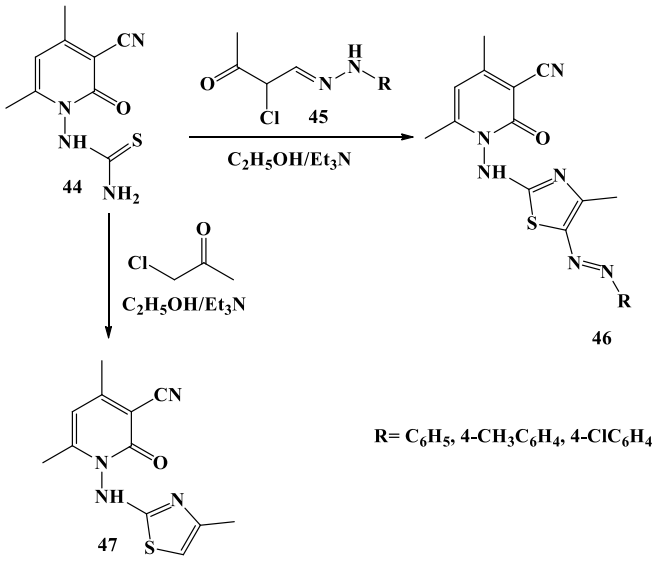
42 **43**

Scheme 26. Synthesis of thiazole derivative **43**.

chlorophenyl)ethanone in the presence of sodium acetate under reflux (Scheme **26**).

Treatment of compound **44** with hydrazonyl chloride **45** in absolute ethanol containing 5 drops of triethylamine at

reflux afforded the corresponding substituted 1, 3-thiazole derivative **46**, in good yields (85-86%). On the other hand, the reaction of **44** with chloroacetone afforded the thiazole derivative **47** (Scheme **27**) [49].



Scheme 27. Synthesis of thiazole derivatives **46** and **47**.

In 2021, the target pyridine-thiazole compounds **49** were obtained by the reaction of equimolar quantities of thiosemicarbazone derivative **48** with phenacyl bromide (Scheme **28**) [50].

The thiosemicarbazone derivative **50** reacted with α-chloro-acetylacetone in refluxing ethanol to afford the acetylthiazole derivative **51** (Scheme **29**) [51].

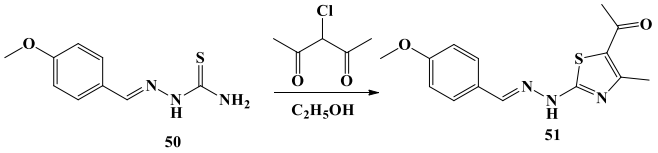
A group of researchers reported that the reaction of bis-thiosemicarbazone **52** with hydrazonoyl chloride **53** in refluxing dioxane in the presence of catalytic triethylamine delivered the target bis-thiazole **54** (Scheme **30**) [52].

3. SYNTHESIS OF THIAZOLES FROM OTHER PRECURSORS

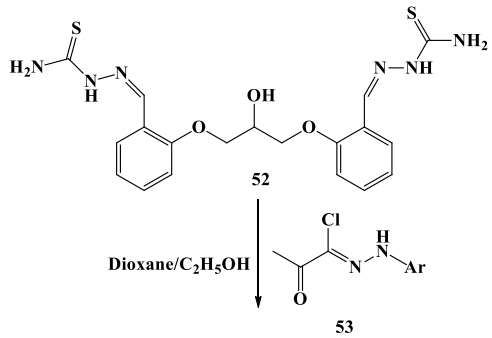
The synthesis of the thiazole ring involves several reagents that react to furnish the target ring other than those in the Hantzch synthesis [53].

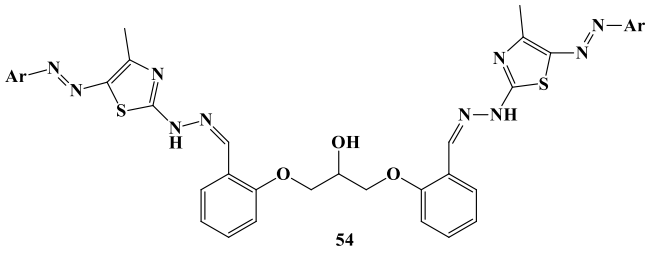
Literature survey revealed that 5-arylthiazoles **56** were also synthesised by incorporating ketone derivative **55** with phosphorus pentasulfide in chloroform and triethylamine as a base (Scheme **31**) [19].

To produce 2-aminothiazole derivative **58** from unconventional progenitor compounds, Sasmal and coworkers [54] designed a mild and efficient procedure where isothiocyanate analogues and ethyl 4-aminobut-2-ynoate hydrochloride salt (**57**) were reacted in THF at room temperature in the presence of trimethylamine (Scheme **32**).



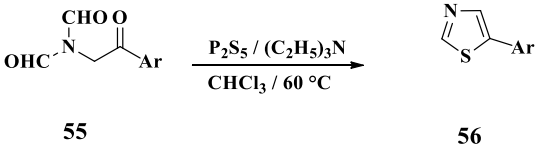
Scheme 29. Synthesis of thiazole derivative **51**.





Ar= C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 2,4-$Cl_2C_6H_3$, 2,4,6-$Br_3C_6H_2$

Scheme 30. Synthesis of thiazole derivatives **54**.

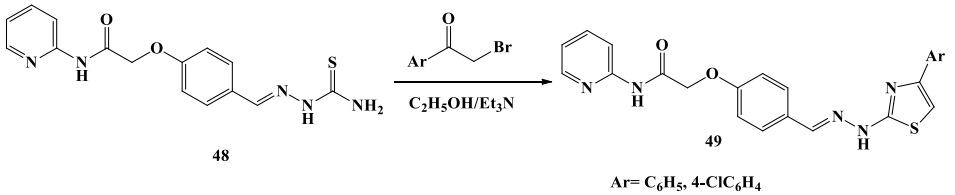


Ar= 2-CH_3-C_6H_4, 4-CH_3-C_6H_4, 2-OCH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-Cl-C_6H_4

Scheme 31. Synthesis of thiazole derivative **56**.

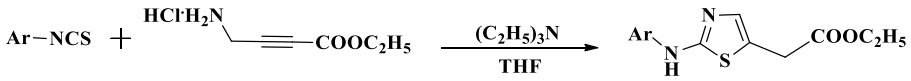
In 2009, Lawesson's reagent was added to the benzyl protected α-amido-β-ketoesters **59** to furnish the corresponding thiazole derivatives **60** (Scheme **33**) [20].

Moreover, Lingaraju *et al.* reacted methylene isocyanides like tosylmethyl isocyanide reacting with dithioesters like methyl benzodithioate in the presence of NaH at room temperature, yielding the expected thiazole **61** (Scheme **34**) [55].



Ar= C_6H_5, 4-ClC_6H_4

Scheme 28. Synthesis of thiazole derivative **49**.



57 **58**

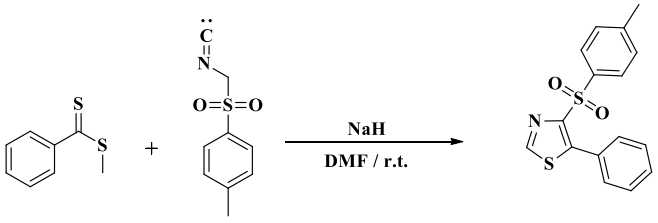
Ar= -CH_2-C_6H_5, 3-pyridyl, 4-Cl-C_6H_4, 4-OCF_3-C_6H_4

Scheme 32. Synthesis of thiazole derivative **58**.

59 **60**

Ar= C_6H_5, 4-CH_3-C_6H_4, 2-OCH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-Cl-C_6H_4
Ar^1= C_6H_5, 2-CH_3-C_6H_4, 2-F-C_6H_4, 2-OCH_3-C_6H_4, 3-OCH_3-C_6H_4

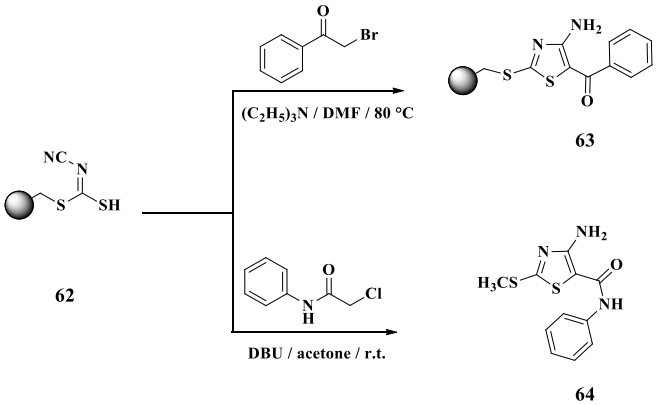
Scheme 33. Synthesis of thiazole derivative **60**.



61

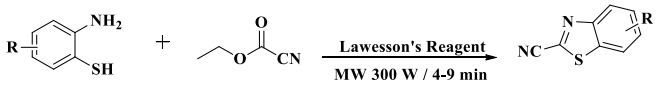
Scheme 34. Synthesis of thiazole derivative **61**.

A novel method for thiazole synthesis was adopted in two research studies by Lee *et al.* [56] and Kim *et al.* [57], where a solid phase support (Merrifield resin) was utilized. In these trials, α-bromoacetophenone or 2-chloro *N*- phenyl acetamide were cyclised through the Thorpe-Ziegler thiazole reaction, with mono-methyl cyanocarbonimidodithioate **62** bound to the resin and in the presence of triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to furnish the substituted thiazoles **63** and **64**, respectively (Scheme **35**).



Scheme 35. Synthesis of thiazole derivatives **63** and **64**.

Further on, Lawesson's reagent was utilized to activate the substituted o-aminothiophenols and ethyl cyanoformate to form an adduct, which then cyclises into the title 2-cyanobenzothiazole derivative **65** under microwave irradiation and eco-friendly solvent-less conditions (Scheme **36**) [58].

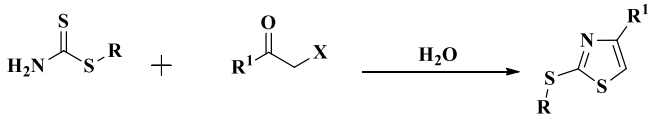


65

R= H, 5-OH, 5-OCH_3, 3-Cl

Scheme 36. Synthesis of thiazole derivative **65**.

In another survey, the researchers performed the reaction in a green nontoxic solvent, where dithiocarbamate was allowed to react with an α-haloketone in H_2O and furnished the proposed 2-alkylsulfanylthiazoles **66** (Scheme **37**) [17].



66

R= C_4H_9, CH_2-C_6H_5, 4-Cl-C_6H_4
R^1= CH_3, C_6H_5
X= Br, Cl

Scheme 37. Synthesis of thiazole derivative **66**.

4. MULTICOMPONENT METHODS FOR SYNTHESIS OF THE THIAZOLE RING

An effective one-pot synthetic method is multicomponent reactions (MCRs), where three or even more reactants can be mixed without the need to separate any intermediates. Their selectivity and manageability make them superior to regular reactions [59-63].

More ecofriendly, one-pot, multicomponent reactions were designed by Shiran and coworkers, where arylamine,

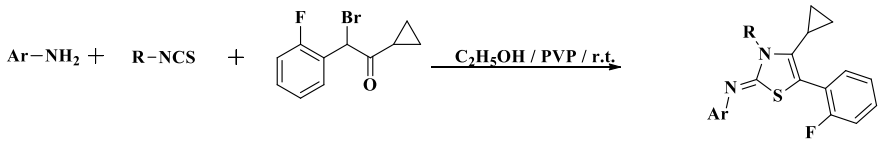
alkyl isothiocyanate, and α-haloketone were stirred at room temperature in the presence of the recyclable catalyst polyvinyl pyridine (PVP) to afford the desired thiazole derivatives **67** (Scheme **38**) [64].

Xiabing *et al.* [12] managed to synthesise thiazole derivative **68** through a green and efficient MCR one-pot method using benign solvents and conditions. The procedure involves treating equimolar mixtures of a series of aldehydes and ketones, thiosemicarbazide, and ethyl 4-chloro-3-oxobutanoate with catalytic amounts of anhydrous sodium acetate in ethanol as a solvent (Scheme **39**).

In 2018, Wang *et al.* [65] designed a novel copper-catalyzed oxidative thiazole reaction involving different amines, aldehyde, sulphur, and the green oxidant O_2, all reacted in one pot step to prepare the designated target compound **69** (Scheme **40**).

Green reactions were also carried out using a multicomponent technique in which an aldehyde and ketone were combined with elemental sulphur in a one-pot pyridine/H2O system to produce phenylthiazole derivatives 70 (Scheme **41**) [66].

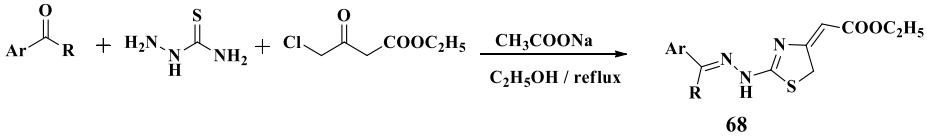
In 2021, a ternary mixture of salicylaldehyde derivative **71**, thiosemicarbazide, and phenacyl bromide were allowed to react with dioxane in the presence of 1.5 equiv. of diethylamine. The mixture was heated at reflux for 6 h, yielding **72** as the sole product (Scheme **42**) [67].



67

R= CH_3, C_2H_5, $CH_2CH=CH_2$
Ar= 4-CH_3-C_6H_4, 4-C_2H_5-C_6H_4, 4-OCH_3-C_6H_4, 4-OC_2H_5-C_6H_4

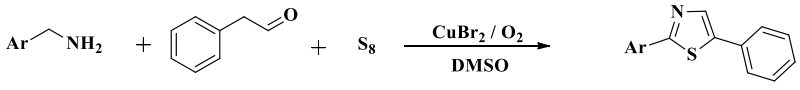
Scheme 38. Synthesis of thiazole derivative **67**.



68

R= H, CH_3
Ar= C_6H_5, 4-OCH_3-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4

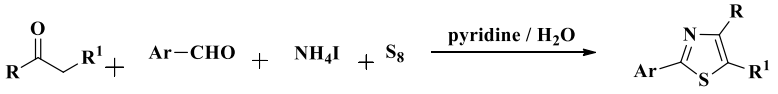
Scheme 39. Synthesis of thiazole derivative **68**.



69

Ar= C_6H_5, 2-CH_3-C_6H_4, 3-CH_3-C_6H_4, 4-CH_3-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4

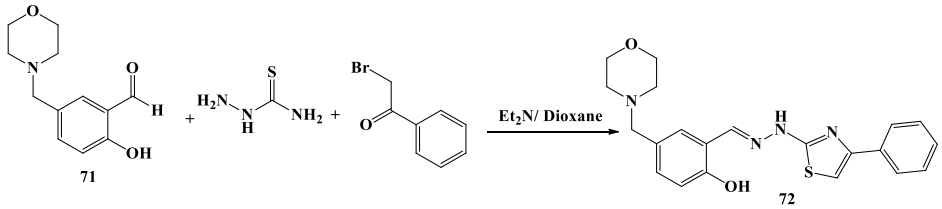
Scheme 40. Synthesis of thiazole derivative **69**.



70

R= CH_2-CH_2-CH_3, C_6H_5
R^1= CH_3, CH_2-CH_3, C_6H_5
Ar= C_6H_5, 2-Cl-C_6H_4, 4-OCH_3-C_6H_4, 4-Br-C_6H_4

Scheme 41. Synthesis of thiazole derivative **70**.

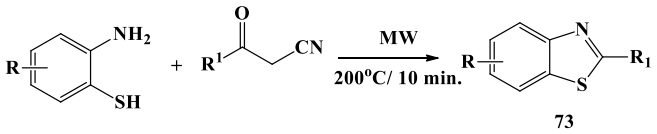


71 72

Scheme 42. Synthesis of thiazole derivative **72**.

5. ENVIRONMENTALLY BENIGN METHODS OF THIAZOLE SYNTHESIS

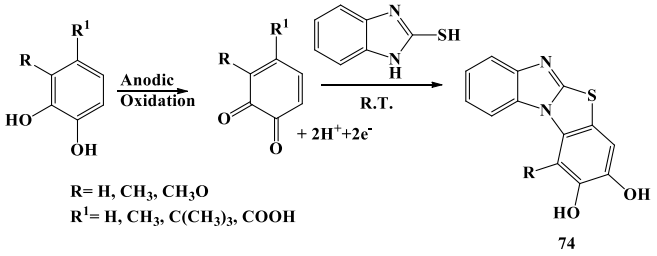
The synthesis of benzothiazole analog **73** was achieved *via* microwave irradiation (MWI) of a 1:1 mixture of *o*-aminothiophenol and alkyl/aryl acylacetonitriles at 200 °C for 10 min. The yields were very good to excellent (86-95%) (Scheme **43**) [68].



R= H, Cl
R^1= Alkyl, Aryl

Scheme 43. Synthesis of thiazole derivative **73**.

A series of novel catechol-fused tetracyclic compounds, with an imidazo[2,1-b]thiazole central core **74**, were successfully synthesized through the anodic oxidation of catechols in the presence of 2-mercaptobenzimidazole in aqueous solution. The cyclic voltammetric results show that 2-mercaptobenzimidazole and electrochemically produced o-benzoquinones undergo a one-pot four-step sequential reaction, affording fused polyheterocyclic compounds (Scheme **44**) [69].

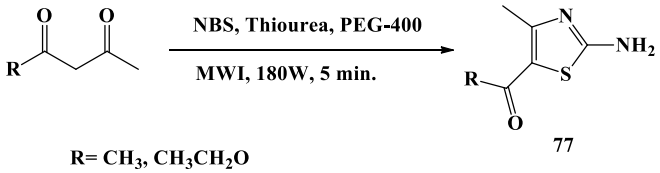


R= H, CH_3, CH_3O
R^1= H, CH_3, $C(CH_3)_3$, COOH

Scheme 44. Synthesis of thiazole derivative **74**.

A clean and environmentally benign route to synthesize a series of benzothiazole derivatives **76** using the reaction between various synthetized aldehydes **75**, thiosemicarbazide, and different acetophenones and N-bromosuccinimide as a substrate instead of haloacetophenones was reported in the previous reactions in the presence of a catalytic amount of silica coated magnetite nanoparticles (Scheme **45**) [70].

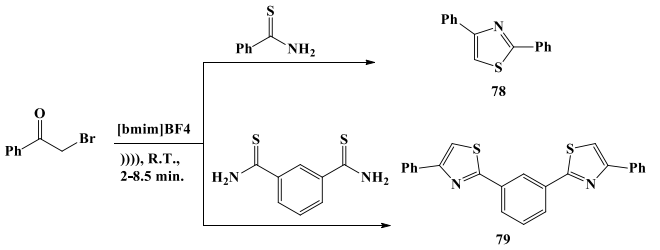
A group of researchers synthesized 1-(2-amino-4-methylthiazol-5-yl)ethanone and ethyl 2-amino-4-methylthiazole-5-carboxylate **77** by one pot reaction of acetyl acetone or ethyl acetoacetate with N-bromosuccinimide (NBS) and thiourea in the presence of PEG-400 under microwave irradiation at 180 W (Scheme **46**) [71].



R= CH_3, CH_3CH_2O

Scheme 46. Synthesis of thiazole derivative **77**.

Noei and Khosropour [72] reported the reaction of arylthioamides with bromoacetophenones in the ionic liquid 1-Butyl-3-methylimidazolium Tetrafluoroborate [bmim]BF4 under ultrasonic irradiation for the synthesis of 2,4-diarylthiazole derivatives **78** and **79** in high yield (84-98%) (Scheme **47**).

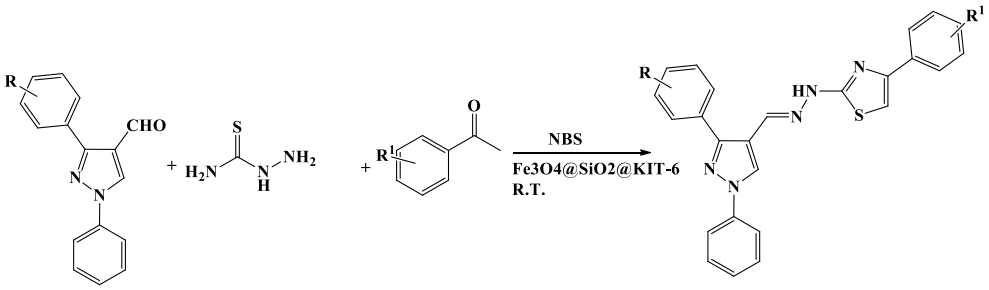


Scheme 47. Synthesis of thiazole derivatives **78** and **79**.

Fe_3O_4@vitamin B1 was designed and prepared as an inexpensive and efficient heterogeneous nanocatalyst for the synthesis of a new 1,3-thiazole derivative **80**. The three-component, one-pot condensation of arylglyoxal monohydrate, cyclic 1,3-dicarbonyls, and thioamides in water as a green solvent was applied for the preparation of 1,3-thiazole derivatives (Scheme **48**) [73].

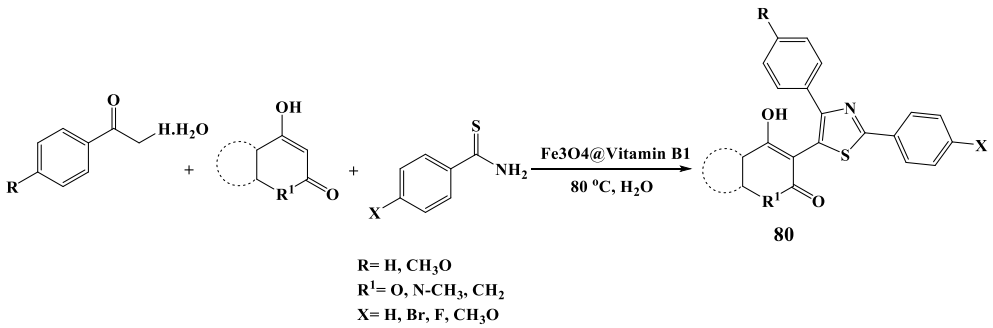
Zhao *et al*. [74] reported a green and regioselective process for the construction of thiazolo[3,2-*a*]benzimidazole skeleton **81** using DMSO-H_2O_2 as an oxidant in H_2O (Scheme **49**) [74].

In 2021, it was reported that ultrasonic irradiation is an ecofriendly, green, efficient approach for the synthesis of new 1,3-thiazoles under solvent-free conditions. Thiocarbohydrazones were reacted with α-Chloroketone or α-bromoester under ultrasonic conditions affording 1,3-thiazoles **82** and **83** (Scheme **50**) [75].

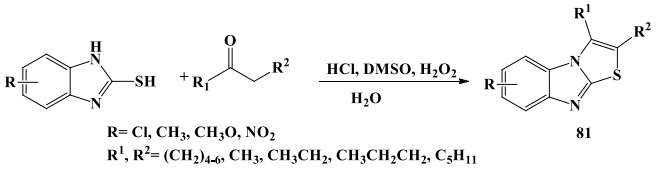


R= H, 4-Cl, 4-OH, $4\text{-}CH_3$
R^1= H, 4-Br, 4-Cl, 2-OH, 4-OH, $4\text{-}CH_3O$, $4\text{-}NO_2$

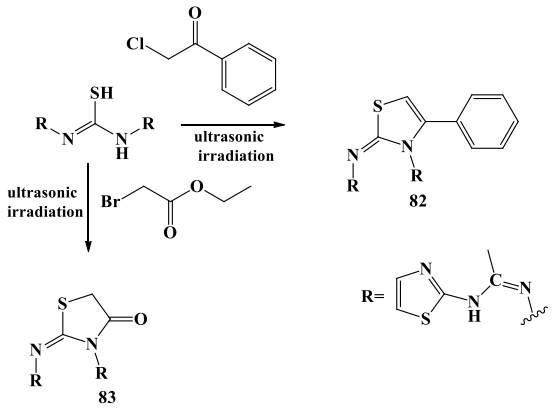
Scheme 45. Synthesis of thiazole derivative **76**.



Scheme 48. Synthesis of thiazole derivative **80**.



Scheme 49. Synthesis of thiazole derivative **81**.

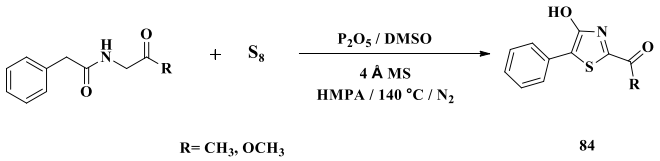


Scheme 50. Synthesis of thiazole derivatives **82** and **83**.

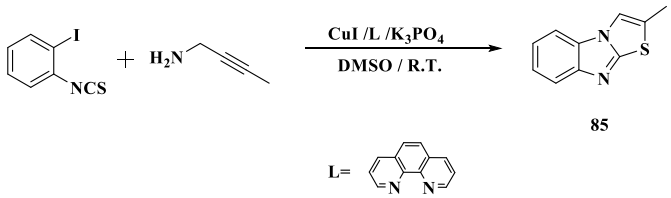
6. RECENT THIAZOLE RING FORMATION REACTIONS

Chen and coworkers managed to enhance their previous work on thiazole synthesis through the cleavage of Csp^3-H bonds in the absence of metal catalysts. Herein, they developed a procedure to prepare 4-hydroxythiazole derivatives **84** *via* the sulphuration/annulation of amides by elemental sulphur in the presence of P_2O_5 in dimethyl sulphoxide (DMSO) and hexamethylphosphoramide (HMPA) as solvents. It was conducted under oxygen free conditions for the optimum yields (69-86%) and electron donating substituents were found to be superior to their electron withdrawing counterparts (Scheme **51**) [76].

Recently in 2021, a team of researchers attempted to develop synthetic pathways that produce benzimidazo[2,1-b]thiazole derivative **85**, requiring mild conditions and readily available reactants. They devised a series of copper catalysed C-N coupling reactions and subsequent cyclisation of 2-iodophenyl isothiocyanates with propargylamine derivatives. Several reaction conditions were investigated, and the highest yield, 78%, was obtained when DMSO was used as a solvent, phenanthroline as a ligand, and CuI as a catalyst at room temperature (Scheme **52**) [77].

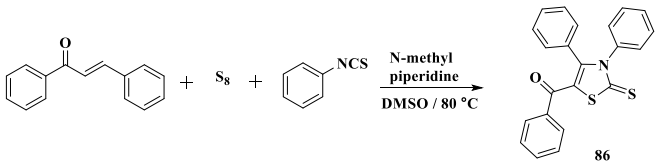


Scheme 51. Synthesis of thiazole derivatives **84.**



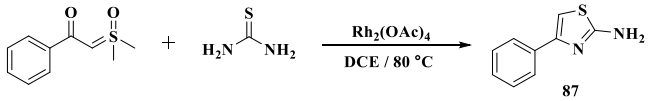
Scheme 52. Synthesis of thiazole derivatives **85.**

In another study, thiazole-2-thione derivatives were synthesised *via* a three-component reaction involving easily accessible reactants, elemental sulphur, chalcones, and isothiocyanates. After numerous trials, the optimum reaction conditions constituted a mixture of chalcone derivative with phenyl isothiocyanate and *N*-methyl piperidine as a sulphur activator in DMSO to afford **86** (Scheme **53**) [78].



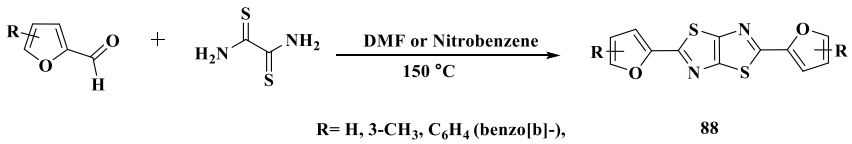
Scheme 53. Synthesis of thiazole derivatives **86**.

Novel 2-aminothiazole derivatives were prepared from sulphoxonium ylides in the presence of the catalyst rhodium (II) acetate, which acts as a carbenoid precursor to couple with thioureas to produce the thiazole derivative **87** in dichloroethane (Scheme **54**) [79].



Scheme 54. Synthesis of thiazole derivatives **87**.

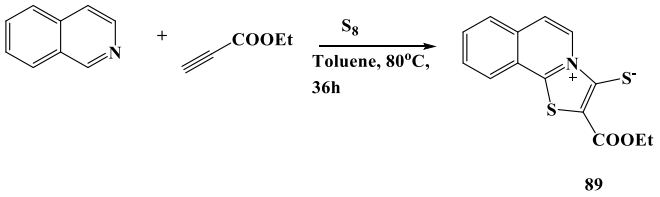
Tokàrovà *et al.* investigated the Ketcham reaction essential to furnish thiazolo[5,4-d]thiazoles (TzTz); they are scaffolds active in photovoltaic and optoelectronic cells. In this study, dithioxamide is reacted with aldehyde derivatives utilizing two different solvents, *N,N*-dimethylformamide



Scheme 55. Synthesis of thiazole derivatives **88.**

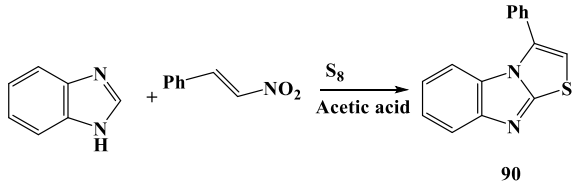
(DMF) and nitrobenzene, to afford the anticipated TzTz derivatives **88** (Scheme **55**) [80].

Compound **89** can be synthesized *via* the three component [2 + 2 + 1] cycloaddition reaction of isoquinoline with ethyl propionate and elemental sulfur in the absence of any metal catalyst and additives (Scheme **56**) [81].



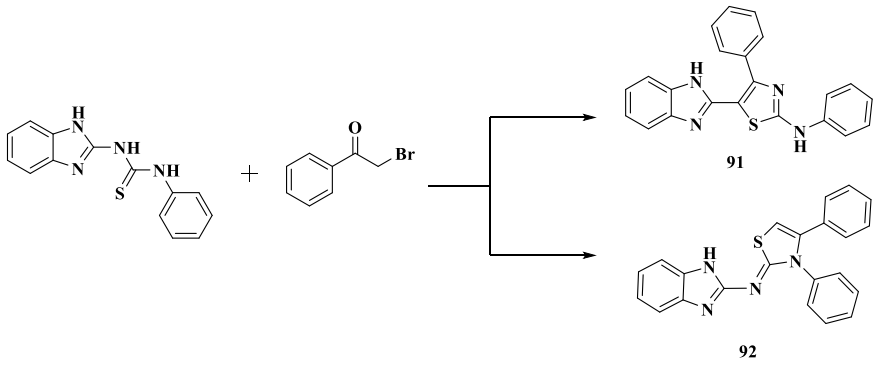
Scheme 56. Synthesis of thiazole derivatives **89**.

Three-component annulation of benzimidazole, *β*-nitrostyrene, and elemental sulfur has been developed to give thiazole derivative **90**. This technique represents an advanced method in modern synthesis that provides an efficient platform for rapid preparation of complex molecules from simple raw materials (Scheme **57**) [82].



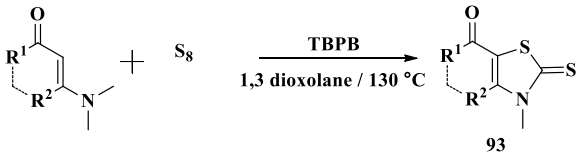
Scheme 57. Synthesis of thiazole derivatives **90**.

Recently in 2021, a microwave-assisted reaction of benzimidazole thiourea and bromoacetophenone furnished benzimidazole-amino thiazole derivatives **91** and **92** without the use of catalysts or additives. This is a novel method of C-N bond cleavage designed for heterocyclic compounds with bifunctional hydrogen bonding through varying the concentration of acetic acid to afford different substrates (Scheme **58**) [83].



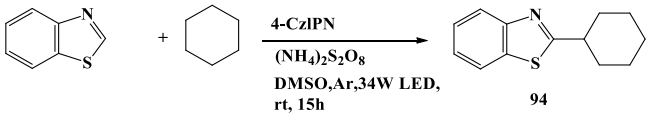
Scheme 58. Synthesis of thiazole derivatives **91 and 92**.

Thiazole-2-thione derivatives **93** were synthesized from enaminone scaffolds and elemental sulphur in the presence of tert-Butyl peroxybenzoate (TBPB) to accelerate oxidative cyclisation and tandem formation of C-S and C=S bonds (Scheme **59**) [84].



Scheme 59. Synthesis of thiazole derivatives **93.**

Recent methods to functionalize sulfur-containing heteroarenes were reported. Thiophene containing compounds were synthesized *via* C-H difluoroalkylation or through C-H arylation of aliphatic and aromatic ketones [85-87]. Thiazole derivative **94** was obtained by sustainable cross-dehydrogenative coupling of strong C(sp^3)-H with N-heteroarenes using an efficient organic photocatalyst such as 2,4,5,6-Tetra(9H-carbazol-9-yl)isophthalonitrile (4-CzIPN) under an argon atmosphere (Scheme **60**). This method is characterized by atomic and steps economy and acid-free conditions [88].



Scheme 60. Synthesis of thiazole derivatives **94.**

CONCLUSION

Thiazole ring is a common structural motif of an extensive range of biologically active compounds, including anticonvulsants, anticancer, antiviral, antibacterial agents, antifungal, anti-inflammatory, analgesic, and antidiabetic agents. Thiazole scaffold has become an interesting structural element in the development of pharmaceutical compounds. In this mini review, we have summarized the advances of thia-

zole synthesis, including ecofriendly, one-pot, multicomponent reactions in the time frame from 2002 to 2021. This could guide medicinal chemists for precise and efficient synthesis of thiazole ring.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Hays, S.J.; Rice, M.J.; Ortwine, D.F.; Johnson, G.; Schwarz, R.D.; Boyd, D.K.; Copeland, L.F.; Vartanian, M.G.; Boxer, P.A. Substituted 2-benzothiazolamines as sodium flux inhibitors: Quantitative structure-activity relationships and anticonvulsant activity. *J. Pharm. Sci.,* **1994**, *83*(10), 1425-1432. http://dx.doi.org/10.1002/jps.2600831013 PMID: 7884664

[2] Hutchinson, I.; Bradshaw, T.D.; Matthews, C.S.; Stevens, M.F.G.; Westwell, A.D. Antitumour benzothiazoles. Part 20: 3′-cyano and 3′-alkynyl-substituted 2-(4′-aminophenyl)benzothiazoles as new potent and selective analogues. *Bioorg. Med. Chem. Lett.,* **2003**, *13*(3), 471-474. http://dx.doi.org/10.1016/S0960-894X(02)00930-7 PMID: 12565953

[3] Dawood, K.M.; Eldebss, T.M.A.; El-Zahabi, H.S.A.; Yousef, M.H. Synthesis and antiviral activity of some new bis-1,3-thiazole derivatives. *Eur. J. Med. Chem.,* **2015**, *102*, 266-276. http://dx.doi.org/10.1016/j.ejmech.2015.08.005 PMID: 26291036

[4] Shelke, S.H.; Mhaske, P.C.; Hande, P.; Bobade, V.D. Synthesis and antimicrobial activities of novel series of 1-((4-methyl-2-substituted thiazol-5-yl)methyleneamino)-2-substituted isothiourea derivatives. *Phosphorus Sulfur Silicon Relat. Elem.,* **2013**, *188*(9), 1262-1270. http://dx.doi.org/10.1080/10426507.2012.745542

[5] Oniga, S.D.; Araniciu, C.; Palage, M.D.; Popa, M.; Chifiriuc, M.C.; Marc, G.; Pirnau, A.; Stoica, C.I.; Lagoudis, I.; Dragoumis, T.; Oniga, O. New 2-phenylthiazoles as potential sortase a inhibitors: Synthesis, biological evaluation and molecular docking. *Molecules,* **2017**, *22*(11), 1-18. http://dx.doi.org/10.3390/molecules22111827 PMID: 29077016

[6] El-Husseiny, W.M. Synthesis and biological evaluation of new 3-phenylthiazolidin-4-one and 3-phenylthiazole derivatives as antimicrobial agents. *Polycycl. Aromat. Compd.,* **2021**, *41*, 1988-2002.

[7] Mohammad, H.; Eldesouky, H.E.; Hazbun, T.; Mayhoub, A.S.; Seleem, M.N. Identification of a phenylthiazole small molecule with dual antifungal and antibiofilm activity against *Candida albicans* and *Candida auris. Sci. Rep.,* **2019**, *9*(1), 18941. http://dx.doi.org/10.1038/s41598-019-55379-1 PMID: 31831822

[8] Helal, M.H.M.; Salem, M.A.; El-Gaby, M.S.A.; Aljahdali, M. Synthesis and biological evaluation of some novel thiazole compounds as potential anti-inflammatory agents. *Eur. J. Med. Chem.,* **2013**, *65*, 517-526. http://dx.doi.org/10.1016/j.ejmech.2013.04.005 PMID: 23787438

[9] Thore, S.N.; Gupta, S.V.; Baheti, K.G. Synthesis and pharmacological evaluation of 5-methyl-2-phenylthiazole-4-substituted heteroazoles as a potential anti-inflammatory and analgesic agents. *J. Saudi Chem. Soc.,* **2016**, *20*, S46-S52. http://dx.doi.org/10.1016/j.jscs.2012.09.002

[10] Ma, L.; Wang, T.; Shi, M.; Ye, H. Synthesis, activity, and docking study of phenylthiazole acids as potential agonists of PPARγ. *Drug Des. Devel. Ther.,* **2016**, *10*, 1807-1815. http://dx.doi.org/10.2147/DDDT.S106406 PMID: 27313447

[11] Wang, D.Z. Hantzsch thiazole synthesis.*Comprehensive organic name reactions and reagents*; Wiley, **2010**, pp. 1330-1334.

[12] Xiabing, M.; Ablajan, K.; Obul, M.; Seydimemet, M.; Ruzi, R.; Wenbo, L. Facile one-pot, three-component synthesis of thiazole compounds by the reactions of aldehyde/ketone, thiosemicarbazide and chlorinated carboxylic ester derivatives. *Tetrahedron,* **2016**, *72*(18), 2349-2353. http://dx.doi.org/10.1016/j.tet.2016.03.053

[13] Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Granese, A.; Carradori, S.; D'Ascenzio, M.; Lilli, D.; Rivanera, D. Synthesis and biological evaluation of novel 2,4-disubstituted-1,3-thiazoles as anti-Candida spp. agents. *Eur. J. Med. Chem.,* **2011**, *46*(1), 378-382. http://dx.doi.org/10.1016/j.ejmech.2010.10.027 PMID: 21084135

[14] Ablajan, K.; Liju, W.; Tuoheti, A. An efficient synthesis of some new hydrazone derivatives containing 1,2,3-triazole and thiazole. *Lett. Org. Chem.,* **2013**, *10*(10), 715-721. http://dx.doi.org/10.2174/15701786101010131126115715

[15] Eriks, J.C.; van der Goot, H.; Sterk, G.J.; Timmerman, H. Histamine H_2-receptor agonists. Synthesis, *in vitro* pharmacology, and qualitative structure-activity relationships of substituted 4- and 5-(2-aminoethyl)thiazoles. *J. Med. Chem.,* **1992**, *35*(17), 3239-3246. http://dx.doi.org/10.1021/jm00095a021 PMID: 1507209

[16] Ochiai, M.; Nishi, Y.; Hashimoto, S.; Tsuchimoto, Y.; Chen, D.W. Synthesis of 2,4-disubstituted thiazoles from (Z)-(2-acetoxyvinyl)phenyl-λ^3-iodanes: Nucleophilic substitution of α-λ^3-iodanyl ketones with thioureas and thioamides. *J. Org. Chem.,* **2003**, *68*(20), 7887-7888. http://dx.doi.org/10.1021/jo020759o PMID: 14510572

[17] Halimehjani, A.Z.; Hasani, L.; Alaei, M.A.; Saidi, M.R. Dithiocarbamates as an efficient intermediate for the synthesis of 2-(alkylsulfanyl) thiazoles. *Tetrahedron Lett.,* **2016**, *57*(8), 883-886. http://dx.doi.org/10.1016/j.tetlet.2016.01.045

[18] Hassan, A.A.; Mohamed, S.K.; Mohamed, N.K.; El-Shaieb, K.M.A.; Abdel-Aziz, A.T.; Mague, J.T.; Akkurt, M. Facile and convenient synthesis of 2,4-disubstituted and 2,3,4-trisubstituted 1,3-thiazoles. *J. Sulfur Chem.,* **2016**, *37*(2), 162-175. http://dx.doi.org/10.1080/17415993.2015.1114621

[19] Sheldrake, P.W.; Matteucci, M.; Mcdonald, E. Facile generation of a library of 5-aryl-2-arylsulfonyl-1,3-thiazoles. *Synlett,* **2006**, *3*(3), 460-462. http://dx.doi.org/10.1055/s-2006-926243

[20] Sanz-Cervera, J.F.; Blasco, R.; Piera, J.; Cynamon, M.; Ibáñez, I.; Murguía, M.; Fustero, S. Solution *versus* fluorous *versus* solid-phase synthesis of 2,5-disubstituted 1,3-azoles. Preliminary antibacterial activity studies. *J. Org. Chem.,* **2009**, *74*(23), 8988-8996. http://dx.doi.org/10.1021/jo9016265 PMID: 19894729

[21] Ghodse, S.M.; Telvekar, V.N. Synthesis of 2-aminothiazole derivatives from easily available thiourea and alkyl/aryl ketones using aqueous $NaICl_2$. *Tetrahedron Lett.,* **2014**, *56*(2), 472-474. http://dx.doi.org/10.1016/j.tetlet.2014.11.140

[22] Ingle, R.D.; Bhingolikar, V.E.; Bondge, S.P.; Mane, R.A. Synthesis of biologically important new 1, 4-benzothiazines bearing thiazole substituted aroyl moiety. *ChemInform,* **2003**, *42*(24), 695-698. http://dx.doi.org/10.1002/chin.200324135

[23] Gaikwad, S.A.; Patil, A.A.; Deshmukh, M.B. An efficient, uncatalyzed, and rapid synthesis of thiazoles and aminothiazoles under microwave irradiation and investigation of their biological activity. *Phosphorus Sulfur Silicon Relat. Elem.,* **2010**, *185*(1), 103-109. http://dx.doi.org/10.1080/10426500802715163

[24] Ameri, M.; Amoozadeh, A.; Asghari, A.; Nematollahi, D.; Bakherad, M. A facile and efficient one-pot electrochemical synthesis of thiazole derivatives in aqueous solution. *Helv. Chim. Acta,* **2015**, *98*(2), 210-223. http://dx.doi.org/10.1002/hlca.201400167

[25] Faidallah, H.M.; Khan, K.A.; Asiri, A.M. Synthesis and biological evaluation of new 3-trifluoromethylpyrazolesulfonyl-urea and thiourea derivatives as antidiabetic and antimicrobial agents. *J. Fluor. Chem.,* **2011**, *132*(2), 131-137. http://dx.doi.org/10.1016/j.jfluchem.2010.12.009

[26] Chen, B.C.; Zhao, R.; Wang, B.; Droghini, R.; Lajeunesse, J.; Sirard, P.; Endo, M.; Balasubramanian, B.; Barrisha, J.C. A new and efficient preparation of 2-aminothiazole-5-carbamides: Applications to the synthesis of the anti-cancer drug dasatinib. *ARKIVOC,* **2010**, **2010**(6), 32-38. http://dx.doi.org/10.3998/ark.5550190.0011.604

[27] Kuarm, B.S.; Madhav, J.V.; Rajitha, B. Xanthan Sulfuric Acid : An efficient bio-supported and recyclable solid acid catalyst for the synthesis of 2-aminothiazole-5-carboxylates and 2-aminoselenazole-5-carboxylates. *Lett. Org. Chem.,* **2011**, *8*, 549-553. http://dx.doi.org/10.2174/157017811797249443

[28] Gomez, J.D.C.; Balcazar, E.; Hagenbach, A.; Noufele, C.N.; Abram, U. Benzoylamido-substituted thiazoles and thiazolidines and their rhenium complexes. *Polyhedron,* **2016**, *117*, 293-299. http://dx.doi.org/10.1016/j.poly.2016.06.004

[29] Alajarín, M.; Cabrera, J.; Pastor, A.; Sánchez-Andrada, P.; Bautista, D. On the [2+2] cycloaddition of 2-aminothiazoles and dimethyl acetylenedicarboxylate. Experimental and computational evidence of a thermal disrotatory ring opening of fused cyclobutenes. *J. Org. Chem.,* **2006**, *71*(14), 5328-5339. http://dx.doi.org/10.1021/jo060664c PMID: 16808523

[30] Lin, P.Y.; Hou, R.S.; Wang, H.M.; Kang, I.J.; Chen, L.C. Efficient synthesis of 2-aminothiazoles and fanetizole in liquid PEG-400 at ambient conditions. *J. Chin. Chem. Soc. (Taipei),* **2009**, *56*(3), 455-458. http://dx.doi.org/10.1002/jccs.200900068

[31] Madhav, B.; Narayana Murthy, S.; Anil Kumar, B.S.P.; Ramesh, K.; Nageswar, Y.V.D. A tandem one-pot aqueous phase synthesis of thiazoles/selenazoles. *Tetrahedron Lett.,* **2012**, *53*(30), 3835-3838. http://dx.doi.org/10.1016/j.tetlet.2012.04.097

[32] Zhu, Y.; Yuan, J.; Zhao, Q.; Lian, M.; Gao, Q.; Liu, M.; Yang, Y.; Wu, A.I. $_2$/CuO-catalyzed tandem cyclisation strategy for one-pot synthesis of substituted 2-aminothiozole from easily available aromatic ketones / α,β -unsaturated ketones and thiourea. *Tetrahedron,* **2012**, *68*(1), 173-178. http://dx.doi.org/10.1016/j.tet.2011.10.074

[33] Xue, W.; Zheng, K.; Li, H.; Gao, F.; Wu, A. Iodine-promoted selective synthesis of substituted aminothiazole *via* a self-sorting reaction network. *Tetrahedron Lett.,* **2014**, *55*(30), 4212-4215. http://dx.doi.org/10.1016/j.tetlet.2014.05.101

[34] Tsai, C.Y.; Kapoor, M.; Huang, Y.P.; Lin, H.H.; Liang, Y.C.; Lin, Y.L.; Huang, S.C.; Liao, W.N.; Chen, J.K.; Huang, J.S.; Hsu, M.H. Synthesis and evaluation of aminothiazole-paeonol derivatives as potential anticancer agents. *Molecules,* **2016**, *21*(2), 145. http://dx.doi.org/10.3390/molecules21020145 PMID: 26821004

[35] Safari, J.; Abedi-Jazini, Z.; Zarnegar, Z.; Sadeghi, M. Nanochitosan: A biopolymer catalytic system for the synthesis of 2-aminothiazoles. *Catal. Commun.,* **2016**, *77*, 108-112. http://dx.doi.org/10.1016/j.catcom.2016.01.007

[36] Shahin, I.G.; Abutaleb, N.S.; Alhashimi, M.; Kassab, A.E.; Mohamed, K.O.; Taher, A.T.; Seleem, M.N.; Mayhoub, A.S. Evaluation of N-phenyl-2-aminothiazoles for treatment of multi-drug resistant and intracellular Staphylococcus aureus infections. *Eur. J. Med. Chem.,* **2020**, *202*, 112497. http://dx.doi.org/10.1016/j.ejmech.2020.112497 PMID: 32707373

[37] Miller, T.J.; Farquar, H.D.; Sheybani, A.; Tallini, C.E.; Saurage, A.S.; Fronczek, F.R.; Hammer, R.P. Synthesis of oligonucleotides containing thiazole and thiazole *N*-oxide nucleobases. *Org. Lett.,* **2002**, *4*(6), 877-880. http://dx.doi.org/10.1021/ol017003g PMID: 11893175

[38] Arunkumar, K.; Reddy, D.N.K.; Chandrasekhar, K.B.; Kumar, P.R.; Kumar, K.S.; Pal, M. Catalysis by zeolite leading to the construction of thiazole ring: An improved synthesis of 4-alkynyl substituted thiazoles. *Tetrahedron Lett.,* **2012**, *53*(30), 3885-3889. http://dx.doi.org/10.1016/j.tetlet.2012.05.062

[39] Azizi, N.; Rahimi, Z.; Alipour, M. Deep eutectic solvent-assisted one-pot synthesis of 2-aminothiazole and 2-aminoxazole derivatives. *C. R. Chim.,* **2015**, *18*(6), 626-629. http://dx.doi.org/10.1016/j.crci.2014.10.001

[40] Heravi, M.M.; Poormohammad, N.; Beheshtiha, Y.S.; Baghernejad, B. Efficient synthesis of 2,4-disubstituted thiazoles under grinding. *Synth. Commun.,* **2011**, *41*(4), 579-582. http://dx.doi.org/10.1080/00397911003629440

[41] Jeankumar, V.U.; Renuka, J.; Santosh, P.; Soni, V.; Sridevi, J.P.; Suryadevara, P.; Yogeeswari, P.; Sriram, D. Thiazole-aminopiperidine hybrid analogues: Design and synthesis of novel *Mycobacterium tuberculosis* GyrB inhibitors. *Eur. J. Med. Chem.,* **2013**, *70*, 143-153. http://dx.doi.org/10.1016/j.ejmech.2013.09.025 PMID: 24148991

[42] Reddy, G.M.; Garcia, J.R.; Reddy, V.H.; de Andrade, A.M.; Camilo, A., Jr; Ribeiro, R.A.P.; de Lazaro, S.R. Synthesis, antimicrobial activity and advances in structure-activity relationships (SARs) of novel tri-substituted thiazole derivatives. *Eur. J. Med. Chem.,* **2016**, *123*, 508-513. http://dx.doi.org/10.1016/j.ejmech.2016.07.062 PMID: 27494167

[43] Fan, T.; Guo, W.; Shao, T.; Zhou, W.; Hu, P.; Liu, M.; Chen, Y.; Yi, Z. Design, synthesis and evaluation of phenylthiazole and phenylthiophene pyrimidindiamine derivatives targeting the bacterial membrane. *Eur. J. Med. Chem.,* **2020**, *190*, 112141. http://dx.doi.org/10.1016/j.ejmech.2020.112141 PMID: 32078862

[44] Kesari, C.; Rama, K.R.; Sedighi, K.; Stenvang, J.; Björkling, F.; Kankala, S.; Thota, N. Synthesis of thiazole linked chalcones and their pyrimidine analogues as anticancer agents. *Synth. Commun.,* **2021**, *51*(9), 1406-1416. http://dx.doi.org/10.1080/00397911.2021.1884262

[45] Makam, P.; Kankanala, R.; Prakash, A.; Kannan, T. 2-(2-Hydrazinyl)thiazole derivatives: Design, synthesis and *in vitro* antimycobacterial studies. *Eur. J. Med. Chem.,* **2013**, *69*, 564-576. http://dx.doi.org/10.1016/j.ejmech.2013.08.054 PMID: 24095750

[46] Aggarwal, R.; Kumar, S.; Singh, S.P. Sodium carbonate-mediated facile synthesis of 4-substituted-2-(3,5-dimethylpyrazol-1-yl)thiazoles under solvent-free conditions. *J. Sulfur Chem.,* **2012**, *33*(5), 521-525. http://dx.doi.org/10.1080/17415993.2012.711331

[47] de Moraes Gomes, P.A.T.; de Oliveira Barbosa, M.; Farias Santiago, E.; de Oliveira Cardoso, M.V.; Capistrano Costa, N.T.; Hernandes, M.Z.; Moreira, D.R.M.; da Silva, A.C.; Dos Santos, T.A.R.; Pereira, V.R.A.; Brayner Dos Santosd, F.A.; do Nascimento Pereira, G.A.; Ferreira, R.S.; Leite, A.C.L. New 1,3-thiazole derivatives and their biological and ultrastructural effects on *Trypanosoma cruzi*. *Eur. J. Med. Chem.,* **2016**, *121*, 387-398. http://dx.doi.org/10.1016/j.ejmech.2016.05.050 PMID: 27295485

[48] Demirici, S. Synthesis of thiazole derivatives as antimicrobial agents by green chemistry techniques. *JOTCSA,* **2018**, *5*, 393-414. http://dx.doi.org/10.18596/jotcsa.375716

[49] Khidre, R.E.; Radini, I.A.M. Design, synthesis and docking studies of novel thiazole derivatives incorporating pyridine moiety and assessment as antimicrobial agents. *Sci. Rep.,* **2021**, *11*(1), 7846. http://dx.doi.org/10.1038/s41598-021-86424-7 PMID: 33846389

[50] Alqahtani, A.M.; Bayazeed, A.A. Synthesis and antiproliferative activity studies of new functionalized pyridine linked thiazole derivatives. *Arab. J. Chem.,* **2021**, *14*(1), 102914. http://dx.doi.org/10.1016/j.arabjc.2020.11.020

[51] Al-Mutabagani, L.A.; Abdelrazek, F.M.; Gomha, S.M.; Hebishy, A.S.; Abdelfattah, M.S.; Hassan, S.M.; Sayed, A.R.; Elaasser, M.M. Synthesis and biological evaluation of thiazolyl-ethylidene hydrazino-thiazole derivatives: a novel heterocyclic system. *Appl. Sci. (Basel),* **2021**, *11*(19), 8908. http://dx.doi.org/10.3390/app11198908

[52] Kassab, R.M.; Gomha, S.M.; Al-Hussain, S.A.; Dena, A.S.; Abdel-Aziz, M.M.; Zaki, M.E.; Muhammad, Z.A. Synthesis and *in-silico* simulation of some new bis-thiazole derivatives and their preliminary antimicrobial profile: Investigation of hydrazonoyl chloride addition to hydroxy-functionalized bis-carbazones. *Arab. J. Chem.,* **2021**, *14*(11), 103396. http://dx.doi.org/10.1016/j.arabjc.2021.103396

[53] Hantzsch, A.; Weber, J.H. About compounds of thiazole (pyridines of the thiophene series). *Ber., 1887*, *20*, 3118-3132. http://dx.doi.org/10.1002/cber.188702002200

[54] Sasmal, P.K.; Chandrasekhar, A.; Sridhar, S.; Iqbal, J. Novel one-step method for the conversion of isothiocyanates to 2-alkyl(aryl)aminothiazoles. *Tetrahedron,* **2008**, *64*(49), 11074-11080.
http://dx.doi.org/10.1016/j.tet.2008.09.074

[55] Lingaraju, G.S.; Swaroop, T.R.; Vinayaka, A.C.; Kumar, K.S.S.; Sadashiva, M.P.; Rangappa, K.S. An easy access to 4,5-disubstituted thiazoles *via* base-induced click reaction of active methylene isocyanides with methyl dithiocarboxylates. *Synthesis,* **2012**, *44*(9), 1373-1379.
http://dx.doi.org/10.1055/s-0031-1290762

[56] Lee, T.; Lee, D.; Lee, I.Y.; Gong, Y.D. Solid-phase synthesis of thiazolo[4,5-b]pyridine derivatives using Friedländer reaction. *J. Comb. Chem.,* **2010**, *12*(1), 95-99.
http://dx.doi.org/10.1021/cc900147y PMID: 19954205

[57] Kim, D.; Baek, D.J.; Lee, D.; Liu, K.H.; Bae, J.S.; Gong, Y.D.; Min, K.H.; Lee, T. Efficient solid-phase synthesis of 2,4-disubstituted 5-carbamoyl-thiazole derivatives using a traceless support. *Tetrahedron,* **2015**, *71*(21), 3367-3377.
http://dx.doi.org/10.1016/j.tet.2015.03.104

[58] Prajapati, N.P.; Vekariya, R.H.; Patel, H.D. Microwave induced facile one-pot access to diverse 2-cyanobenzothiazole-A key intermediate for the synthesis of firefly Luciferin. *Int. Lett. Chem. Phys. Astron.,* **2015**, *44*, 81-89.
http://dx.doi.org/10.18052/www.scipress.com/ILCPA.44.81

[59] Singh, M.S.; Chowdhury, S. Recent developments in solvent-free multicomponent reactions: A perfect synergy for eco-compatible organic synthesis. *RSC Advances,* **2012**, *2*(11), 4547-4592.
http://dx.doi.org/10.1039/c2ra01056a

[60] Elinson, M.N.; Vereshchagin, A.N.; Nasybullin, R.F.; Bobrovsky, S.I.; Ilovaisky, A.I.; Merkulova, V.M.; Bushmarinov, I.S.; Egorov, M.P. General approach to a spiro indole-3,1′-naphthalene tetracyclic system: Stereoselective pseudo four-component reaction of isatins and cyclic ketones with two molecules of malononitrile. *RSC Advances,* **2015**, *5*(62), 50421-50424.
http://dx.doi.org/10.1039/C5RA03452C

[61] Sujatha, K.; Vedula, R.R. Novel one-pot expeditious synthesis of 2,4-disubstituted thiazoles through a three-component reaction under solvent free conditions. *Synth. Commun.,* **2018**, *48*(3), 302-308.
http://dx.doi.org/10.1080/00397911.2017.1399422

[62] Arandkar, V.; Vaarla, K.; Vedula, R.R. Facile one pot multicomponent synthesis of novel 4-(benzofuran-2-yl)-2-(3-(aryl/heteryl)-5-(aryl/heteryl)-4,5-dihydro-1H-pyrazol-1yl)thiazole derivatives. *Synth. Commun.,* **2018**, *48*(11), 1285-1290.
http://dx.doi.org/10.1080/00397911.2018.1440600

[63] Reddy, G.T.; Kumar, G.; Reddy, N.C.G. Water-mediated one-pot three-component synthesis of hydrazinyl-thiazoles catalyzed by copper oxide nanoparticles dispersed on titanium dioxide support: A green catalytic process. *Adv. Synth. Catal.,* **2018**, *360*(5), 995-1006.
http://dx.doi.org/10.1002/adsc.201701063

[64] Shiran, J.A.; Yahyazadeh, A.; Mamaghani, M.; Yamin, B.M.; Albadi, J.; Shirini, F.; Rassa, M. Novel, one-pot, three-component, regioselective synthesis of fluorine-containing thiazole and bis-3H-thiazole derivatives using polyvinyl pyridine as heterogeneous catalyst, and evaluation of their antibacterial activity. *Synth. Commun.,* **2015**, *45*(13), 1520-1532.
http://dx.doi.org/10.1080/00397911.2015.1025909

[65] Wang, X.; Qiu, X.; Wei, J.; Liu, J.; Song, S.; Wang, W.; Jiao, N. Cu-catalyzed aerobic oxidative sulfuration/annulation approach to thiazoles *via* multiple Csp^3–H bond cleavage. *Org. Lett.,* **2018**, *20*(9), 2632-2636.
http://dx.doi.org/10.1021/acs.orglett.8b00840 PMID: 29659292

[66] Jiang, J.; Huang, H.; Deng, G.J. Four-component thiazole formation from simple chemicals under metal-free conditions. *Green Chem.,* **2019**, *21*(5), 986-990.
http://dx.doi.org/10.1039/C8GC03895C

[67] Mekky, A.E.; Sanad, S.M.; El-Idreesy, T.T. New thiazole and thiazole-chromene hybrids possessing morpholine units: Piperazine-mediated one-pot synthesis of potential acetylcholinesterase inhibitors. *Synth. Commun.,* **2021**, *51*(21), 3332-3344.
http://dx.doi.org/10.1080/00397911.2021.1970774

[68] Kamila, S.; Koh, B.; Biehl, E.R. Microwave-assisted "green" synthesis of 2-alkyl/arylbenzothiazoles in one pot: A facile approach to anti-tumor drugs. *J. Heterocycl. Chem.,* **2006**, *43*(6), 1609-1612.
http://dx.doi.org/10.1002/jhet.5570430627

[69] Khodaei, M.M.; Alizadeh, A.; Kanjouri, T. An efficient, one-pot, green synthesis of tetracyclic imidazo [2,1-b] thiazoles *via* electrochemically induced tandem heteroannulation reactions. *J. Heterocycl. Chem.,* **2013**, *50*(1), 23-28.
http://dx.doi.org/10.1002/jhet.959

[70] Nikpassand, M.; Fekri, L.Z.; Sanagou, S. Green synthesis of 2-hydrazonyl-4-phenylthiazoles using KIT-6 mesoporous silica coated magnetite nanoparticles. *Dyes Pigments,* **2017**, *136*, 140-144.
http://dx.doi.org/10.1016/j.dyepig.2016.08.044

[71] Vekariya, R.H.; Patel, K.D.; Vekariya, M.K.; Prajapati, N.P.; Rajani, D.P.; Rajani, S.D.; Pat, H.D. Microwave-assisted green synthesis of new imidazo [2, 1-b] thiazole derivatives and their antimicrobial, antimalarial, and antitubercular activities. *Res. Chem. Intermed.,* **2017**, *43*(11), 6207-6231.
http://dx.doi.org/10.1007/s11164-017-2985-5

[72] Kaur, N. Ultrasound-assisted green synthesis of five-membered O- and S-heterocycles. *Synth. Commun.,* **2018**, *48*(14), 1715-1738.
http://dx.doi.org/10.1080/00397911.2018.1460671

[73] Shaterian, H.R.; Molaei, P. Fe_3O_4@ vitamin B1 as a sustainable superparamagnetic heterogeneous nanocatalyst promoting green synthesis of trisubstituted 1,3-thiazole derivatives. *Appl. Organomet. Chem.,* **2019**, *33*(7), e4964.
http://dx.doi.org/10.1002/aoc.4964

[74] Xu, J.; Deng, R.; Chen, J.; Tang, X.; Zhao, J. DMSO/H_2O_2 Promoted Regioselective Synthesis of Benzoimidazo [2,1-b] thiazoles from 2-Mercaptobenzimidazoles and Ketones in Water. *Adv. Synth. Catal.,* **2019**, *361*(22), 5144-5148.
http://dx.doi.org/10.1002/adsc.201900909

[75] Shabaan, S.N.; Baaiu, B.S.; Abdel-Aziem, A.; Abdel-Aziz, M.S. Ultrasound-assisted green synthesis and antimicrobial assessment of 1, 3-thiazoles and 1, 3, 4-thiadiazines. *Green Chem. Lett. Rev.,* **2021**, *14*(4), 689-698.
http://dx.doi.org/10.1080/17518253.2021.1999508

[76] Chen, L.; Xuchen, X.; Wang, F.; Yang, Y.; Deng, G.; Liu, Y.; Liang, Y. Double C-S bond formation *via* multiple Csp^3-H bond cleavage: Synthesis of 4-hydroxythiazoles from amides and elemental sulfur under metal-free conditions. *Org. Biomol. Chem.,* **2021**, *19*(46), 10068-10072.
http://dx.doi.org/10.1039/D1OB01989A PMID: 34762083

[77] Zhong, X.; He, F.; Ran, Q.; Li, W.; Xiong, H.; Zhou, W. Cascade nucleophilic addition/cyclization/c−n coupling of o-Iodo-phenyl isothiocyanates with propargylamines: Access to benzimidazo[2,1-b]thiazole derivatives. *Asian J. Org. Chem.,* **2021**, *10*(12), 3253-3256.
http://dx.doi.org/10.1002/ajoc.202100545

[78] Nguyen, T.B.; Retailleau, P. Base-catalyzed three-component reaction between chalcones, isothiocyanates, and sulfur: Access to thiazole-2-thiones. *Org. Lett.,* **2021**, *23*(14), 5344-5348.
http://dx.doi.org/10.1021/acs.orglett.1c01653 PMID: 34227811

[79] Chen, Y.; Lv, S.; Lai, R.; Xu, Y.; Huang, X.; Li, J.; Lv, G.; Wu, Y. Synthesis of 2-aminothiazoles *via* rhodium-catalyzed carbenoid insertion/annulation of sulfoxonium ylides with thioureas. *Chin. Chem. Lett.,* **2021**, *32*(8), 2555-2558.
http://dx.doi.org/10.1016/j.cclet.2021.02.052

[80] Tokárová, Z.; Eckstein-Andicsová, A.; Balogh, R.; Tokár, K. Survey of the Ketcham reaction for series of furan-substituted thiazolo[5,4-d]thiazoles. *Tetrahedron,* **2021**, *89*, 132155.
http://dx.doi.org/10.1016/j.tet.2021.132155

[81] Ahmed, W.; Huang, Z.H.; Cui, Z.N.; Tang, R.Y. Design and synthesis of unique thiazoloisoquinolinium thiolates and derivatives. *Chin. Chem. Lett.,* **2021**, *32*(10), 3211-3214.
http://dx.doi.org/10.1016/j.cclet.2021.03.065

[82] Mei, R.; Xiong, F.; Yang, C.; Zhao, J. Salicylic acid-promoted three-component annulation of benzimidazoles, aryl nitroalkenes and elemental sulfur. *Adv. Synth. Catal.,* **2021**, *363*(7), 1861-1866.
http://dx.doi.org/10.1002/adsc.202001564

[83] Bangade, V.M.; Mali, P.R.; Meshram, H.M. Synthesis of potent anticancer substituted 5-benzimidazol-2-amino thiazoles controlled by bifunctional hydrogen bonding under microwave irradiations. *J. Org. Chem.,* **2021**, *86*(9), 6056-6065. http://dx.doi.org/10.1021/acs.joc.0c02542 PMID: 33872008

[84] Zhang, B.; Liu, D.; Sun, Y.; Zhang, Y.; Feng, J.; Yu, F. Preparation of thiazole-2-thiones through tbpb-promoted oxidative cascade cyclization of enaminones with elemental sulfur. *Org. Lett.,* **2021**, *23*(8), 3076-3082. http://dx.doi.org/10.1021/acs.orglett.1c00751 PMID: 33769063

[85] Cheng, Y.; He, Y.; Zheng, J.; Yang, H.; Liu, J.; An, G.; Li, G. Ruthenium (II)-catalyzed para-selective C-H difluoroalkylation of aromatic aldehydes and ketones using transient directing groups. *Chin. Chem. Lett.,* **2021**, *32*(4), 1437-1441. http://dx.doi.org/10.1016/j.cclet.2020.09.044

[86] Cheng, Y.; Yu, S.; He, Y.; An, G.; Li, G.; Yang, Z. C4-arylation and domino C4-arylation/3,2-carbonyl migration of indoles by tuning Pd catalytic modes: Pd(i)-Pd(ii) catalysis *vs.* Pd(ii) catalysis. *Chem. Sci. (Camb.),* **2021**, *12*(9), 3216-3225. http://dx.doi.org/10.1039/D0SC05409G PMID: 34164090

[87] Cheng, Y.; Zheng, J.; Tian, C.; He, Y.; Zhang, C.; Tan, Q.; An, G.; Li, G. Palladium-Catalyzed C-H Arylation of Aliphatic and Aromatic Ketones using Dipeptide Transient Directing Groups. *Asian J. Org. Chem.,* **2019**, *8*(4), 526-531. http://dx.doi.org/10.1002/ajoc.201900037

[88] Tian, H.; Yang, H.; Tian, C.; An, G.; Li, G. Cross-dehydrogenative coupling of strong C(sp^3)-H with *N*-heteroarenes through visible-light-induced energy transfer. *Org. Lett.,* **2020**, *22*(19), 7709-7715. http://dx.doi.org/10.1021/acs.orglett.0c02912 PMID: 32942860