Chapter 12
Synthesis and Biological Evaluation of Fused Thiazolotriazole and Imidazothiadiazole Scaffolds

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12.1 Introduction

The fundamental structure of many clinically utilized drugs contains heterocyclic moieties, highlighting the significance of heterocycles in the formation of new pharmacologically active molecules [1]. Many S-containing scaffolds are found in a variety of medicines and natural products which act as biologically active molecules in multitude pathophysiological circumstances [2]. Because of sulfur strong volatility and reactivity, several chemicals containing sulfur also play a part in flavoring foods including meat, vegetables, and roasted goods including peanuts, cocoa, and coffee. Heterocycles containing sulfur showed a numerous range of pharmacological effects, comprising antiviral, antibacterial, anticancer, anti-tubercular, and anti-inflammatory. Thiazole, thiazepine, isothiazole, thiopyran, thiophene, and thiazolidine, which consist of five, six, and seven-membered rings, represent some of the sulfur-containing heterocycles that have been extensively studied in the branch of drug development [3].

The thiazole scaffold is present in Ravuconazole [4], Carumonam [5], Cefotaxime [6, 7], Cefdinir [8], and these all are FDA-approved drugs (Fig. 12.1).

Over the past 15 years, heterocyclic compounds have been increasingly prominent in the branch of organic synthesis and medicinal chemistry. Particularly, S-containing [5,5]-fused ring systems with a bridgehead nitrogen (Fig. 12.2) have gained recognition. These structural frameworks, serving as bioisosteres of imidazopyridazines, indolizines, and their analogs, are linked to a broad array of biological

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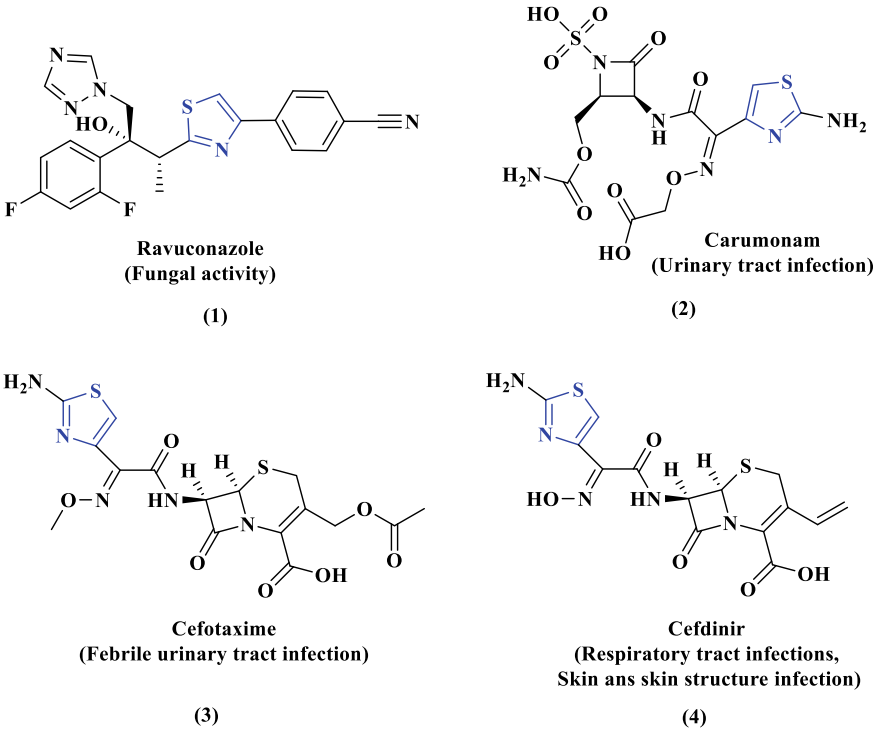


Fig. 12.1 Thiazole containing drugs

effects. Their utility in medicinal chemistry has increased as a result of these characteristics, particularly in light of molecular diversity and the continual search for new chemical space [9]. This chapter presents the one-pot synthesis and biological profile of thiazolotriazoles, imidazothiadiazole, and some miscellaneous reaction.

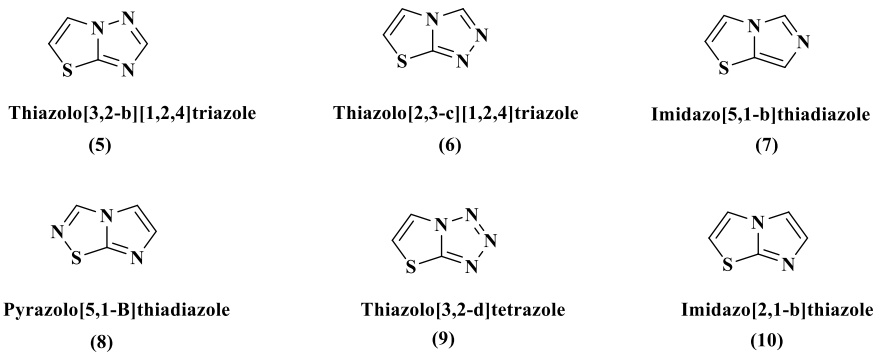


Fig. 12.2 [5,5]-fused ring systems with a bridgehead nitrogen

12.2 Thiazolotriazoles

12.2.1 Introduction

The thiazolotriazoles are those substances that have two fused triazole and thiazole rings in their structure and can occur in two main isomeric forms: thiazolo[3,2-b][1,2,4]triazoles and thiazolo[2,3-c][1,2,4]triazoles. The synthesis of thiazolo-1,2,4-triazoles has drawn a lot of focus recently because of the extensive range of biological activities they exhibit analgesic [10], antimicrobial [11], antipyretic [12], anti-inflammatory [13], anticancer, and vasodilatory [14].

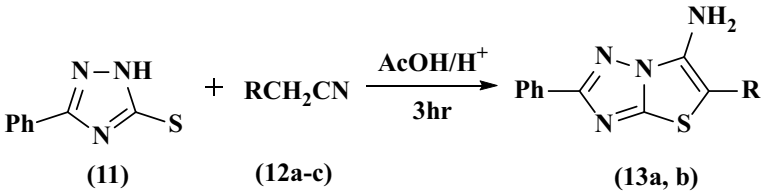
The acidified acetic acid environment ($AcOH/H^+$), employed in the synthesis of a range of multifunctional compounds, offers several advantages. These include reduced reaction duration, the possibility of one-pot reactions, and the direct utilization of cost-effective and safe cyano compounds containing active methylene groups, all without the formation of highly toxic, irritating, or hazardous halocyano derivatives [15].

12.2.2 Synthesis of Thiazolotriazoles

On heating of phenyltriazole **(11)** treating with CN compounds containing $-CH_2$ group like ethyl cyanoacetate, malononitrile and cyanoacetamide **(12a-c)** under standard reflux conditions through acidified acetic acid method furnished the phenyl-thiazolotriazoles **(13a,b)** in moderate yield (Scheme 12.1).

The synthesis of 6-amino-2-phenylthiazolotriazole-5-carboxamide **(13b)** by treating phenyltriazole **(11)** with bromocyanoacetamide **(14)** using KOH at room temperature (Scheme 12.2).

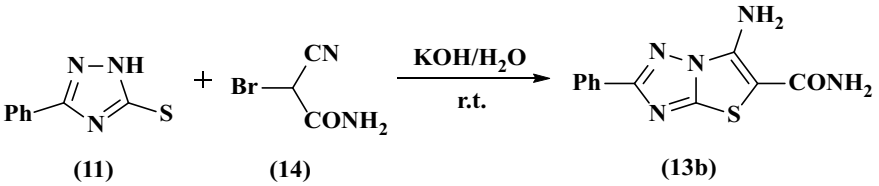
Generation of dimeric disulfide **(15)** with 81% yield on refluxing phenyltriazole **(11)** in the presence of acidified acetic acid formed dimeric disulfide **(15)** by nucleophilic attack on imine form. The formed compound **(16)**, followed by the intramolecular cyclization reaction, yielded the cyclized imino structures **(17)** via



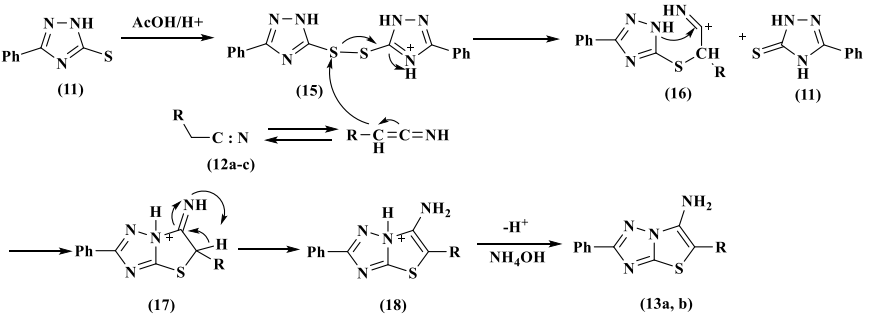
(11) **(12a-c)** **(13a, b)**

R = a; COOEt, b; $CONH_2$, c; CN

Scheme 12.1 Synthesis of phenyl-thiazolotriazoles



Scheme 12.2 Synthesis of phenyltriazole with bromocyanoacetamide



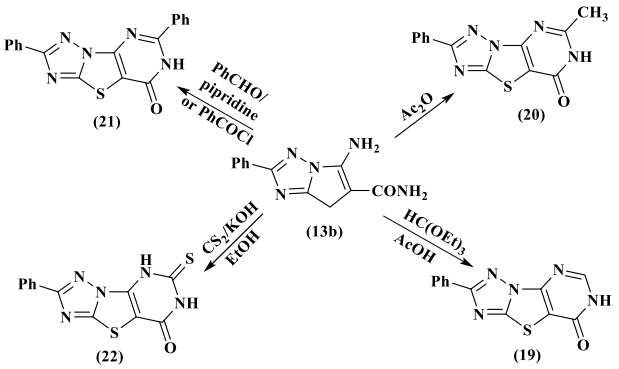
Scheme 12.3 Synthesis of phenyl-thiazolotriazoles

the protonation of **(17)** through H^+ furnished cyclized carbonium ion **(18)** followed by deportation generates the phenyl-thiazolotriazoles **(13a,b)** (Scheme 12.3) [16, 17].

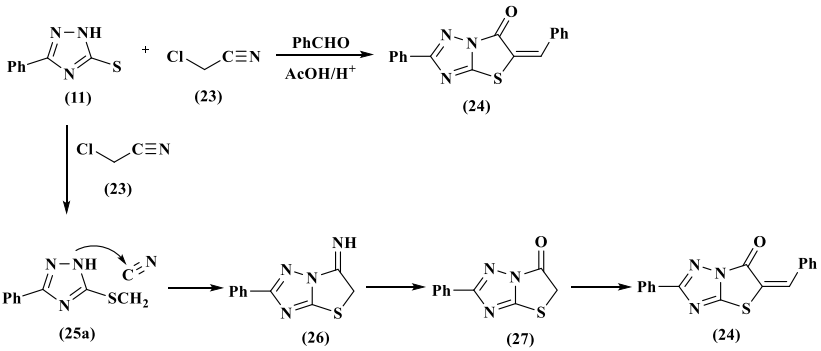
Formation of 2-phenyltriazolothiazolopyrimidin-8-one **(19)**, 6-methyl-2-phenyltriazolothiazolopyrimidin-8-one **(20)**, 2,6-diphenyltriazolothiazolopyrimid in-8-one **(21),** and 2-phenyl-6-thioxotriazolothiazolopyrimidin-8-one **(22)** and the reaction of 5-amino-2-phenylthiazolotriazole-6-carboxamide **(13b)** with acetic anhydride, triethyl orthoformate, benzaldehyde using piperidine (or C_7H_5ClO) and CS_2 in alcoholic KOH furnished the desired product with moderate yield (Scheme 12.4) [15].

5-benzylidene-2-phenylthiazolotriazol-6-one **(24)** has been synthesized by treating phenyltriazole **(11)** with $ClCH_2CN$ **(23)** and C_6H_5CHO using AcOH. The mechanism of **(24)** comprises the S-alkylation of phenyltriazole **(11)** and intramolecular cyclization. It occurs by the nucleophilic attack of NH on the CN group, leading to in the cyclized imine derivative **(26)**. The ketone is then hydrolyzed, and finally, the desired product **(27)** is obtained by condensation with benzaldehyde (Scheme 12.5) [15].

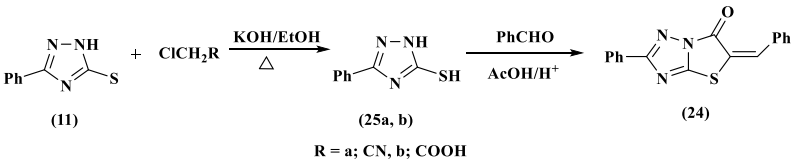
On refluxing 2-[(5-phenyltriazolo-3-yl)thio]acetonitrile/acetic acid **(25a,b)**, which is synthesized by treating phenyltriazole **(11)** with chloroacetic acid or chloroacetonitrile in alcoholic KOH, and benzaldehyde under the same reaction conditions yielded 5-benzylidene-2-phenylthiazolotriazol-6-one **(24)** (Scheme 12.6).



Scheme 12.4 Synthesis of triazolothiazolopyrimidine derivatives



Scheme 12.5 Synthesis of phenyltriazole with chloroacetonitrile



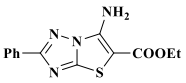
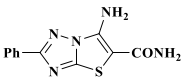
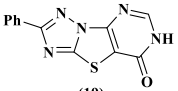
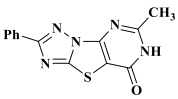
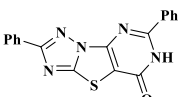
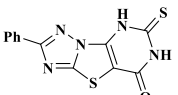
Scheme 12.6 Synthesis of 5-benzylidene-2-phenylthiazolotriazol-6-one

12.2.3 Biological Activity

Generating novel heterocyclic compounds with potential biological value was one of the goals of the current effort. The anti-fungal and anti-bacterial activity of a few of the recently synthesized compounds was illustrated. *Pseudomonas aeruginosa*, *Bacillus cereus*, *Escherichia coli*, *Staphylococcus aureus*, and *Serratia marcescens* were the microorganisms employed in the antibacterial research. *Scopulariopsis brevicaulis*,

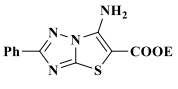
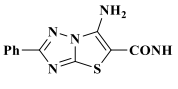
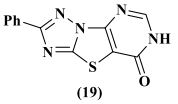
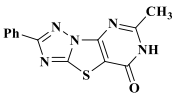
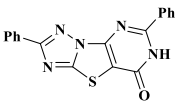
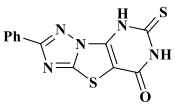
Geotrichum candidum, *Aspergillus flavus*, *Candida albicans*, *Fusarium oxysporum*, and *Trichophyton rubrum* were utilized as antifungal agents. Minimal Inhibitory Concentration (MIC) testing using the serial dilution approach was performed on both microbiological investigations [18]. The chemical whose MIC must be determined was diluted serially and concentrations were added to standard drops of the culture generated for the experiment. The resulting mixtures were then incubated for 16–18 h at 37 °C (Tables 12.1 and 12.2) [15].

Table 12.1 Antibacterial activity of certain selected chemicals [15]

Sample	*S. marcescens*	*P. aeruginosa*	*E. coli*	*S. aureus*	*B. cereus*
 (13a)	10(20)	–	12(20)	–	–
 (13b)	10(20)	–	15(20)	–	12(10)
 (19)	10(20)	–	–	–	–
 (20)	10(20)	–	12(20)	–	–
 (21)	10(20)	–	12(20)	–	–
 (22)	10(20)	–	12(20)	13(20)	12(2.5)
DMSO	10(20)	–	–	–	–
CHL[a]	12(1.25)	14(5.0)	12(0.3)	10(1.25)	34(0.3)

[a] CHL = Chloramphenicol as standard
MICs shown in brackets and inhibition zone measured in millimeters

Table 12.2 Antifungal activity of certain selected chemicals [15]

Sample	*G. candidum*	*C. albicans*	*A. flavus*	*T. rubrum*	*F. oxysporum*
 (13a)	11(20)	–	–	10(20)	–
 (13b)	11(20)	–	–	–	–
 (19)	–	–	–	–	–
 (20)	12(20)	–	–	–	–
 (21)	11(20)	–	–	–	–
 (22)	12(20)	–	–	–	–
DMSO	–	–	–	–	–
CHL[a]	24(0.3)	25(0.3)	24(2.5)	36(1.25)	20(10)

[a] CHL = Chloramphenicol as standard
MICs shown in brackets and inhibition zone measured in millimeters

12.3 Imidazothiadiazole

12.3.1 Introduction

Imidazothiadiazole is formed by two fused moieties imidazole and thiadiazole. Two possible forms of this compound are imidazo[1,3,4]thiadiazole **(28)** and imidazo[1,2,4] thiadiazole **(29)** and important scaffold for bioactive compounds (Fig. 12.3) [19].

Imidazo[2,1-b][1,3,4]thiadiazole **Imidazo[1,2-d][1,2,4]thiadiazole**

Fig. 12.3 Isomeric form of imidazothiadiazole

Subsequently, in these two isomeric forms, imidazo[1,3,4]thiadiazole **(28)** and its derivatives are broadly reported, and another isomer is rarely studied [20–22]. Imidazo[2,1-b][1,3,4]thiadiazole derivatives include multifarious biological activities including tubulin inhibitor [23], anti-microbial [24], antibacterial [25], anti-inflammatory [26], anti-fungal [27], anti-convulsant [28], anti-tumor [29], anti-cancer [30], and anti-tubercular [31]. The 1,3,4-thiadiazole molecule has a broad range of medical uses, with anti-inflammatory [32], anticancer [33], antibacterial [34], antiviral [35], and antioxidant [36]. Numerous imidazo[2,1-b]thiadiazole derivatives have been generated and show biological activities such as the phenylimidazo[2,1-b][1,3,4]thiadiazole derivatives **(30)** (antifungal agents) [37], diaryl substituted Hybrids **(31)** (anti-tubercular agents) [38], carbamic acid analogues **(32)** (anti-inflammatory or analgesic agents) [39], bromo-benzene substituted derivative **(33)** (anti-cancer agent) [40], ethylimidazo[1,3,4]thiadiazol-2-yl)-3-(imidazolidin-2-yl)acrylate **(34)** (anti-leishmanial agents) [41], and methylimidazo[1,3,4]thiadiazol-6-yl)phenoxy)propyl **(35)** (anesthetic agent) [42] (Fig. 12.4).

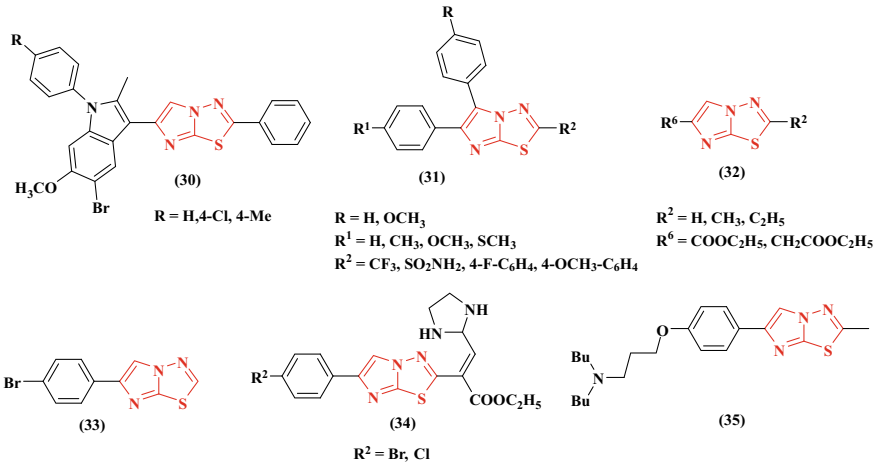


Fig. 12.4 Biologically active imidazo[2,1-b][1,3,4]thiadiazole derivatives

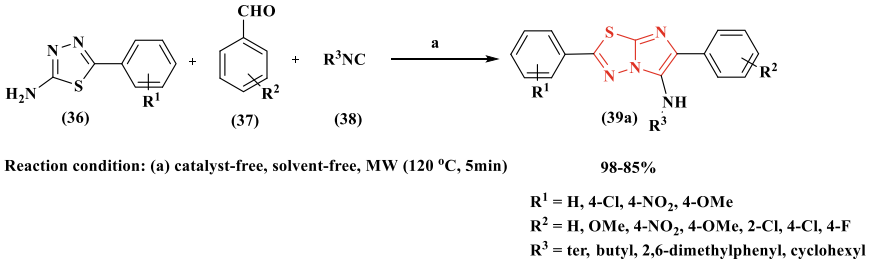
Several imidazo[2,1-b][1,3,4]thiadiazoles have been synthesized and examined for a wide spectrum of biological importance. These compounds differ in the substitutions at the 2, 5, and 6 positions of the scaffold [28].

12.3.2 Synthesis of Imidazothiadiazole

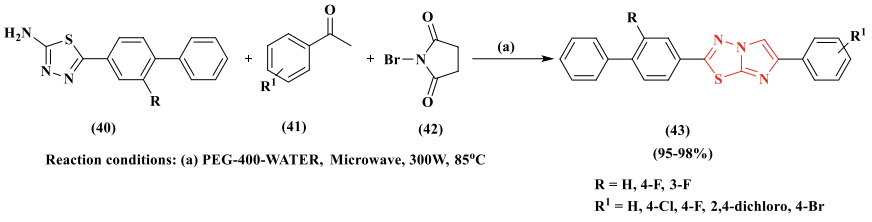
Wadhwa et al. demonstrated a one-pot reaction of imidazole[1,3,4]thiadiazole **(39a)** through Groebke–Blackburn–Bienayme reaction via the reaction between amines **(36)**, aromatic aldehydes **(37),** and isonitriles **(38)** under microwave irradiation at 120 °C furnished arylimidazothiadiazole in good yield (Scheme 12.7) [43].

A greener and effective approach for the reaction of biphenylimidazo[2,1-b][1,3,4]thiadiazole derivatives **(43)** was developed by Wagere et al. via three-component reaction of aminothiadiazole derivatives **(40)**, acetophenones **(41)**, and NBS **(42)** under microwave reaction condition in PEG-400 using water in high yield (Scheme 12.8) [44].

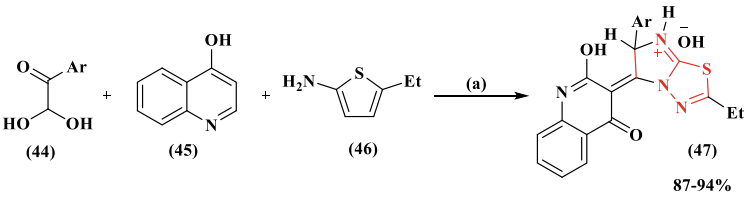
Khalafy et al. demonstrated a green and catalytic approach for the reaction of **(47)** via one-pot MCRs. The reaction of compound **(44)**, Quinolin-4-ol **(45)**, and 5-ethylthiophen-2-amine **(46)** under refluxed condition using Et_3N/NH_2SO_3H in water is to be furnished good yield of the desired product (Scheme 12.9) [45].



Scheme 12.7 One-pot synthesis of imidazo[1,3,4]thiadiazole derivatives



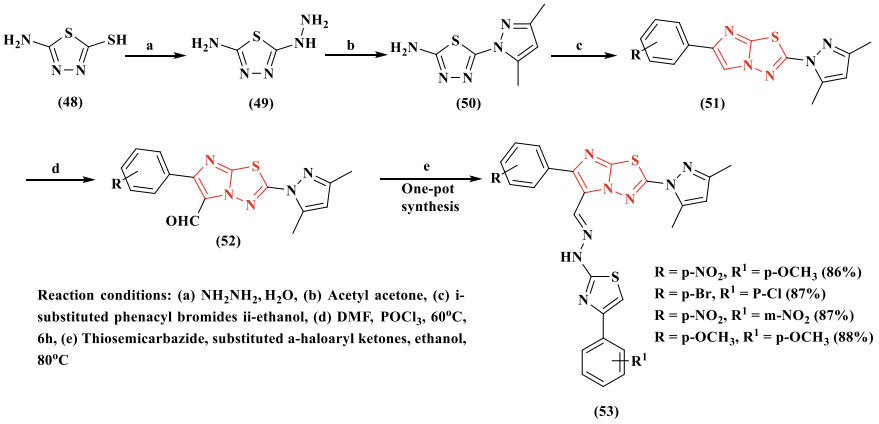
Scheme 12.8 Synthesis of biphenylimidazo[2,1-b][1,3,4]thiadiazole



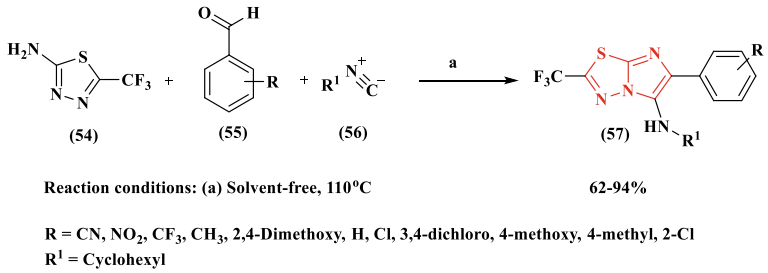
Scheme 12.9 Multi-component reaction of imidazo[1,3,4]thiadiazol-7-ium hydroxides

Syed et al. demonstrated that a one-pot efficient synthetic strategy was synthesized between **(52)**, thiosemicarbazide, and substituted α-halo ketones through ethanol at 80 °C to furnished imidazo[1,3,4]thiadiazole derivatives **(53)** in high yield including anti-tubercular and anti-fungal activities (Scheme 12.10) [46].

Sarchahi et al. demonstrated one-pot reaction for the generation of CF_3- comprising imidazo[2,1-b][1,3,4]thiadiazole derivative **(57)**, and the chemical methodology involves component **(54)**, aromatic aldehydes **(55)**, and third component **(56)** under standard conditions at 110 °C to be furnished the product **(57)** with good yield (Scheme 12.11) [47].



Scheme 12.10 Synthesis of imidazo [2,1-b][1,3,4]thiadiazole derivatives



Scheme 12.11 Derivatives containing $-CF_3$ functionalization

12.3.3 Biological Activity of Imidazo[2,1-b][1,3,4]Thiadiazole

In recent years, a broad amount of physiologically active imidazo[2,1-b][1,3,4]thiadiazole derivatives has been synthesized. Anti-inflammatory, anti-tubercular, anti-bacterial, anti-fungal, anti-leishmanial, anti-viral, and anti-cancer activities are among the most often noted. It has been discovered that the numerous substituents affect the biological data of the parent heterocycle. These derivatives have various substitutes at positions 2, 5, and 6 of the ring system. Among the tri-substituted imidazothiadiazole derivatives that exhibited strong anti-tubercular properties are **(59)** (MIC value = 3.125 mg/mL) [48], **(60)**, **(62)** (0.24–0.29 μ g/mL) [49] **(61)** (3.125 μg/mL) [50], and **(78)**(1.6–6.25 μg/mL) [46]. Anti-fungal activities were synthesized for compounds **(74)**, **(75)**, **(76)** [51], **(78)** [46], and **(79)** [52], with MIC values in the range of 5–100 μg/mL. Anti-bacterial activities were illustrated by derivatives **(72)** [53], **(73)** [54], **(74)**, **(75)**, **(76)** [51], and **(78)** [55], Compounds **(65)** (IC50 = 8 μM), **(66)** (IC50 = 0.11–2.98 μM) [56], **(67)** [57], **(68)** (IC50 = 489 nM) [58], **(69)** [59], and **(70)** [60]. Table 12.3 displays potential anti-cancer activities. 2,6-disubstituted imidazo[1,3,4]thiadiazole compounds have also shown anti-viral, anti-leishmanial, and anti-inflammatory properties [61].

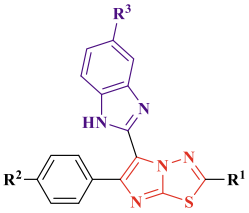
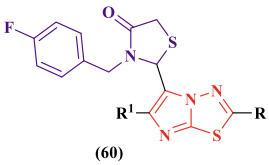
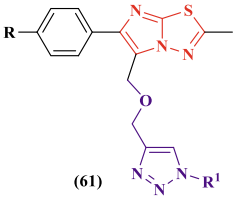
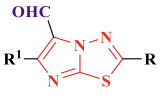
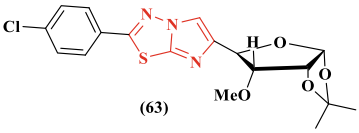
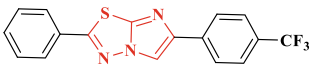
12.4 Miscellaneous Reaction

12.4.1 Pyrrolo[2,1-b]thiazole

12.4.1.1 Introduction

The hydrocarbon skeleton of pyrrolothiazoles is identical to that of imidazothiazoles, with the exception that nitrogen has been isosterically substituted at seventh position of the heterocyclic ring. The development of approach for synthesizing this heterocyclic scaffold is a crucial undertaking since pyrrolothiazoles and their derivatives also demonstrate anti-psychotic, anti-inflammatory, anti-convulsant, anti-cancer, and

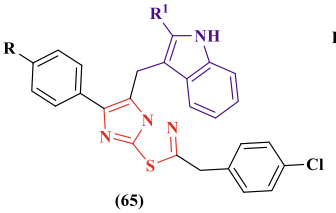
Table 12.3 Biological properties of imidazo[2,1-b][1,3,4]thiadiazole derivatives [19]

Imidazo[2,1-b][1,3,4]thiadiazole derivatives and its biological properties
 (58)
Anti-tubercular
 (59)  (60)  (61)  (62)
Anti-viral
 (63)
Anti-inflammatory
 (64)

(continued)

Table 12.3 (continued)

Anti-cancer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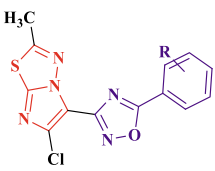
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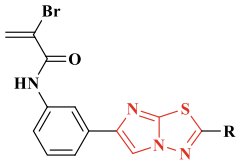
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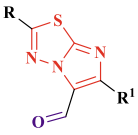
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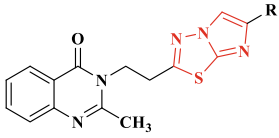
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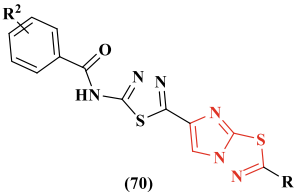
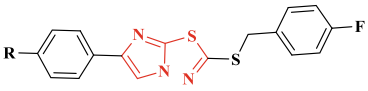

(70)

Anti-leishmanial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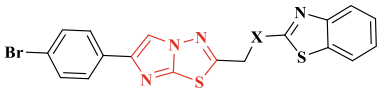
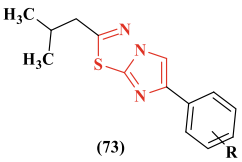

(72)

Anti-bacterial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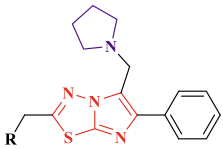
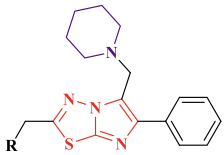

(74)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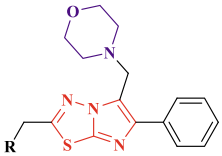
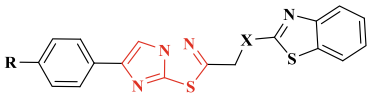
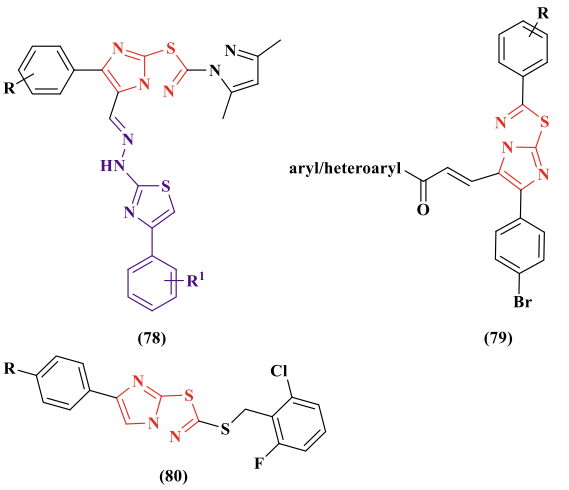

(76)


(77)

(continued)

Table 12.3 (continued)

Anti-fungal


other activity [62, 63]. Pyrrolo[2,1-b]thiazoles were mostly made by generating the bicyclic system from an existing pyrrole or thiazole ring by the use of alkylation and dipolar cycloaddition processes; however, they could also be made from acyclic synthons [64].

12.4.1.2 Synthesis of Pyrrolo[2,1-b]thiazoles

The simplest component of the [5,5]-fused N and S ring systems is the pyrrolothiazole **(81)** (Fig. 12.5) [64]. The fact that there are so many alternative synthetic pathways for their production may be due to their simplicity.

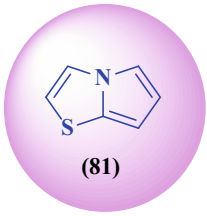
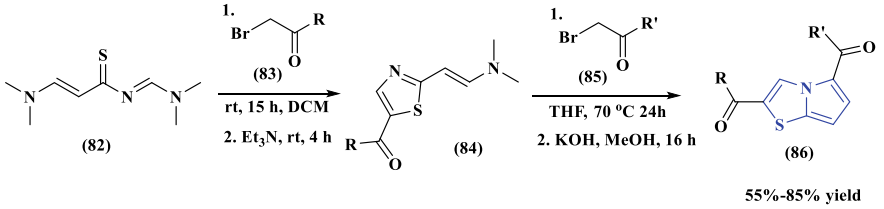
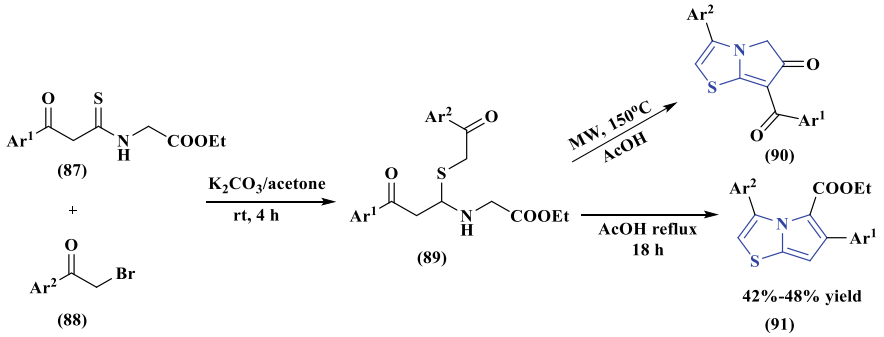


Fig. 12.5 Structure of pyrrolo[2,1-b]thiazoles



Scheme 12.12 Synthesis of pyrrolothiazoles derivatives



Scheme 12.13 Synthesis of pyrrolo[2,1-b] thiazol-6-ones and pyrrolo[2,1-b]thiazoles

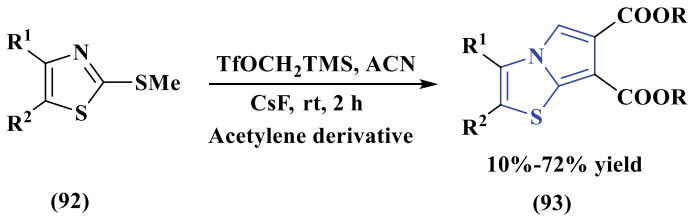
From α-Bromoketones and Thiazole Precursors

The initial reactant for this scaffold is compound **(82)**. As α-bromoketone's first molecule operates, a thiazole ring appears. A second reaction produces the required bicyclic structure **(86)** with substitutions in positions 2 and 5 [65]. The reaction of pyrrolo [2,1-b]thiazoles associated to a carbohydrate moiety in position 2 or 5 of the intended product was carried out by the authors through microwave heating and plausible yields (Scheme 12.12) [66].

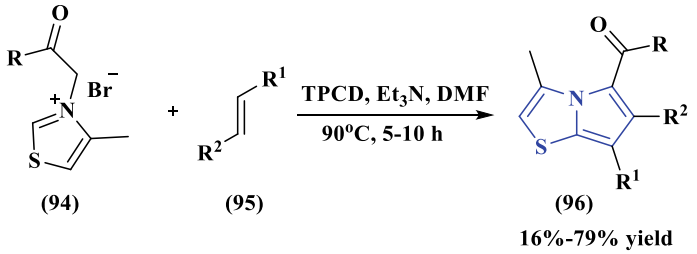
Reaction of α-aroyl ketene-N,S-acetals **(87)** with compound **(88)** through K_2CO_3/acetone at room temperature for 4 h leads to generation of an intermediate **(89)** followed by sequential cyclization under microwave condition at 150 °C furnished the pyrrolo[2,1-b] thiazol-6-ones **(90)**. After that same intermediate refluxed using AcOH formed the pyrrolo[2,1-b]thiazoles**(91)** with moderate yield (Scheme 12.13) [67].

From Thiazoles

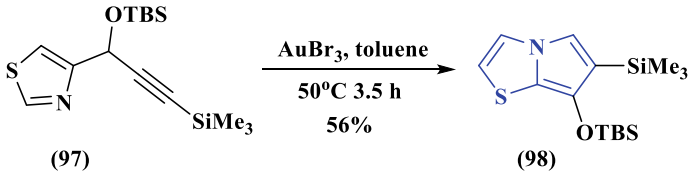
Berry et al. reported that alkylation of 2-methylthio-1,3-thiazole **(92)** they undergo cycloaddition reactions after quaternization with $TMSCH_2OTf$ and synthesis with



Scheme 12.14 Synthesis of pyrrolo [2,1-b]thiazoles derivatives



Scheme 12.15 Synthesis of pyrrolo [2,1-b]thiazole derivatives



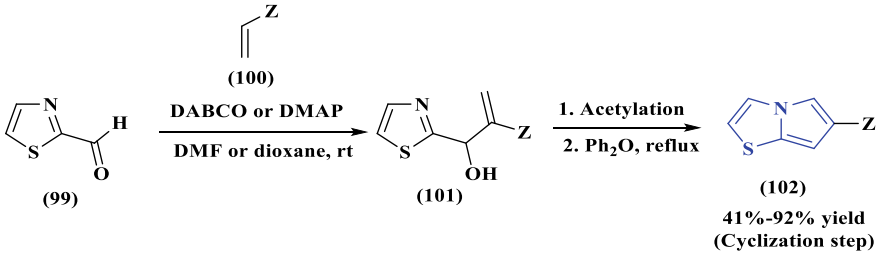
Scheme 12.16 Synthesis of pyrrolo[2,1-b]thiazole derivatives

alkynes at room temperature for 2 h furnished the desired product **(93)** with moderate yield (Scheme 12.14) [68].

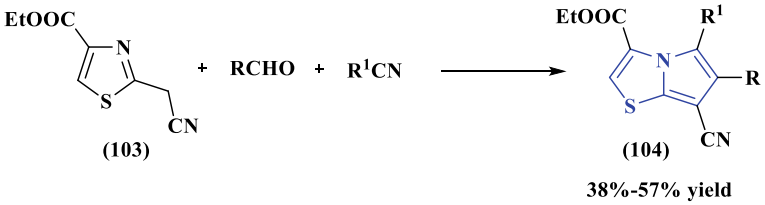
Shen et al. demonstrated the one-pot reaction of pyrrolo [2,1-b]thiazole derivatives. Subsequently, the treatment of ylide species **(94)** with electron-deficient alkene through TPCD, Et_3N, and DMF at 90 °C for 5–10 h afforded the desired product **(96)** with moderate yield exhibits anti-proliferative activity for Hep-G2 cancer cells (Scheme 12.15) [69].

The migration of Si, Sn, and Ge facilitated by gold for the reaction of fused pyrrole heterocycles was reported by Gevorgyan et al. [70] Compound **(98)** with moderate yield was obtained by a reaction with a single thiazole ring (Scheme 12.16). Through a transition metal-catalyzed cycloisomerization methodology, the same group has synthesized numerous additional 5,7-substituted pyrrolo[2,1-b]thiazole rings [71, 72].

The synthesis of pyrrolo[2,1-b] thiazoles derivatives has been synthesized for treatingthiazole-2-carboxaldehyde **(99)** with alkene through DABCO or DMAP,

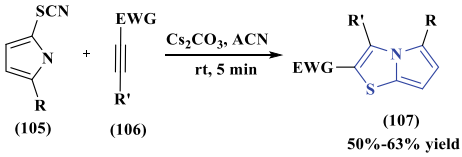


Scheme 12.17 Synthesis of pyrrolothiazoles' derivatives



Scheme 12.18 Synthesis of pyrrolo[2,1-b]thiazoles derivatives

Scheme 12.19 Synthesis of pyrrolo[2,1-b]thiazoles derivatives with electron withdrawing group



DMF at room temperature formed methyl thiazolyl adduct. Therefore, the resulting intermediate reaction with Ph_2O under standard reflux condition undergoes the desired compound fused bicyclic product **(102)** with good yield (Scheme 12.17) [73].

Bienayme and coworkers reported multicomponent reaction (MCR) of aldehyde and 2-cyanomethylthiazole **(103)** using DBU in n-butanol at room temperature. The [4 + 1] adduct was formed to an isocyanide at 100 °C to yield the desired product **(104)** with moderate yield (Scheme 12.18) [74].

From Pyrrole Derivatives

Werz et al. investigated that the reaction of pyrrole containing nitrogen **(105)** with the alkyne using Michael acceptor undergoes the loss of cyano group followed by cyclization under reaction condition to furnish appropriate fused ring system **(107)** with moderate yield (Scheme 12.19) [75].

12.4.2 Imidazotriazoles

Numerous studies have reported the pharmacological activities of [1,2,4]-triazoles. Here are a few examples: alprazolam [76], rilmazafon, trazodon benatradin, estazolam, trapidil, etoperidone, letrozole, nefazodone, anastrozole, vorozole, fluconazole, terconazole, itraconazole, and ribavirin which illustrate anti-depressant, hypotensive, transquillizer, anti-fungal, anti-viral, and so on [77–79]. The synthesis of imidazotriazoles has been prompted by the diverse range of biological activity, with the goal of exploring their potential therapeutic applications. Imidazole [80] or 1,2,4-triazole derivatives [81] are the starting materials used in traditional methods for the synthesis of imidazotriazoles.

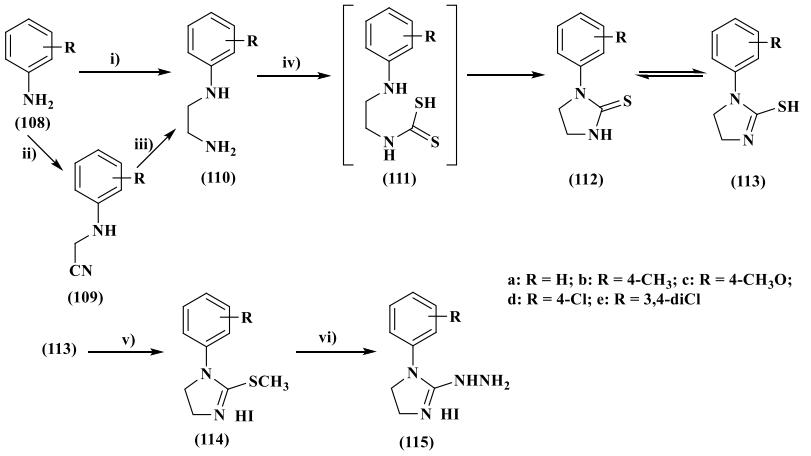
12.4.2.1 Synthesis and Biological Activity of Imidazotriazoles

These bridgehead nitrogen heterocyclic systems were demonstrated by Sztanke et al. fusing the [1,2,4]triazole and 4,5-dihydroimidazole nuclei [82]. Commercially accessible anilines were first transformed into equivalent N-arylethylenediamines. Subsequent condensation of these compounds in a xylene medium with carbon disulfide resulted in the synthesis of dithiocarbaminic acid derivatives. These compounds underwent cyclization in a boiling solvent to yield 1-arylimidazolidine-2-thiones **(112)**, along with the simultaneous release of H_2S gas. Methyl iodide alkylation of these compounds produced 75–85% yields of 1-aryl-2-methylthioimidazolines **(114)**. Therefore, refluxing these desired compounds with hydrazine hydrate, the excellent yields of 1-aryl-2-hydrazinoimidazolines were generated (Scheme 12.20).

Reaction of compound **(115)** with $HC(OEt)_3$ or derivatives of phenoxyacetic acid **(117)** under standard reflux condition for 6 h furnished the desired product 3-unsubstituted **(116)** or phenoxymethyl **(118–126)** 7-aryl-6,7-dihydroimidazo[1,2,4]triazoles.

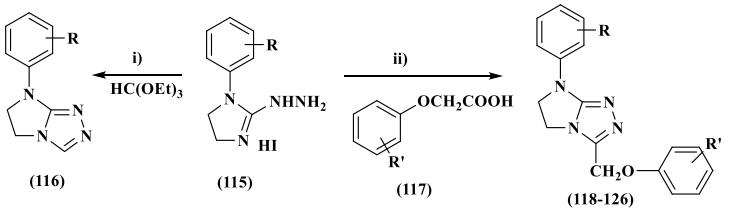
Subsequently, on boiling 2-hydrazineyl-1-(p-tolyl)-4,5-dihydro-1H-imidazole **(127)** with carbon sulfide in aqueous NaOH at room temperature for 30 min under standard reflux condition generates the 7-aryl-6,7-dihydroimidazo[1,2,4]triazol-3-thiol **(128).** Therefore, compound **(128)** treated with methyl iodide under optimized reaction condition afforded the desired product compound **(129)** with good yield. Compared to ampicillin, compound **(129)** demonstrated stronger antibacterial activity with the MIC value of 31.7 mM against Staphylococcus aureus ATCC 25,923 (Scheme 12.21).

Compounds **(120)** and **(125)** were verified against various human tumor cell lines, including LS180, SiHa, and T47D, showing anti-proliferative and apoptotic properties. Against the LS180 cell line, compound **(125)** was found to be the most active, with growth inhibition values of **(129)** and 54% for each tested concentration. On normal cell lines, particularly human skin fibroblasts, they demonstrated reduced cytotoxicity. These findings indicate that compound **(125)** should be investigated as a possible cancer-fighting substance. Compound **(120)** demonstrated effectiveness

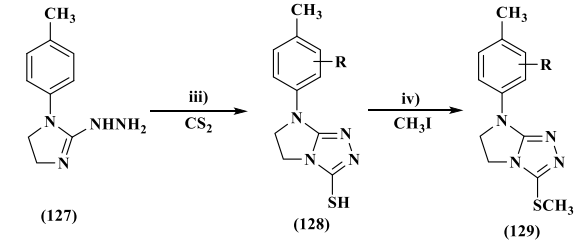


Reaction Conditions: i) aziridine, $AlCl_3$, dry toluene; ii) HCHO, $Na_2S_2O_5$, NaCN, water, reflux; iii) H_2, Ni/Ra, methanol/NH_3, 100 ^{0}C; iv) CS, xylene, rt, 20 min, reflux, 7 h; v) CH_3I/MeOH, rt, 48 h, reflux, 6 h; vi) hydrazine hydrate-MeOH, reflux, 24 h

Scheme 12.20 Synthesis of imidazotriazoles' derivatives

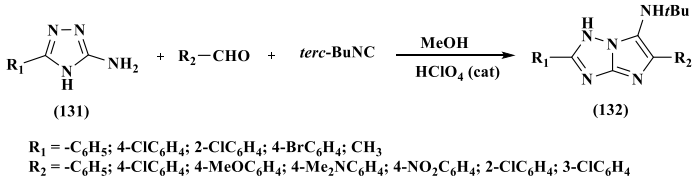


	R	R'
(118)	H	H
(119)	4-OCH_3	4-Cl
(120)	H	2-CH_3; 4-Cl
(121)	4-CH_3	4-Cl
(122)	4-CH_3	2-CH_3; 4-Cl
(123)	4-Cl	4-Cl
(124)	4-Cl	2-CH_3; 4-Cl
(125)	4-Cl	2,4-diCl
(126)	3,4-diCl	2,4-diCl



Reaction conditions: i) DMF, reflux, 6 h; ii) DMF, reflux, 6 h, NaOH 6%; iii) MeOH, NaOH-water, rt, 30 min, reflux, 14 h; iv) abs EtOH, rt, 24 h, reflux, 5 h, Na_2CO_3.

Scheme 12.21 Synthesis of imidazotriazoles derivatives



Scheme 12.22 Multi-component synthetic strategy to obtain imidazotriazoles

in breaking DNA strands in cancer cell lines, indicating that it might hold promise for the generation of new agents capable of breaking DNA strands.

Yan Huang et al. demonstrated the multi-component reactions' methodology for the generation of imidazo[1,2-b]-1,2,4-triazoles. Reaction of 1,2,4-triazoles derivatives **(131)** with aldehydes, and tert-butyl isocyanide using MeOH and HClO4 to obtain the product **(132)** with moderate yield (Scheme 12.22) [83].

12.5 Conclusion

These small, versatile organic scaffolds, known as sulfur- and nitrogen-containing [5,5]-fused ring structures, have found extensive use in medicinal chemistry and physiologically active compounds. Strategies for synthesizing these compounds have developed significantly over the past 15 years, with considering that some of these compounds' chemistry and preparation are not usually novel. This chapter discussed the S-containing [5,5]-fused ring system and a bridgehead nitrogen with numerous applications in medicinal chemistry. Protocol for thiazolotriazoles and imidazo[1,3,4]thiadiazole ring synthesis that utilizes one-pot multicomponent reactions under ideal reaction conditions has been proven to be active and beneficial. Various physiologically active scaffolds were generated by functionalization of the imidazo[1,3,4]thiadiazole ring system on positions 2, 5, and 6. Some miscellaneous reactions are also demonstrated and exhibit diverse medicinal application. However, as the number of applications has increased, imidazothiadiazole has recently attracted the interest of researchers. Imidazotriazoles and imidazothiadiazole derivatives have demonstrated efficacy in treating a broad spectrum of diseases. These compounds remain fascinating platforms for molecular variety, and this chapter certainly contributes to the further development of distinctive synthetic and chemical strategies.

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