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SHORT REVIEW

Strategies for synthesis of 1,2,4-triazole-containing scaffolds using 3-amino-1,2,4-triazole

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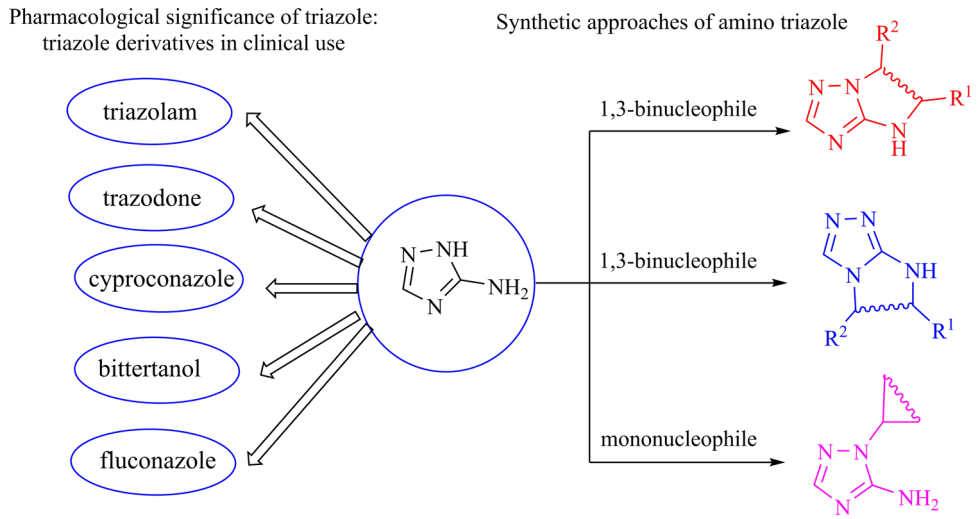
Abstract

1,2,4-Triazole-containing scaffolds are unique heterocyclic compounds present in an array of pharmaceuticals and biologically important compounds used in the drug-discovery studies against cancer cells, microbes, and various types of disease in the human body. This review article summarizes the pharmacological significance of the 1,2,4-triazole-containing scaffolds and highlights the latest strategies for the synthesis of these privileged scaffolds using 3-amino-1,2,4-triazole. This review stimulates further research to find new and efficient methodologies for accessing new 1,2,4-triazole-containing scaffolds which would be very useful for the discover of new drug candidates.

Graphic abstract



Keywords Heterocycles · Multicomponent reaction · Triazole · 3-Amino-1,2,4-triazole

Introduction

It has been demonstrated that nitrogen-containing heterocycles have a significant effect on the process of discovering new structures for pharmaceutical applications. In addition, these compounds are extensively observed in nature and metabolic systems which are vital for living creatures [1–3]. Among the various nitrogen-containing heterocycles, 1,2,4-triazoles especially with unique structure and properties have usages in various fields such as pharmaceutic chemistry, agrochemistry, materials sciences, and organic catalysts. 1,2,4-Triazoles operate as main pharmacophores through hydrogen-bonding and dipole interactions with the biological receptors [4, 5]. The various 1,2,4-triazole

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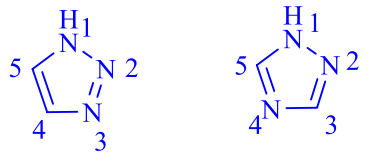
products due to having N–C–S linkage in the skeleton have been introduced as an antimicrobial agent and various medicines such as Fluconazole, Flupoxam, and Anastrozole which containing 1,2,4-triazole group are common and well known [6, 7]. Among the different heterocyclic compounds, 1,2,4-triazoles attracted remarkable attention especially in the last two decades due to its widespread potential pharmaceutical activity including antibacterial, antifungal, anti-inflammatory, antioxidant, analgesic, and anticancer activities [8–11].

The biological importance of 1,2,4-triazole has led to the design of many methods for the synthesis of this scaffold that exhibits biological activity. Synthetic methods reported to date provide access to a wide range of 1,2,4-triazole via multistep synthetic routes [12–16]. In view of the increasing demand for the convenient and rapid synthesis of heterocycles with biological activities, surveys of the effective synthetic methods to products containing 1,2,4-triazole systems have increasingly raised in recent articles. The established previous methods demonstrate that multicomponent reactions (MCRs) are a direct and powerful process for the synthesis of different functionalized heterocyclic structures including triazoles [17–19]. Given the growing importance of 1,2,4-triazole in emerging sciences, it is necessary to provide a comprehensive review of this distinguished heterocyclic scaffold using 3-amino-1,2,4-triazole.

The Chemistry of triazole

One of the important heterocyclic products containing three nitrogen atoms in a five-membered ring is known as triazole with molecular formula $C_2H_3N_3$ operates as isosteres of amide, ester and carboxylic acid. According to the position of the nitrogen atom in the five-membered ring, there are two possible isomers of triazole for instance, 1,2,3 and 1,2,4-triazoles (**1** and **2**) are numbered as illustrated in Fig. 1 [20, 21].



1 1,2,3-triazole **2** 1,2,4-triazole

Fig. 1 Chemical structure and numbering of 1,2,3-triazole and 1,2,4-triazole

Triazole, also introduced as pyrrodiazole with a five-membered di-unsaturated ring skeleton consists of two carbon atoms and three nitrogen atoms at non-adjacent sites. Each of these has three tautomers (**1a-c** and **2a-c**) which vary due to the fact that which nitrogen has hydrogen bonded that for 1,2,4-triazole, 1*H*-1,2,4-triazole (**2a**) is more stable than 4*H*-1,2,4-triazole (**2b**) as demonstrated in Fig. 2 [22].

Pharmacological significance of triazole scaffold

1,2,4-Triazole is one of the most significant scaffolds that can meet the needs of pharmaceutical chemistry and offers a variety of biological activities: for example, antihypertensive [23], anti-inflammatory [24], anticancer [25], antibiotic [26], anti-HIV [27], antioxidant [28], antileishmanial [29], and anticonvulsant [30]. This heterocyclic structure is the main component of a diverse kind of drugs available in clinical therapy, such as terconazole **3**, itraconazole **4**, fluconazole **5**, bittertanol **6**, cyproconazole (fungicides) **7**, trazodone **8** (anti-depressant) and triazolam **9** (sedative and hypnotic), etc., represented in Fig. 3 which are frequently used in the pharmaceutical domain [4, 11, 31]. Triazole derivation is introduced according to the concept of bioisosterism, in which the oxygen exchange of the oxadiazole cores with the nitrogen atom happens and generates the triazole analogue. [21].

This wide range of biological and pharmaceutical properties has been facilitated by the synthetic diversity of triazole, which provides structural diversity and this has been surveyed by a number of synthetic researchers [32]. On the other hand, among other heterocyclic structures containing nitrogen, triazole derivatives were introduced as the most promising option for anti-tuberculosis properties [33].

The use of triazole-based drugs is the main method for the treatment of fungal diseases in both human and agriculture [34]. Triazole-based antifungals have been introduced as the third generation of antifungal drugs that have a broad range of antifungal properties in the treatment of a diversity of pathogenic fungi (Fig. 4) [5]. Also, triazole antifungal drugs are the first choice to treat infections due to Aspergillus Fumigatus [35].

In 2015, the group of Miceli and Kauffman defined the function of novel triazoles in the treatment of infections caused by invasive fungi. Isavuconazole **10** is a novel triazole with a wide range of therapeutic activity against dimorphic fungi, molds and yeasts. The use of this compound has

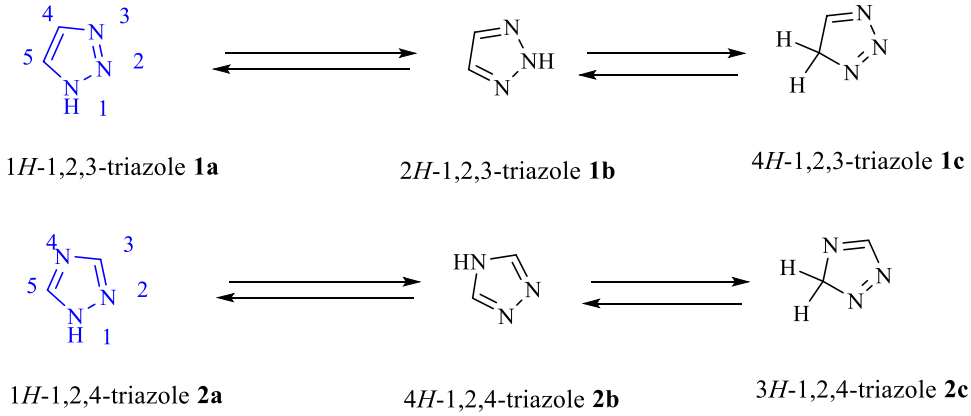


Fig. 2 The tautomers of 1,2,3-triazole and 1,2,4-triazole

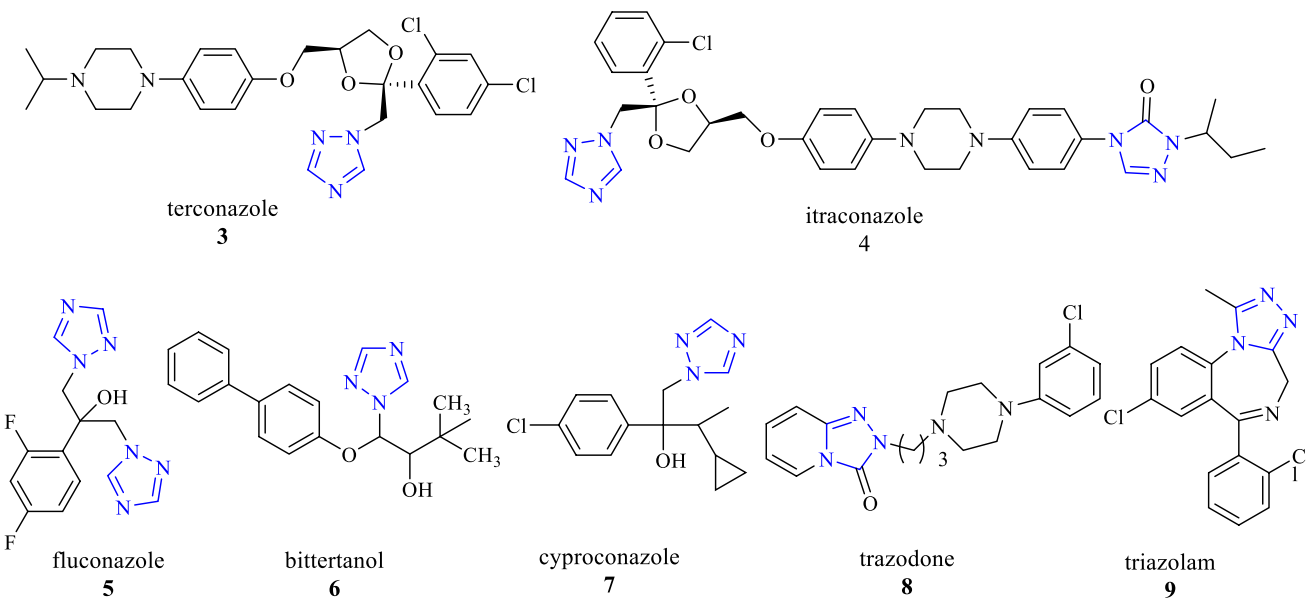


Fig. 3 A number of triazole derivatives in clinical applications

also been verified as a therapeutic agent for mucormycosis and invasive aspergillosis (Fig. 5). The benefits of this triazole-based compound consist of the excellent bioavailability of the oral formulation, water-soluble formulation, availability, and expected pharmacokinetics in adults' people [36].

Oral triazole efficiency is fully verified for the therapy of chronic (CPA), invasive (IPA), and allergic (ABPA) pulmonary aspergillosis that is often longtime. Microbiological recognition of aspergillosis is restricted by poor culture yield, result into indeterminacy about the frequency of triazole resistance. In 2011 Denning et al. found further indications for the stability of triazole for human antifungal treatment [37].

Although triazole derivatives are functional synthetic targets, some triazole-based drugs are not soluble in water and most other suitable medicinal solvents, so this leads to their negligible bioaccessibility and restricts their use in many drug release systems [38]. Some solubility modification attempts have been developed in recent years, including the use of microemulsion systems, polymer-based solid dispersions, and the formation of complex structures with

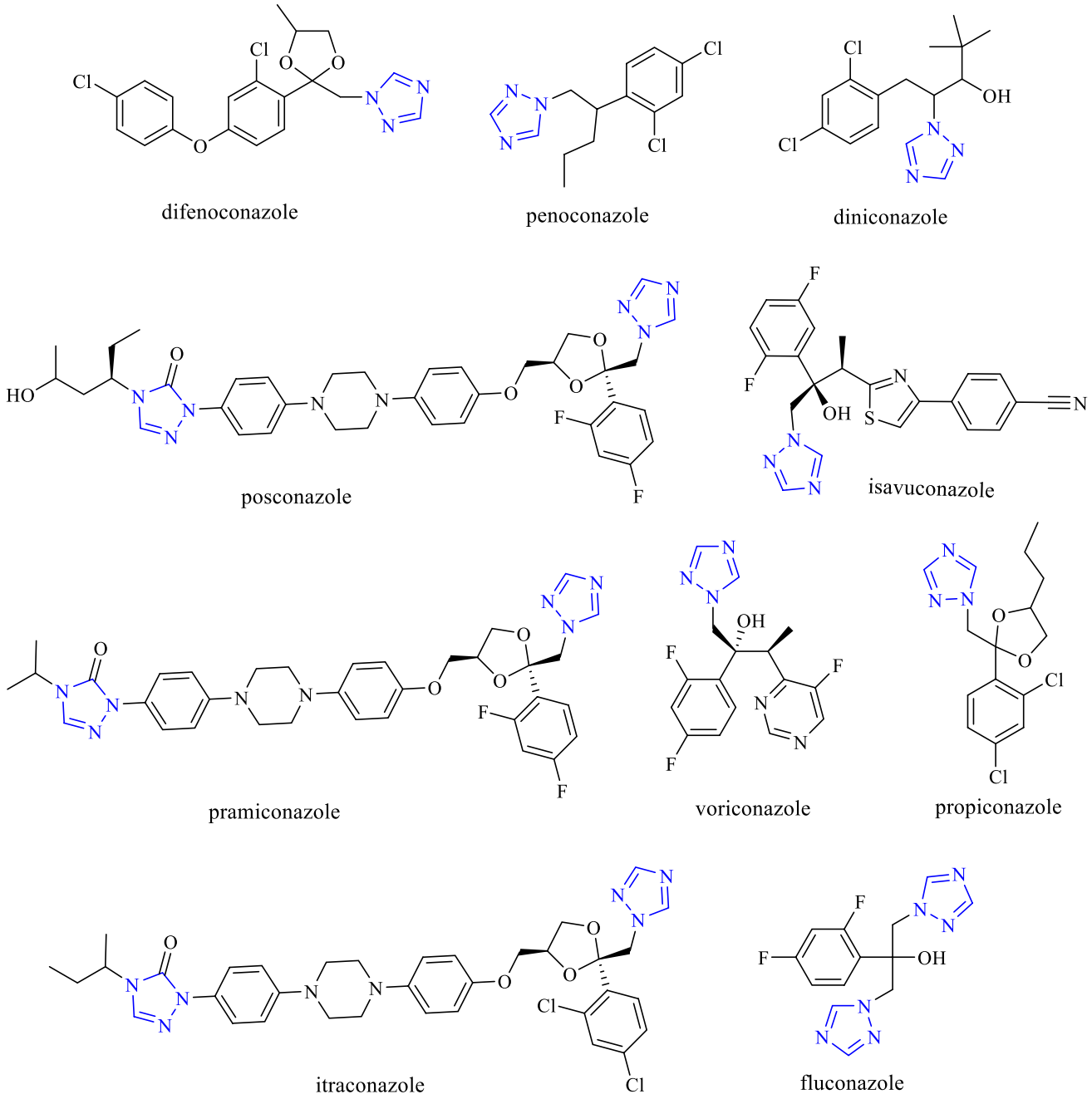


Fig. 4 Triazole-based antifungal medications for the treatment of serious fungal infections in human and plants

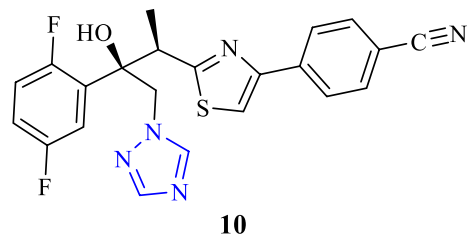


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Fig. 5 The structure of Isavuconazole as a new triazole to treat the invasive fungal infections

crown ethers to increase the solubility of a triazole-based drug in water [39].

In order to solve this problem, in 2013 Kumar et al. prepared acid addition salts of itraconazole as a triazole-based antifungal agent to improve the water solubility and drug dissolution properties. Sulfuric, nitric, and *p*-toluenesulfonic acid addition salts were produced via straightforward preparation methods [40].

In 2010 Jubie et al. designed some new ciprofloxacin analogues **11** as antimicrobial agents (Fig. 6).

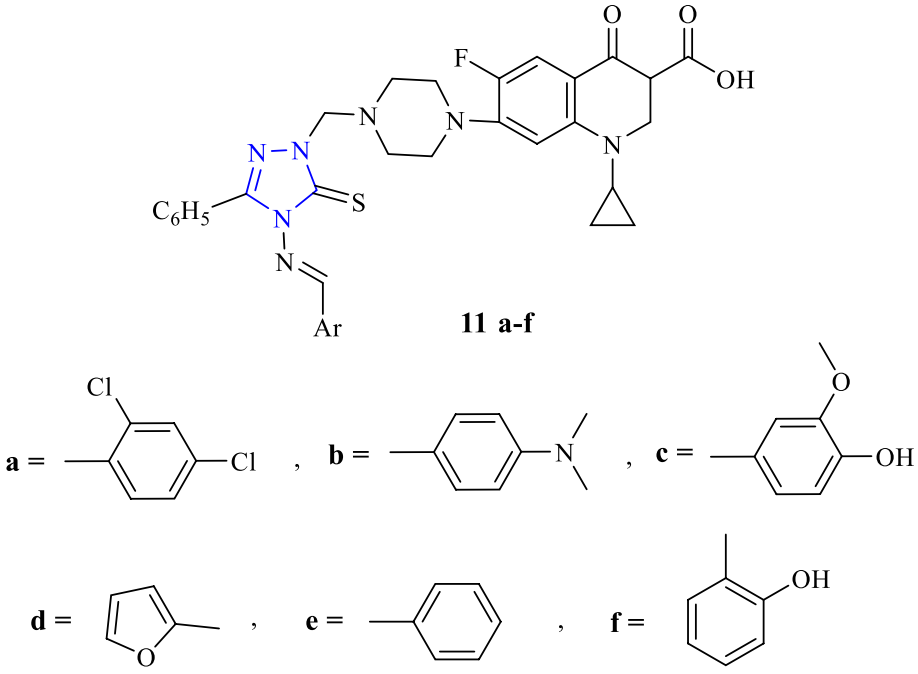


Fig. 6 Several novel ciprofloxacin analogues **11** as antimicrobial agents

Ciprofloxacin participates in the Mannich reaction to produce a novel class of 1,2,4-triazole Schiff bases. The novel products have been examined in vitro for their antimicrobial properties in order to eliminate B. subtilis, K. pneumoniae, and P. aeruginosa at 10 µg/ml concentration. Almost all the synthesized products demonstrated in vitro gram-positive and gram-negative properties that are generally analogous to ciprofloxacin or even better [41].

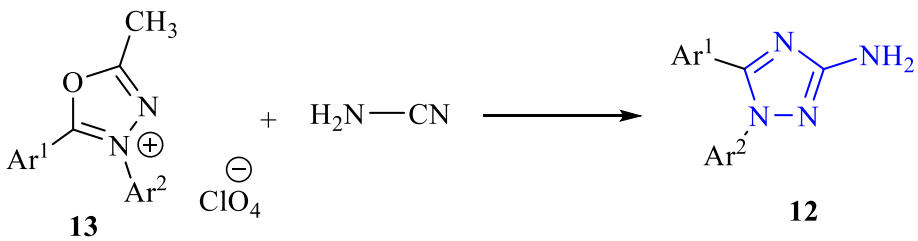
General procedures for the synthesis of 3-amino-1*H*-1,2,4-triazoles

Various methods have been reported for the formation of 3-amino-1*H*-1,2,4-triazoles **12**, and most of these methods are based on the combinatorial synthesis, solid-phase reaction, and using microwave [42]. Some of these methods are described below. The first procedure, proposed by Bozo, including a two-step mechanism: first opening of 1,3,4-oxadiazolium perchlorate motifs **13** by the nucleophile cyanamide and subsequent recyclization (Scheme 1) [43].

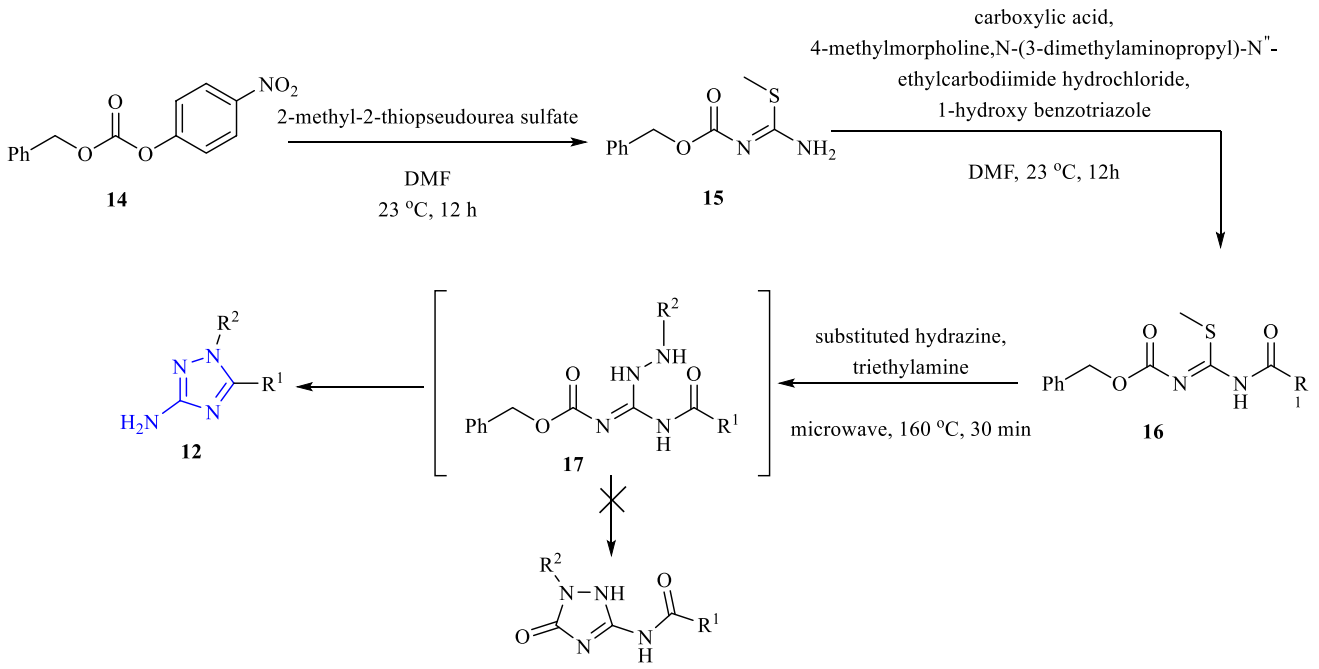
The second procedure, introduced by Meng is based on a robust, regioselective method for the formation of 3-amino-1,2,4-triazoles **12**. This method used a basic intermediate **15**, which is reacted with carboxylic acids in good efficiency to proposed intermediates **16**. In the following, these intermediates, interact with a diversity of hydrazines or hydrazine hydrochlorides to generate offered intermediates **17**, which using microwave-assisted heating under controlled conditions to produce 3-amino-1,2,4-triazoles **12** (Scheme 2). This method provided the rapid synthesis of regioselective N1-substituted 3-amino-1,2,4-triazoles and obtained different products with structural diversity.

The third procedure was recently described by Bogolyubsky and coworkers, presenting an interesting one-pot synthetic procedure for the fast formation of a class of 3-amino-1,2,4-triazoles **12** with structural diversity of products. In the main steps, the formed thioureas undergoes *S*-alkylation with 1,3-propane sultone and subsequential ring closure led to the synthesis of expected 1,2,4-triazoles (Scheme 3). Parallel synthesis generates many 1,2,4-triazoles with structural diversity in a cost- and time-effective process from simple and commercially available materials [45].

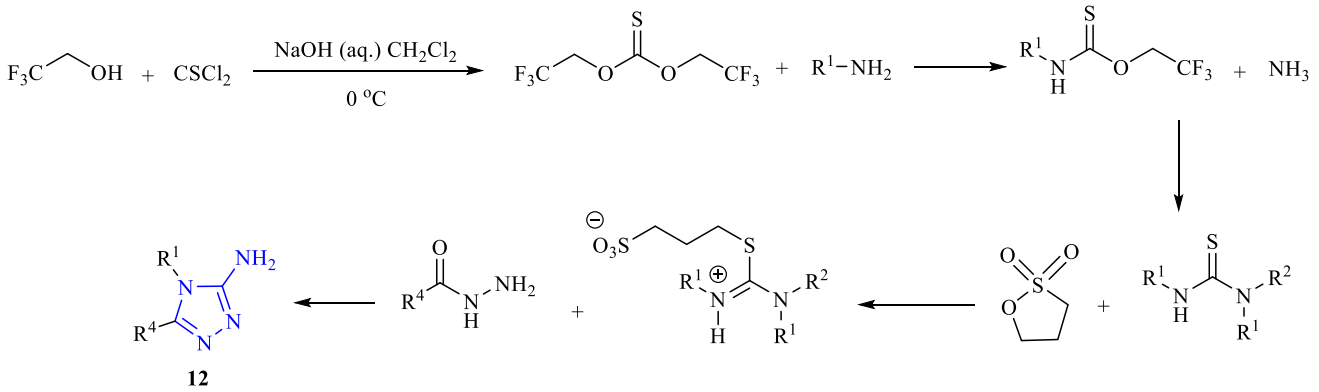
The next synthesis method includes the development of a straightforward and suitable new methodology for the



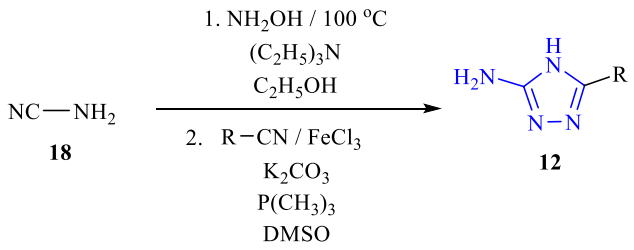
Scheme 1 Synthesis of 1,5-diphenyl-1*H*-1,2,4-triazol-3-amine



Scheme 2 Synthesis of N1-substituted 3-amino-1,2,4-triazoles



Scheme 3 The synthetic pathway for the formation of a class of triazoles



Scheme 4 Synthesis of 3-amino-1*H*-1,2,4-triazoles via iron(III) chloride catalyzed reaction

formation of 3-amino-1,2,4-triazoles 12 that illustrated in Scheme 4. This process includes a one-pot reaction of aminonitrile **18** with various alkyl and aryl nitriles that catalyzed with iron (III) chloride. Trimethylphosphine is applied as a ligand without the use of any further additive. This one-pot reaction takes place under mild conditions for the synthesis of various types of aryl-3-amino-1,2,4-triazoles with excellent efficiencies. This new procedure is highly sustainable in comparison with previously reported methodologies. Rohand and coworkers' research team suggested that these processes could be used to synthesize the 3-amino-1,2,4-triazole required for new drug synthesis [46].

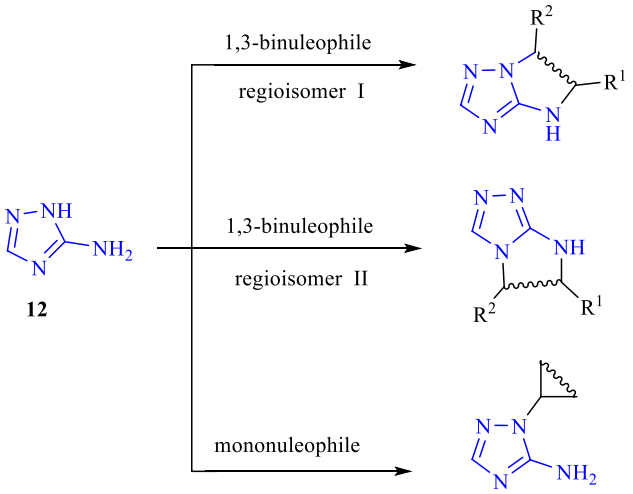


Fig. 7 Diversity of heterocyclizations involving aminoazoles

Strategies for synthesis of triazole-containing scaffolds using of 3-amino-1,2,4-triazole

One of the suitable procedures to produce nitrogen-containing heterocycles is the use of 3-amino-1,2,4-triazole **12** as an effective mono-, bi- and polynucleophile with different electrophiles in two, three or multi-component and one-pot reaction. 3-Amino-1,2,4-triazoles **12** are beneficial reagents in controlled multidirectional reactions because they have multiple alternative reaction centers, makes it possible to synthesize a variety of chemical types of heterocyclic products (some examples in Fig. 7) [47].

Multicomponent reactions (MCRs) containing 3-amino-1,2,4-triazoles **12** and aldehydes with diverse CH-acids are analogous to the classic Hantzsch or Biginelly condensation reactions. In previous literature these reactions had mostly led to the generation of mixtures of positional and regioisomers, accordingly, several effective procedures were found and developed for adjustment chemo- and regioselectivity of these reactions which heterocycle formed via cyclization, containing strategies for changing reaction conditions such as temperature, type of solvent and type of energy source required for activation; microwave irradiation (MW) and ultra-sonication (US), type of catalyst and, etc., for switching their directions of heterocyclization [47].

In 2012, Sedash and coworkers published a review article that completely justified the structural diversity and complexity of the MCRs of 3-amino-1,2,4-triazoles **12** as 1,3-binucleophiles with carbonyl compounds and non-cyclic CH-acids on the Biginelly-type reaction. It was displayed that the step-by-step properties of the MCRs and the existence of various nucleophilic sites on the 3-amino-1,2,4-triazoles **12** could result in at least eight plausible structural diverse compounds **A–H** from the similar precursors. Reaction conditions and also the type of precursors' structure determine which of these products can be the major product. The pairs **A–B**, **C–D**, **E–F**, and **G–F** could be demonstrated as positional isomers while the pairs **A–C**, **B–D**, **E–G**, and **F–H** as regioisomers. Due to such a possible structural variety in obtained products, it is most difficult to determine the structure of the final product (Fig. 8).

They studied the literature related to these kind of reactions and found that the available information about the structure of the products **A–H** obtained from these reactions

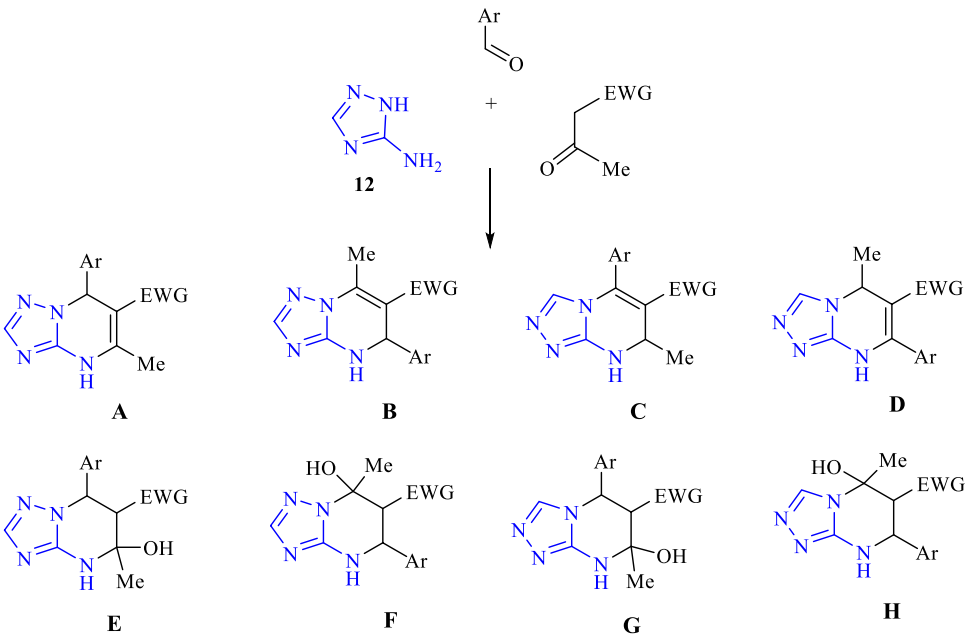


Fig. 8 Variety and complexity of Biginelly-type MCRs of carbonyl compounds, aminoazoles, and non-cyclic CH-acids

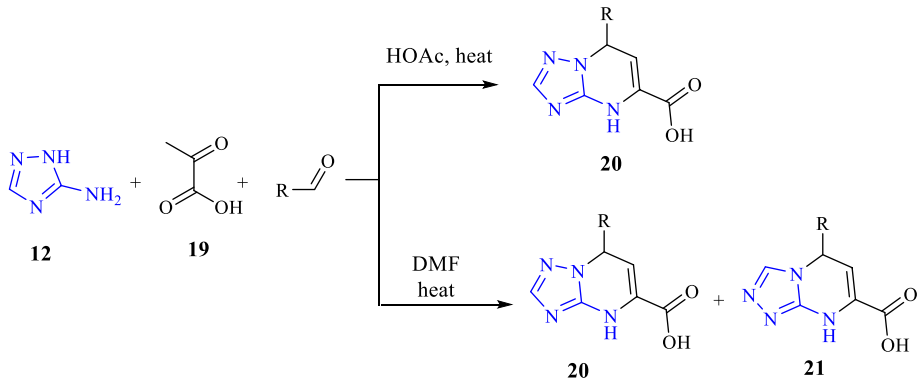
was not always reliable and concluded that structure **A** as the most usual product in most articles which described Biginelli-like MCRs containing 3-amino-1,2,4-triazoles **12** using really harsh conditions and various precursors. The product **C** is sometimes created as a by-product along with the generation of the major product **A**. Only the reaction of 3-amino-1,2,4-triazoles **12** with acetylpyrazole precursor led to the synthesis of compound **C** as the sole product. Synthesis of tetrahydro derivatives **F** were reported in the reactions with phenyl pyruvic acid or ethyl acetoacetate in mild conditions. The product **E** could be acquired in kinetic conditions from the reaction of fluorinated esters of acetoacetic acid and further converted to type **A** heterocycles in thermodynamically controlled conditions. Products with structure **B** could only be obtained if two molecules of acetophenone or cyclohexanone involved with 3-amino-1,2,4-triazole **12**. The compound **D** is synthesized by methods other than the Biginelli-like MCRs method, and also, the synthesis of products with **G** and **H** structure has not been reported so far. The facts about the dominant product formation with structure **A** in the multicomponent reactions containing 3-amino-1,2,4-triazole that suggested by Sedash et al. were verified by the other subsequent literature [48].

This section presents research into the expansion of new methods for the formation of triazole-containing scaffolds using 3-amino-1,2,4-triazole **12** in multi-component reactions as follows:

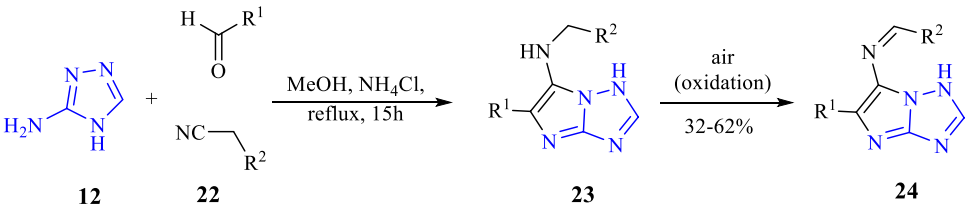
In 2005 Chebanov et al. developed three-component reaction of aromatic aldehydes with pyruvic acid **19** and 3-amino-1,2,4-triazole **12** as starting materials for the formation of 5-aryl-5,8-dihydroazolo[1,5-*a*]pyrimidine-7-carboxylic acids **20** in glacial AcOH. They realized that refluxing of pyruvic acid with aldehydes and 3-amino-1,2,4-triazole in DMF results in the synthesize of two isomers **20** and **21** (Scheme 5). The structure of the obtained products depends on the type of solvent used in the reaction [49].

Later Parchinsky and co-workers examined the three-component condensation between aromatic aldehydes, isonitriles **22**, and 3-amino-1,2,4-triazole **12** in order to conveniently synthesize structural diversity ranges of imidazo[1,2-*b*][1,2,4]triazoles **23**. They found when benzylic isonitriles are used; the obtained heterocyclic products can be produced in an oxidized form in moderate to good yields. Oxidation process happened at the benzylic moiety to synthesize *N*-alkylidene-4*H*-imidazo[1,2-*b*][1,2,4]triazol-6-amines **24** that confirmed the unusual resistance to reduction and acid hydrolysis (Scheme 6). It is thought that the attendance of a readily oxidized benzyl moiety in final structures is a prerequisite for the success of Groebke-type MCR of 3-amino-1,2,4-triazole [50].

In 2008 Sakhno and coworkers studied the multicomponent condensation of 3-amino-1,2,4-triazoles/5-aminotetrazole with phenyl pyruvic acids **25** and aromatic aldehydes in different conditions including, ultrasonication, microwave-assisted heating, and thermal heating. In kinetic or thermodynamic control conditions, the type of obtained product and the reaction pathways for cyclocondensations depend on the reaction temperature and the type of precursors. In the



Scheme 5 Synthesis of two isomers of 5-aryl-5,8-dihydroazolo[1,5-*a*]pyrimidine-7-carboxylic acids



Scheme 6 GBB condensation between 3-amino-1,2,4-triazole, aldehyde and isonitriles

R^1= Ph, 4-OMe-C_6H_4, 4-NMe_2-C_6H_4, 3,4--$(Me)_2$-C_6H_3, 3,4-$(OMe)_2$-C_6H_3, 3,4-OCH_2O-C_6H_3
R^2= Ph, 2-OMe-C_6H_4, 2-Me-C_6H_4, 4-F-C_6H_4, 6-$(Me)_2$-C_6H_3

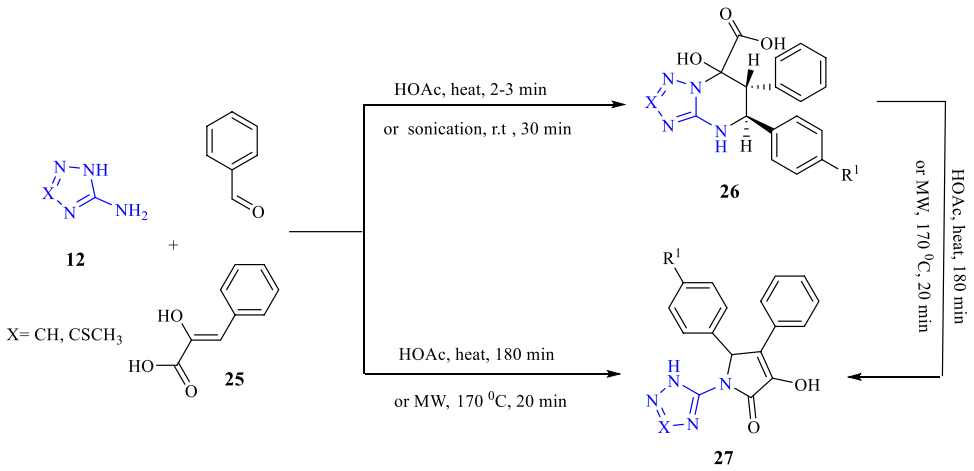
case of amino triazole, they realized that an unprecedented reaction route resulted in the synthesize of 5-aryl-7-hydroxy-6-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acids.

The outcomes reported above verify their supposition about thermodynamic and kinetic control in the reactions illustrated in Scheme 7 and therefore provide an easy adjusting of chemoselectivity through alteration of the medium temperature. The kinetic triazolopyrimidine derivatives **26** obtained when the precursors undergo sonication for 30 min at ambient temperature or heating at 120 °C in acetic acid solvent for 2 min, while pyrrolones **27** obtained as thermodynamically control products in microwave-assisted conditions at 150 °C for 180 min or refluxing conditions at 120 °C for 180 min. Furthermore, it was confirmed when the reaction of Schiff bases **28** and phenyl pyruvic acid **25** irradiated with sonication source in HOAc solvent and ambient temperature for 30 min or heated with a thermal source for 2–5 min also provided triazolopyrimidines **26** as selective product (Scheme 8) [51].

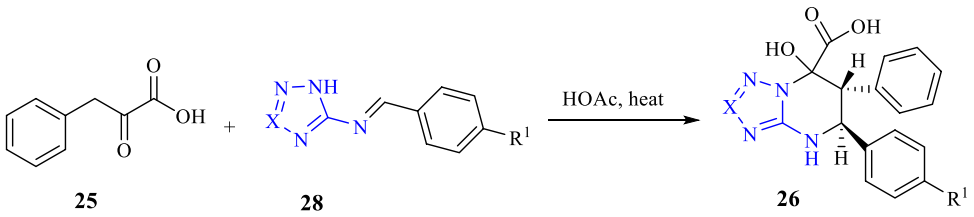
In 2009 Chen and coworkers studied the three-component reaction of 3-amino-5-alkylthio-1,2,4-triazoles **12** with *β*-ketoester **29** and aromatic aldehydes to introduce a Biginelli-analogous reaction with the regioselective manner for the synthesize of **30** and **31** (Scheme 9). The results demonstrated that the solvent type of reaction and the structure of the *β*-ketoester material showed a significant effect on the regioselectivity. This reaction, for the first time, shows the regioselectivity of a Biginelli reaction that uses aminotriazole as one of the starting materials [52].

In 2009 Lipson et al. found the reaction of 3-amino-1,2,4-triazoles **12** with cinnamaldehyde **32** proceeds through two directions and resulted in 5-[*N*-(3-phenylpropenylideneamino)]-1*H*-1,2,4-triazoles **33** and 5-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ols **34** (Scheme 10) [53].

Scheme 7 Two different reaction pathways for the synthesis of triazolopyrimidine and pyrrolones

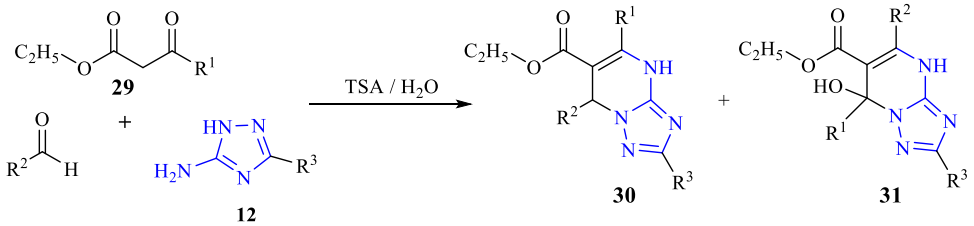


Scheme 8 Synthesis of triazolopyrimidines through the reaction of Schiff base with phenylpyruvic acid



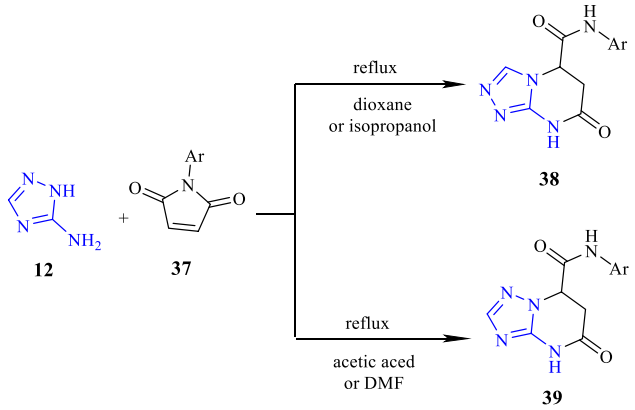
28 a R^1 = H, X= CH, **b** R^1= Cl, X= CH, **c** R^1=CH_3 X= CH

Scheme 9 Products of the Biginelli-analogous reaction in ethanol solvent



In 2010 Gorobets et al. understood that using 3-amino-1,2,4-triazole in Biginelli-like three-component condensation led to synthesis of tetrahydro pyrimidone ring via an unexpected alternative direction. They concluded that the 3-amino-1,2,4-triazole operates in a different way in comparison to other aminoazoles in the Biginelli-analogous multicomponent condensation. The aldehyde precursor interacted with the exocyclic amino group of the 3-amino-1,2,4-triazole **12** instead of the endocyclic nitrogen of the triazole ring and results in the product **35**. The conventional and microwave heating were identified as optimized reaction conditions using salicylic aldehydes as a model reaction. Also, in order to form the related oxygen-bridged compounds **36**, they developed an efficient microwave-assisted procedure (Scheme 11) [54].

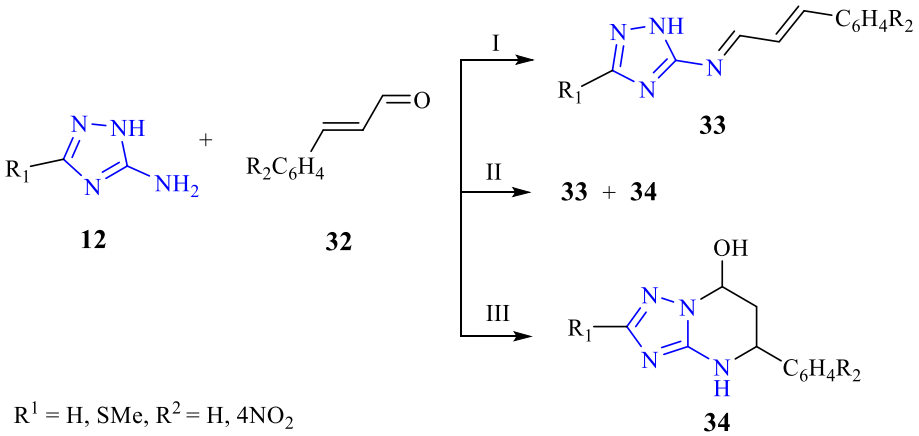
In 2011 Rudenko et al. reported the reaction of *N*-arylmaleimides **37** with 3-amino-1,2,4-triazole **12** in various solvents including dioxane in heating condition, in n-pentanol, acetic acid and ethanol and also without solvent by melting together by 150–160 °C that compounds **38** and **39** were obtained (Scheme 12). It has been confirmed that performing the reaction under dioxane or isopropanol solvent conditions results in the regioselective generation of product **38**. product **39** can be prepared selectively by heating **37** and **12** in acetic acid solvent for not more than 1 h; performing this reaction under these conditions for a longtime results in mixture of products **38** and **39** [55].



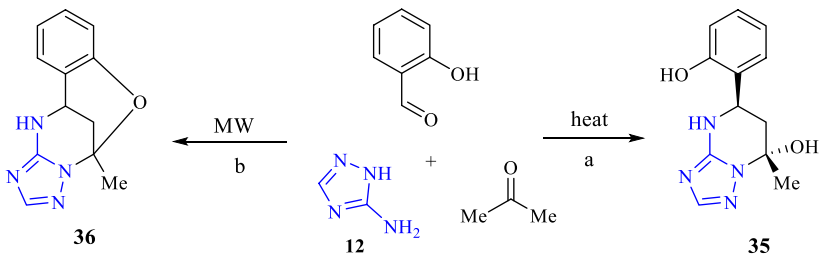
Scheme 12 Reaction of *N*-arylmaleimides with 3-amino-1,2,4-triazole in different solvents

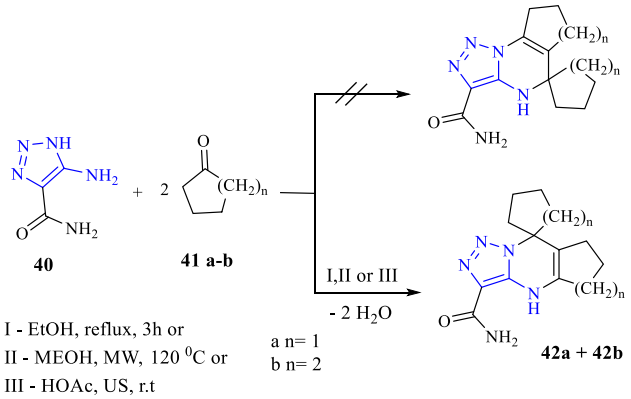
In 2012 Gladkov and coworkers investigated two kinds of heterocyclization reactions between 4-amino-5-carboxamido-1,2,3-triazole **40** and cyclic ketones **41** under normal thermal heating, using the microwave as well as ultrasonic irradiation. ABB′-type MCR carrying out with chemo-differentiation of cyclopentanone or cyclohexanone precursors and obtains 4,5,6,7-tetrahydrospiro{cyclopent a[*d*][1,2,3]triazolo[1,5-*a*]pyrimidine-8,1′-cyclopentane}-3-carboxamide **42a** or 5,6,7,8-tetrahydro-4*H*-spiro{[1,2,3]

Scheme 10 Reaction of 3-amino-5-methylthio-1,2,4-triazoles with cinnamaldehyde



Scheme 11 Direction of the tetrahydropyrimidine ring formation depending on the applied conditions





Scheme 13 Reaction of 4-amino-5-carboxamido-1,2,3-triazole and cyclic ketones under microwave assisted conditions

triazolo[5,1-*b*]quinazoline-9,1′-cyclohexane}-3-carboxamide **42b** in all tested conditions (Scheme 13). The use of methanol as solvent with microwave irradiation conditions at 120 °C were reported as optimal conditions [56].

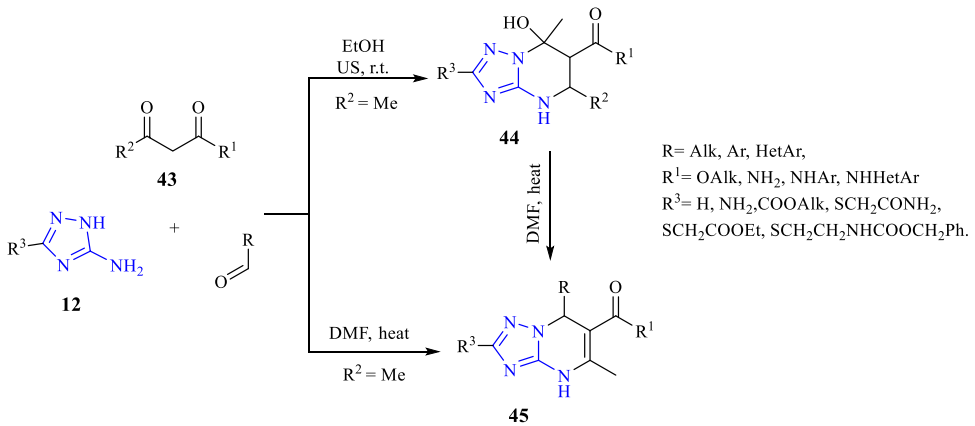
Another example of the direct relationship between reaction path and applied conditions reported in the paper published by Muravyova et al. (2011) and illustrated in Scheme 14. By changing the temperature of the reaction system and using ultrasonic, the direction of reaction including aromatic aldehydes, acetoacetamides **43**, and substituted 3-amino-1,2,4-triazole **12** switches between kinetically and thermodynamically controlled paths and selectively generate tetrahydro- or dihydro derivatives **44** or **45**, respectively (Scheme 14) [57].

In 2011 Kolos et al. found that cyclocondensation of esters **46** was also done with the 3-aminotriazole **12**. It has already been explained that the synthesis of [1, 2, 4] triazolo[1,5-*a*]pyrimidine compounds using *α*,*β*-unsaturated ketones, and amine **12** requires really harsh conditions, including using of DMF or butanol as solvent under reflux condition. Because the reaction of esters **46** and amine **12** in DMF under reflux conditions resulted in the tarring of products, so they used of ethanol and reflux conditions that led to the formation of the triazolo[1,5-*a*]pyrimidines **47** with good efficiencies (Scheme 15) [58]. Optimization of the ester functional group was performed by the involving of compounds **47** with hydrazine hydrate. But, reported in the literature that 6-arylpyridazin-3(2*H*)-ones acquired as products of this reaction instead of the expected hydrazides.

To improve the triazolopyrimidine classes to clinical application, it was essential to recognize and synthesize an optimized product that exhibits both ability and good pharmacokinetic characteristics. The application of 1,3-dielectrophiles in the azoloazine formation is not restricted to the enones. For example, in 2011 Gujjar and coworkers used *β*-dicarbonyl compounds, such as substituted ethyl acetoacetate **48** for the synthesis of the pyrimidine core with substituents in C4 and C6 of **49a-c** (Scheme 16). The asymmetric *β*-dicarbonyl precursors can provide positional isomers, while most processes show only one of the isomers. The aminoazoles-containing pyrrole *N*-atom in the α-position relative to the NH_2-group are often applied as 1,3-binucleophiles [59].

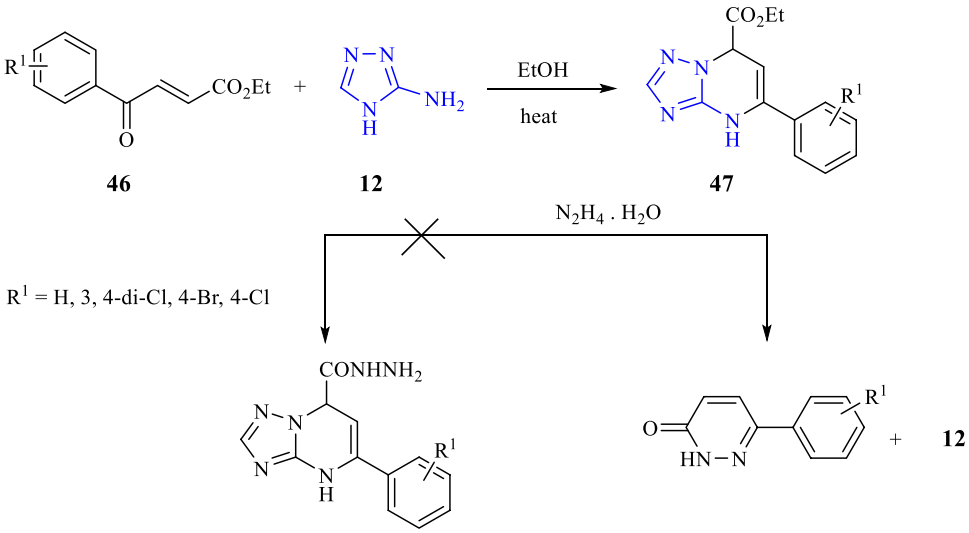
In 2011 Saito et al. replaced easily acetoacetic esters using sodium nitromalonaldehyde monohydrate or malonic ester. The malonic ester **50** was applied as impressive precursor for the formation of the azoloazines **51** with substitute in the C5 (Scheme 17) [60].

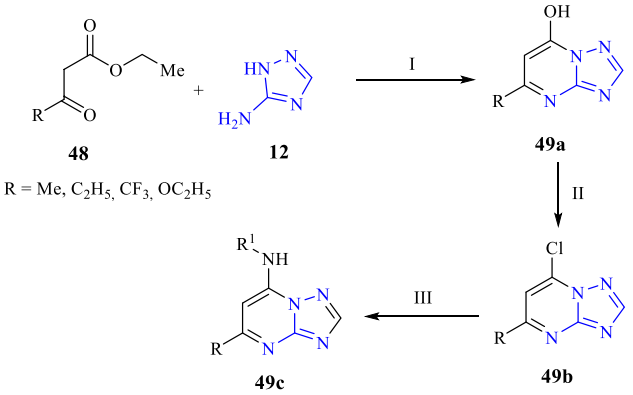
In 2013 Petrova and coworkers reported a new three-component condensation between cyclic 1,3-diketones, 3-aminotriazole **12**, and glyoxal for the formation of a new series of indolo[1,2-*c*]azolo[1,5-*a*]quinazoline-8,10-diones. In these MCRs, if glyoxales and arylglyoxales **52** are used instead of aldehyde, the reaction can proceed via a variety of routes. Therefore, Petrova and coworkers examined the reactions of a broad range of aminoazoles with glyoxales **52** and 1,3-diketones under refluxing condition in ethanol solvent and the new heterocyclic compounds indolo[1,2-*c*]polycyclic compounds **53** were obtained (Scheme 18) instead of expected 4,5,6,7,8,9-hexahydro-8-oxoazolo[5,1-*b*]quinazoline-9-carbaldehyde products [61].



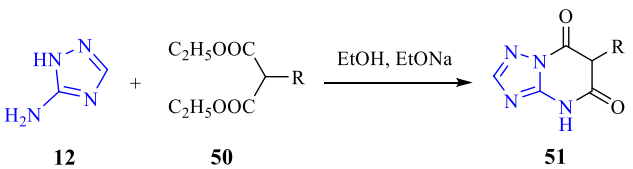
Scheme 14 Condition-dependent multicomponent reactions of 3-amino-1,2,4-triazoles, aldehydes, and acetoacetamides

Scheme 15 Synthesis of [1, 2, 4]triazolo[1,5-*a*]pyrimidine compounds using *α*,*β*-unsaturated ketones, and amine in refluxing ethanol



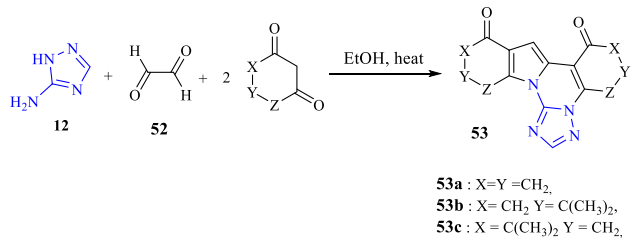


Scheme 16 Synthesis of triazolopyrimidine compounds based on asymmetric *β*-dicarbonyl compounds

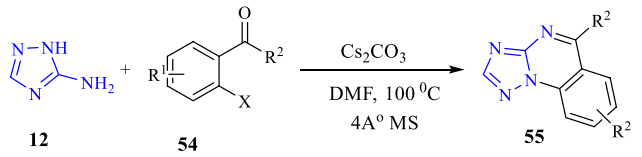


Scheme 17 Use of malonic esters for the synthesis of the azoloazines

In 2014 Niu and coworkers developed a new method for the synthesis of tricyclic systems named 1,2,4-triazoloquinoxalines **55** via a transition metal-free tandem method and in a one-pot condensation/nucleophilic aromatic substitution process. This protocol used to a wide spectrum of precursors such as 2-halogenated or 2-nitro aryl aldehydes and ketones



Scheme 18 MCRs involving aminoazole, 1,3-diketones, and glyoxal using as a carbonyl-containing precursor



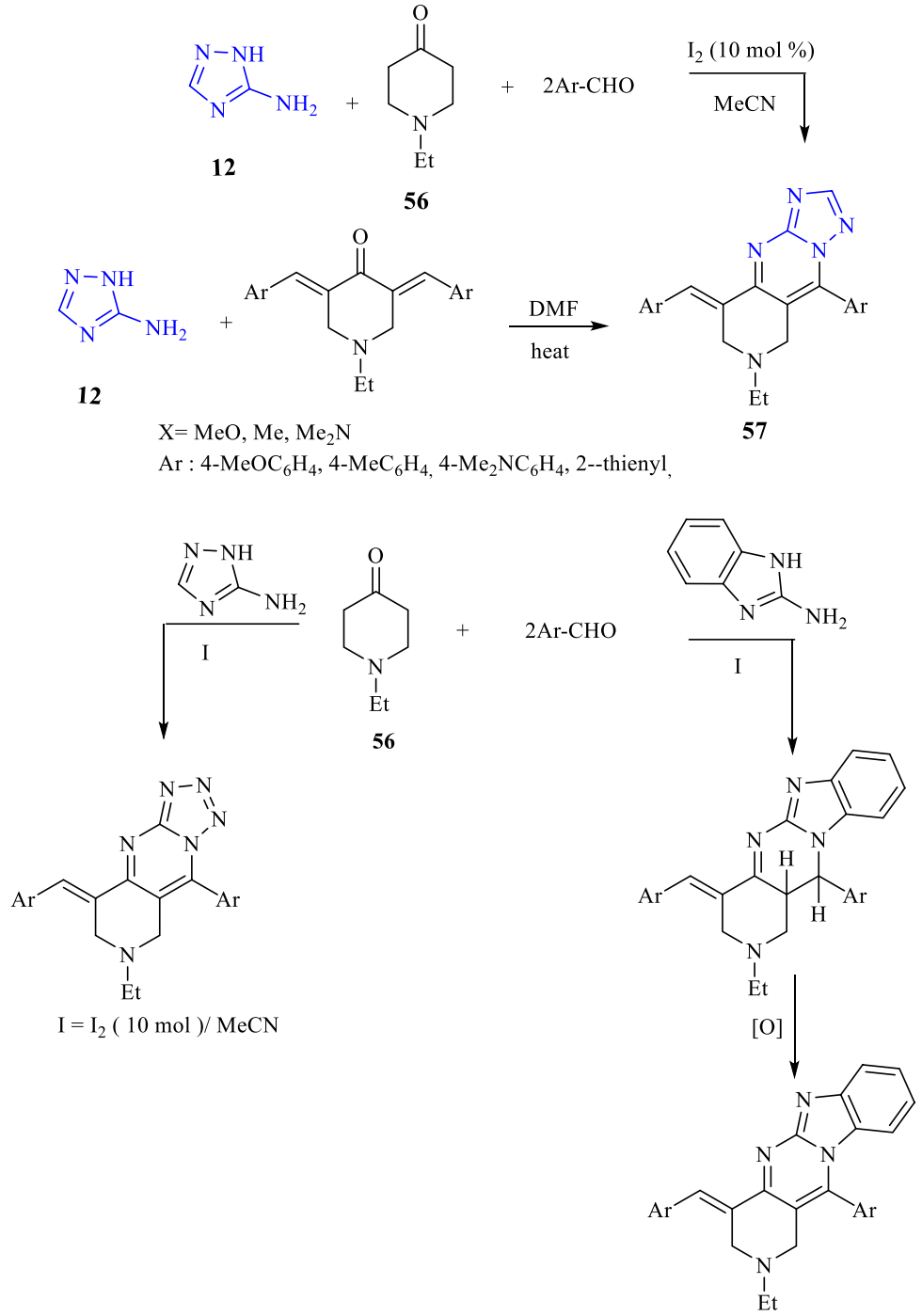
Scheme 19 Synthesis of 1,2,4-triazoloquinoxaline in a one-pot transition metal-free tandem process

54 (Scheme 19). In addition to aldehydes, ketones also react well, resulting in tricyclic products [62].

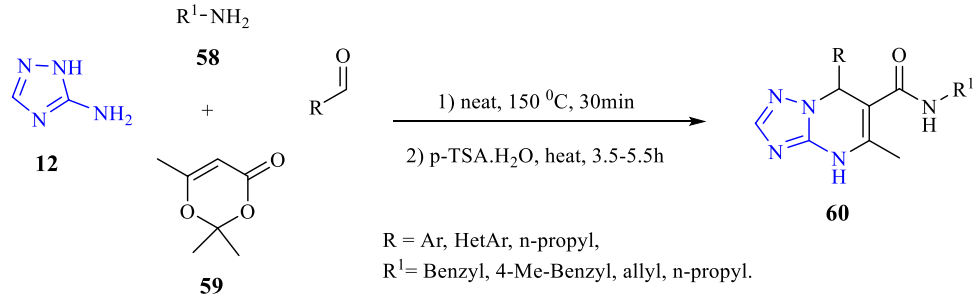
In 2015 A Farghaly and coworkers introduced a method for the formation of pyrido[4,3-*d*]triazolo[1′,5′-*a*]pyrimidines **57** 7 via in situ oxidized triazolopyrimidine process, using 1-ethyl-4-piperidinone **56** as a cyclic ketone in the condensation with two equivalents of aromatic aldehyde and 3-amino-1,2,4-triazole **12** with convenient thermal heating (acetonitrile-I_2, 10% mol, 100 °C) (Scheme 20) [63].

In 2015 Shaabani et al. described a green multi-component procedure for the formation [1, 2, 4]triazolo[1,5-*a*]pyrimidine-6-carboxamides **60** using a one-pot reaction involving an aldehyde, 3-amino-1,2,4-triazole **12**, a primary aliphatic or aromatic amines **58**, and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one

Scheme 20 Synthesis of pyrido[4,3-*d*]triazolo[1′,5′-*a*] pyrimidines by condensation of 1-ethyl-4-piperidinone as a cyclic ketone



Scheme 21 A green one-pot multi-component procedure for the formation [1, 2, 4] triazolo[1,5-*a*]pyrimidine-6-carboxamide products



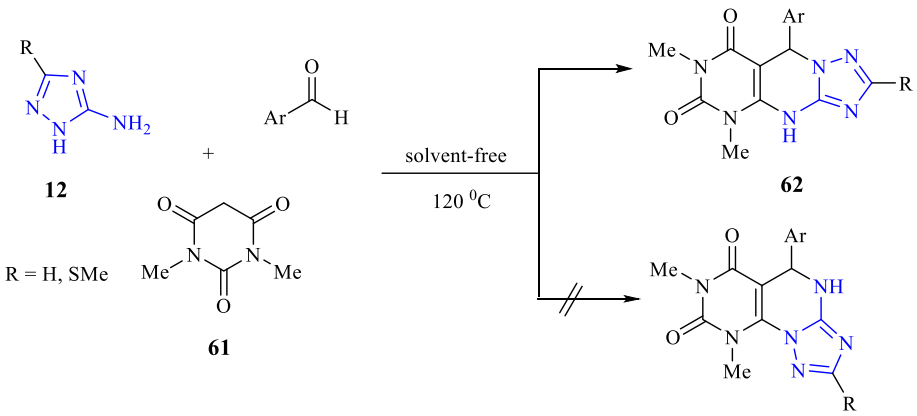
59 (Scheme 21). The first step is performed in solvent-free conditions and heating at 150 °C for 30 min, then the second step is followed using a catalytic amount of *p*-toluene sulfonic acid in water for 4–6 h [64].

In 2015 Karami et al. developed a novel, environmentally friendly formation of 5,9-dihydropyrimido[5,4-*e*][1,2,4]triazolo[1,5-*a*]pyrimidine-6,8(4*H*,7*H*)-diones **62** by using a one-pot condensation of 1,3-dimethylbarbituric acid **61**, 3-amino-1*H*-1,2,4-triazoles **12**, and aromatic aldehydes (Scheme 22). The reactions follow the principles of green chemistry without using any catalysts or solvents throughout the processes.

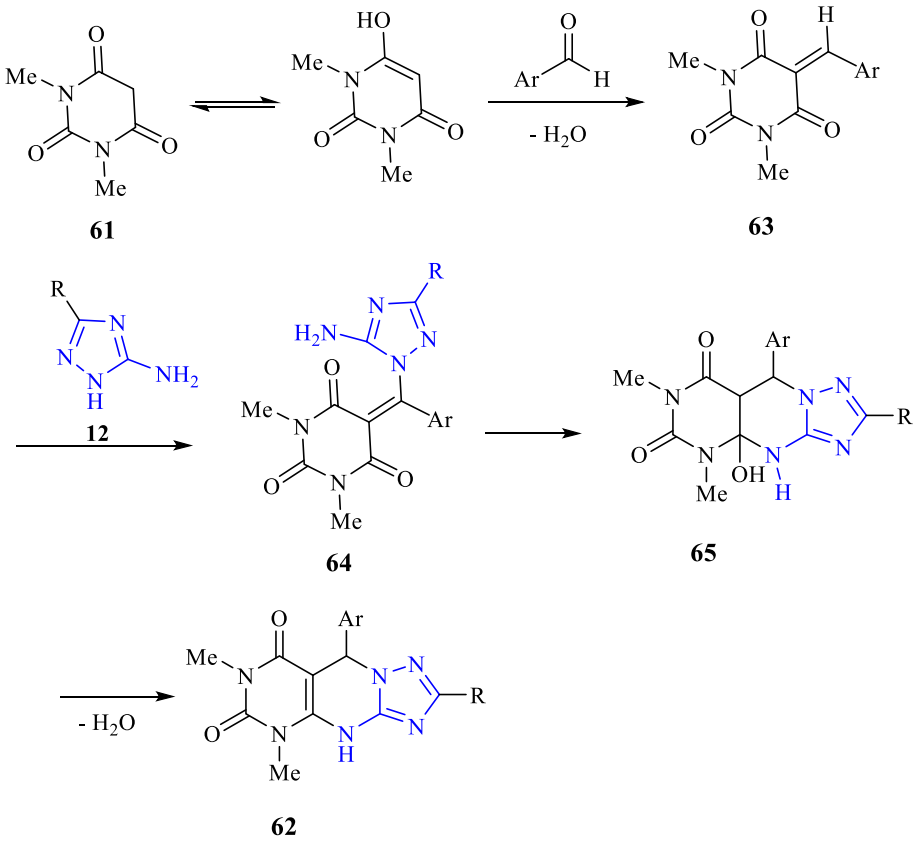
An acceptable mechanism for the synthesis of derivatives **62** is illustrated in Scheme 23. It is plausible that arylidene-1,3-dimethyl barbituric acid **63** is formed via Knoevenagel condensation between 1,3-dimethyl barbituric acid **61** and aldehyde. Then 3-amino-1*H*-1,2,4-triazole **12** can be attacked to intermediate **63** to generate intermediate **64**, which transformed into **65** via an *N*-cyclization, in following, dehydration leads to generate the expected compound [65].

In 2015 Murlykina et al. developed techniques for determination of the selectivity of MCRs containing 3-amino-1,2,4-triazole **12** and pyruvic acids **19**. The route of the reaction depends on the temperature and structures

Scheme 22 Regioselective synthesis of pyrimido triazolo pyrimidine diones



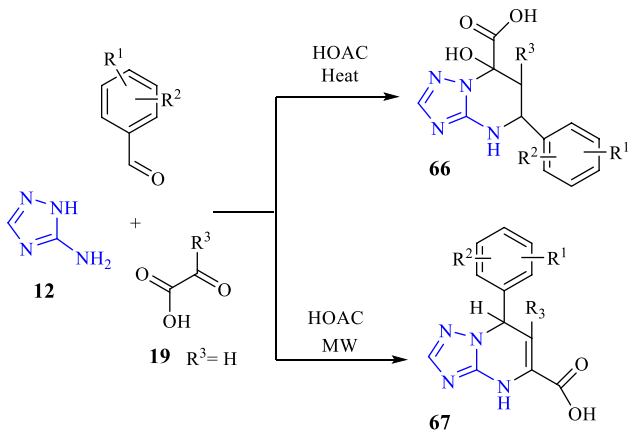
Scheme 23 The rational mechanism for the formation of compound **62**



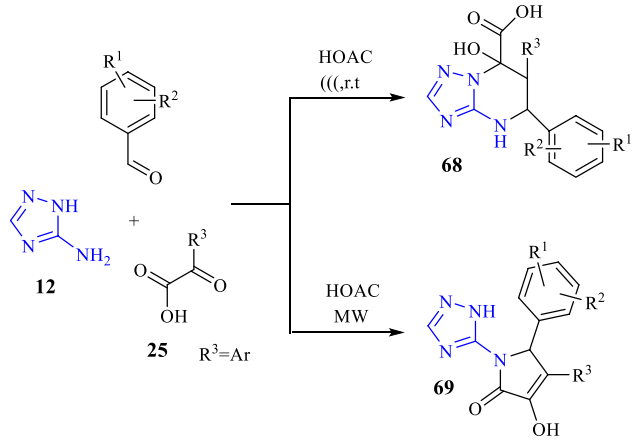
of the starting materials, so it is possible to switch between alternative pathways and synthesize several structural varieties of products.

Accordingly, the product **66** named 7-hydroxy-5-aryl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acids obtained from three-component condensation of 3-amino-1,2,4-triazole **98** and pyruvic acid **99** with salicylic aldehydes and anisaldehydes in mild heating condition. But when reaction carried out in reflux condition or microwave irradiation, the condensation of the similar precursors provides 7-aryl-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-5-carboxylic acids with a free carboxylic group **67**, that could potentially create complexes with various metals (Scheme 24). When they used arylpyruvic acids **25**, the reaction in sonication condition results in compounds analogous to products synthesized with pyruvic acid, *i.e.*, 7-hydroxy-5,6-diaryl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-carboxylic acids **68**. But using heating to reflux temperature or microwave irradiation condition, the similar precursors results in 3-hydroxy-4,5-diaryl-1-(1*H*-1,2,4-triazol-5-yl)-1*H*-pyrrol-2(5*H*)-ones **69** (Scheme 25) [66].

In 2015 Aouali and coworkers reported a rapid and effective microwave-assisted procedure for the formation of a spectrum of fused imidazo-5-amino-1-phenyl-1,2,4-triazoles **70** in good to excellent efficiencies through Groebke–Blackburn–Bienaymé three-component reaction (GBB-3CR) with involving of 3-amino-1,2,4-triazoles **12**, aromatic or aliphatic aldehydes and substituted isocyanides (Scheme 26). This protocol should be effective for the formation of classes of these products with modified yield and high-throughput synthetic procedures. In GBB-3CR and sometimes in Ugi-4CR, Brønsted or Lewis acids are mostly applied to activate intermediate imine. In this GBB-3CR, in order to optimize the reaction conditions, almost all types of solvents such as water and ionic liquids, different catalysts, and different



Scheme 24 Heterocyclizations of 3-aminopyrazoles with salicylic aldehydes and pyruvic acids

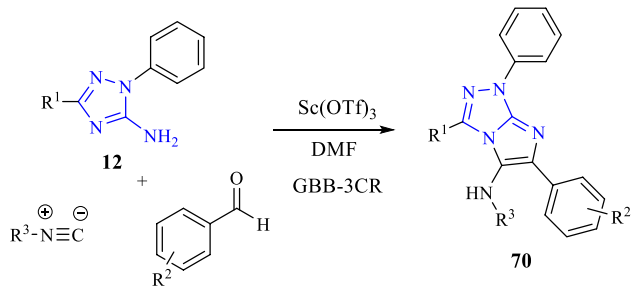


Scheme 25 MCRs containing 3-aminopyrazoles and arylpyruvic acid

temperature treatments (thermal heating or microwave irradiation) were examined.

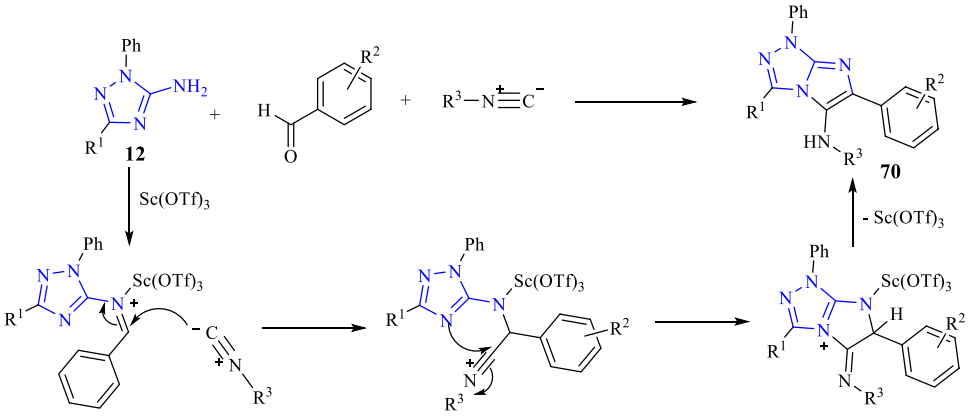
A plausible mechanism for this scandium triflate triggered Groebke–Bienayme´–Blackburn reaction is illustrated in Scheme 27. In this case, the reaction of the amine group with aromatic aldehyde provides an intermediate imine. The use of a broad range of aromatic aldehydes provides structurally diverse iminium intermediates. The trapping of these more electrophilic iminium intermediates using the isocyanide produced imidazo[2,1-*c*][1,2,4]triazoles **70** in middle efficiency [67].

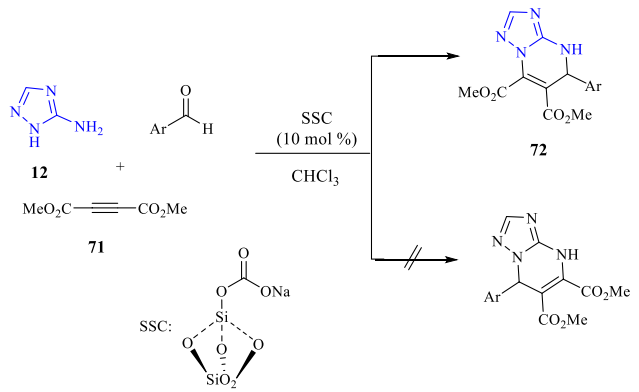
In 2015 Karami and coworkers described a novel method involving a one-pot reaction of 3-amino-1*H*-1,2,4-triazole **12**, dimethyl acetylenedicarboxylate (DMAD) **71**, and aryl aldehydes applying silica sodium carbonate (SSC) as a solid base catalyst for the synthesis of dimethyl 4,5-dihydro-5-aryl-[1,2,4]triazolo[1,5-*a*]pyrimidine-6,7-dicarboxylates **72** (Scheme 28). Using of heterogeneous solid base (SSC), provides the possibility of the separation of dimethyl 4,5-dihydrotriazolopyrimidine-6,7-dicarboxylates **72** in this reaction. The authors proposed that the use of base assist the synthesis of an intermediate due to reaction between NH group in C2 of 3-amino-1,2,4-triazole **12** and active carbon



Scheme 26 GBB-3CR containing 3-amino-1,2,4-triazoles, aromatic or aliphatic aldehydes, and substituted isocyanides

Scheme 27 Proposed mechanism for the formation of imidazo[2,1-*c*][1,2,4]triazoles products **70**





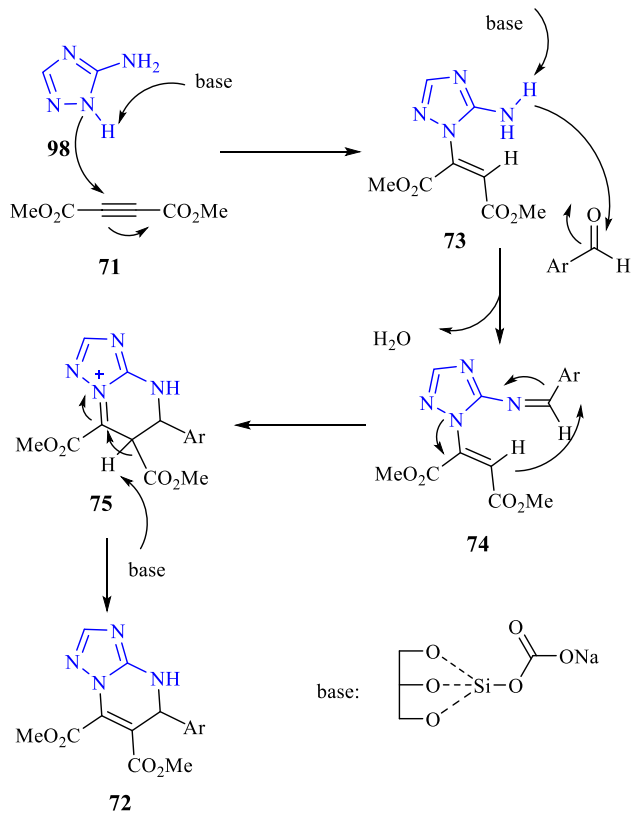
Scheme 28 Regioselective formation of triazolo pyrimidine dicarboxylates catalyzed by SSC

of dimethyl acetylenedicarboxylate **71** that in the continuation of the reaction, the involving of aldehyde, cyclization and dehydration process occurs.

A rational mechanism for the formation of product **72** is illustrated in Scheme 29. At first step, intermediate **73** is formed through the reaction of 3-amino-1*H*-1,2,4-triazole **98** and DMAD **71** using SSC. In the following, intermediate **73** attacks the aldehyde to generate intermediate **74**. Eventually, heterocyclization and dehydration processes occurred on intermediate **75** led to formation 152 [68].

In 2017 Moustafa and coworkers found an impressive and green method for the formation of novel classes of nitrogen bridgehead [1, 2, 4]triazolo[5,1-*c*][1,2,4]triazepine derivatives **77** via one-pot three-component condensation of polyfunctional triazole **76** with aromatic aldehydes and acetophenone in alcoholic sodium hydroxide solution (Scheme 30) [69].

In 2017 Komykhov and coworkers developed a three-component reaction of 1*H*-1,2,4-triazol-3-amine **12**, aromatic aldehydes and acetone in the presence of TsOH as a Brønsted–Lowry acid for the synthesis

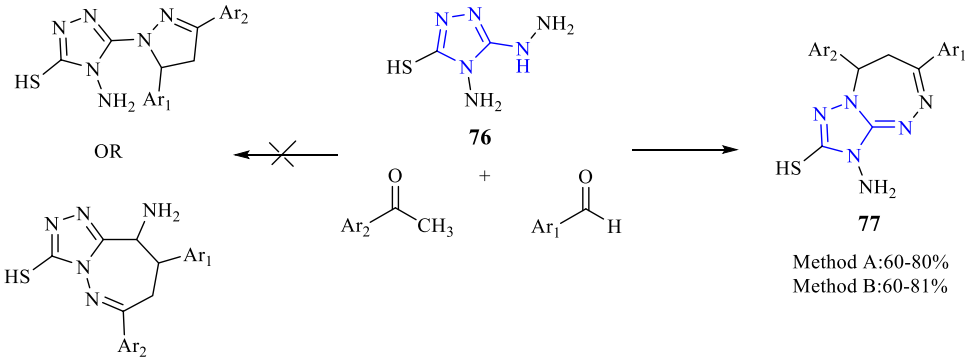


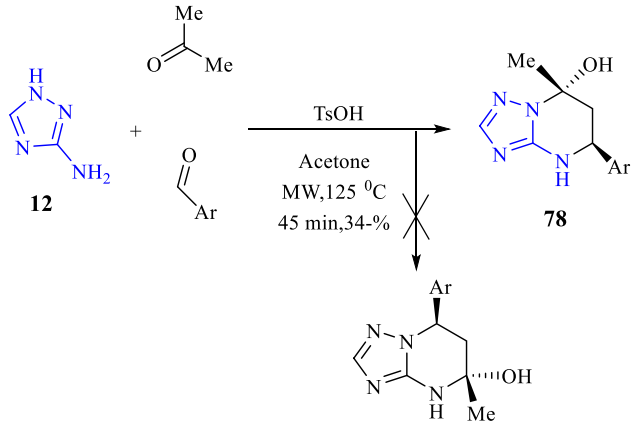
Scheme 29 The rational mechanism for the synthesis of product **72** in the presence of SSC

of (5S,7R)-5-Aryl-7-methyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ols **78** (Scheme 31). They studied the antimicrobial and antifungal properties of these novel compounds in vitro tests [70].

In 2017 Miszczyk and coworkers investigated the reaction of 3-amino-1,2,4-triazole, triethyl orthoformate and diethyl phosphite led to the synthesis of the anticipated 1,2,4-triazoly-3-ylaminomethylenebisphosphonic acid

Scheme 30 Formation of a novel nitrogen bridgehead triazolo triazepine via one-pot three-component reaction of polyfunctional triazole



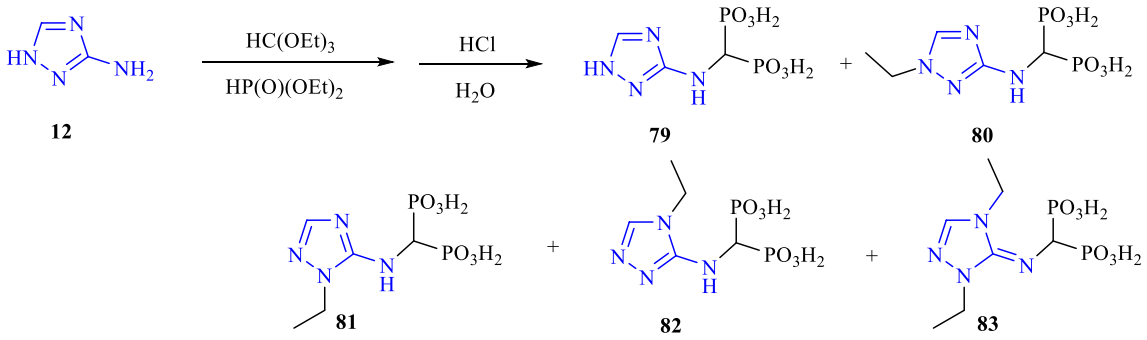


Scheme 31 Formation of tetrahydro triazolo pyrimidin in the presence of TsOH

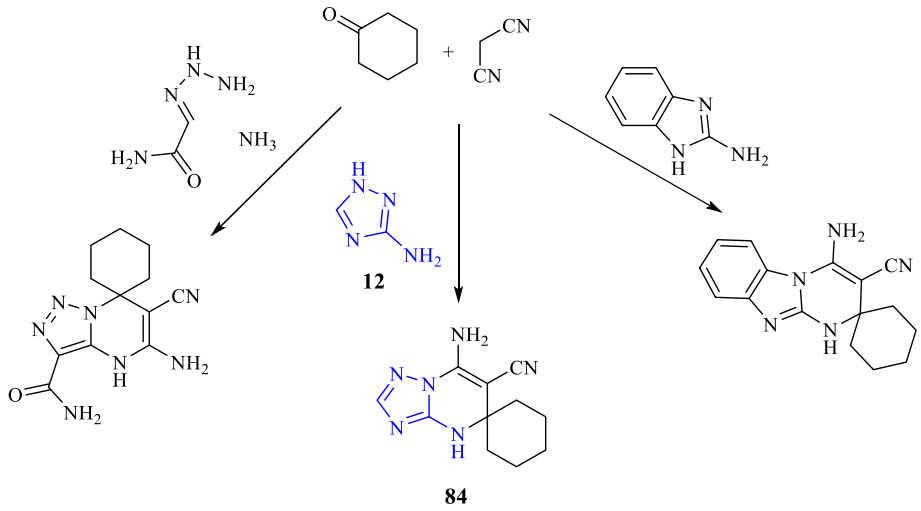
79; although, in this reaction, remarkable quantities of *N*-ethylated products (**80**–**83**) was synthesized which these structures verified by isolation (Scheme 32). Acid–base characteristics of both obtained products **79** and **80** were specified applying potentiometry, UV and NMR titrations. Although there is a potential for substitution of the ethyl functional group in the 1,2,4-triazole scaffold, it was confirmed that product **80** similar to compound **79**, contained an acidic CH on the triazole scaffold that be able to create H-bonding [71].

In 2018 Gladkov et al. prepared a new spiro derivative of dihydro-1,2,3-triazolo[1,5-*a*]pyrimidine **84** by three-component condensation of 3-amino-1,2,4-triazole **12** and various amines with malononitrile and cyclohexanone (Scheme 33). The activation of precursors by microwave irradiation and thermal heating led to the synthesis of a single product that follows a similar heterocyclization pathway [72].

In 2018 El-Saghier et al. synthesized novel 3-(2-hydroxyphenyl)-3*H*-imidazo[2,1-*c*][1,2,4]triazol-6(5*H*)-one **86**, **87**, **88** and 3-*N*-arly(alkyl) amino acid connected triazoles **89**, **90** as potential antileishmanial agents using from 3-amino-5-(2-hydroxyphenyl) amino acid connected triazoles **85** as starting substance (Scheme 34) [73].



Scheme 32 Reaction of 3-amino-1,2,4-triazole with tetraethyl orthoformate and diethyl phosphite

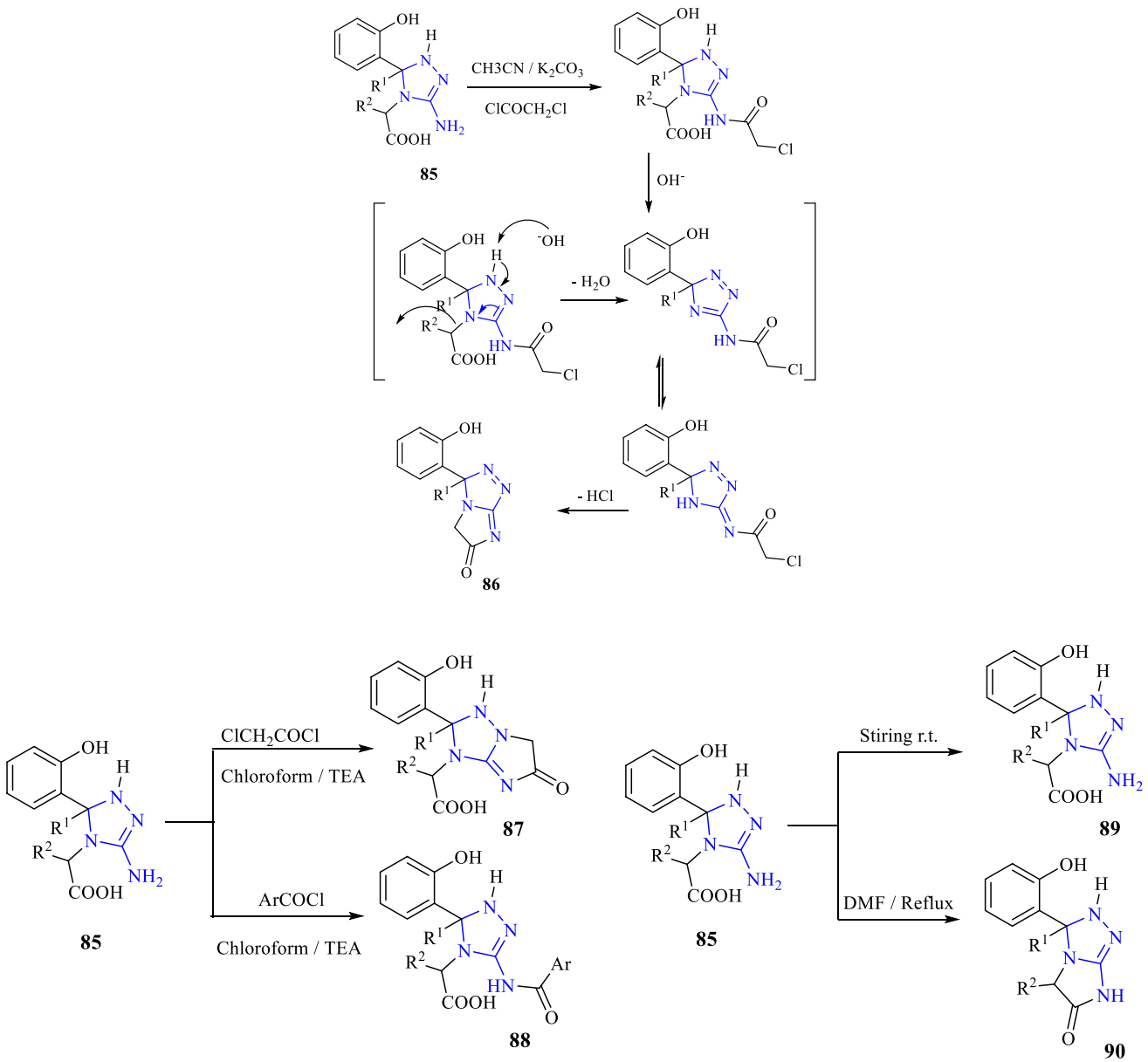


Scheme 33 Three-component condensation between amines, cyclohexanone, and malononitrile

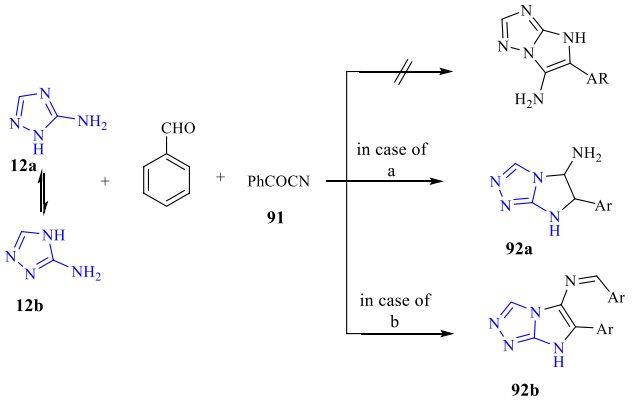
A more effective multi-component one-pot procedure for the formation of imidazo[2,1-*c*][1,2,4]triazole-5-amine products **92** has been reported based on the reaction of easily accessible aromatic aldehydes, benzoyl cyanide **91** and 3-amino-1,2,4-triazole **12** in pyridine undergo controlled microwave irradiation condition (Scheme 35). This protocol has some advantages including; environmentally friendly, simple operation, short reaction time and excellent efficiencies [74].

In the view of above-mentioned points about the biological importance of triazole containing scaffolds, in 2020 Safari and coworkers described an interesting one-pot three-component condensation for the formation of novel triazolo pyrimidine compounds introduced as *N*-methyl-6-nitro-5-phenyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-7-amine **95** using condensation of 3-amino-1,2,4-triazole **12**, aliphatic or aromatic aldehydes **93** or **93′** and *N*-methyl-1-(methylthio)-2-nitroethenamine **94** using trichloroacetic acid (TCAA) as a Brønsted–Lowry acidic catalyst in acetonitrile (for aryl aldehydes) or water (for heterocyclic aldehyde) as reaction solvent and at ambient temperature (Scheme 36). In the case of using heteroaromatic aldehydes, this method usually results in oxidized [1, 2, 4]triazolo[1,5-*a*]pyrimidine **96**, but in other cases where aromatic aldehydes were used, the last dehydration process did not occur and the reaction stopped on the synthesis of the corresponding dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine **95**. The attendance of five nitrogen heteroatoms in these products leads to an increase in the potential of biological values that has attracted considerable attention of chemists and biologists [75].

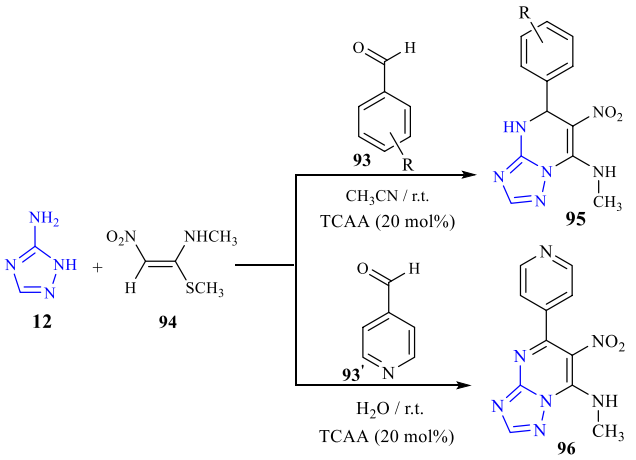
A rational mechanism for the synthesis of compound **95** is illustrated in Scheme 37. At the first step, the reaction of 3-amino-1,2,4-triazole and aldehyde in the presence of TCAA led to form an imine (Schiff base) **97**. The important point is that aldehyde precursor condensed with the 3-amino-1,2,4-triazole **12** via the exocyclic amino group not the endocyclic nitrogen of the triazole moiety. In the following, the reaction of *N*-Methyl-1-(methylthio)-2-nitroethenamine **94** as an enamine type with intermediate **97** carried out through an aza-ene addition continues by imine–enamine tautomerism to produce open-chain intermediate **98**. Then two processes including *N*-heterocyclization and the removal of thiol occur on intermediate **99** and the product



Scheme 34 Synthesis of new amino acid coupled triazoles as potential antileishmanial agents



Scheme 35 Formation of imidazo[2,1-*c*][1,2,4]triazole compounds **92**

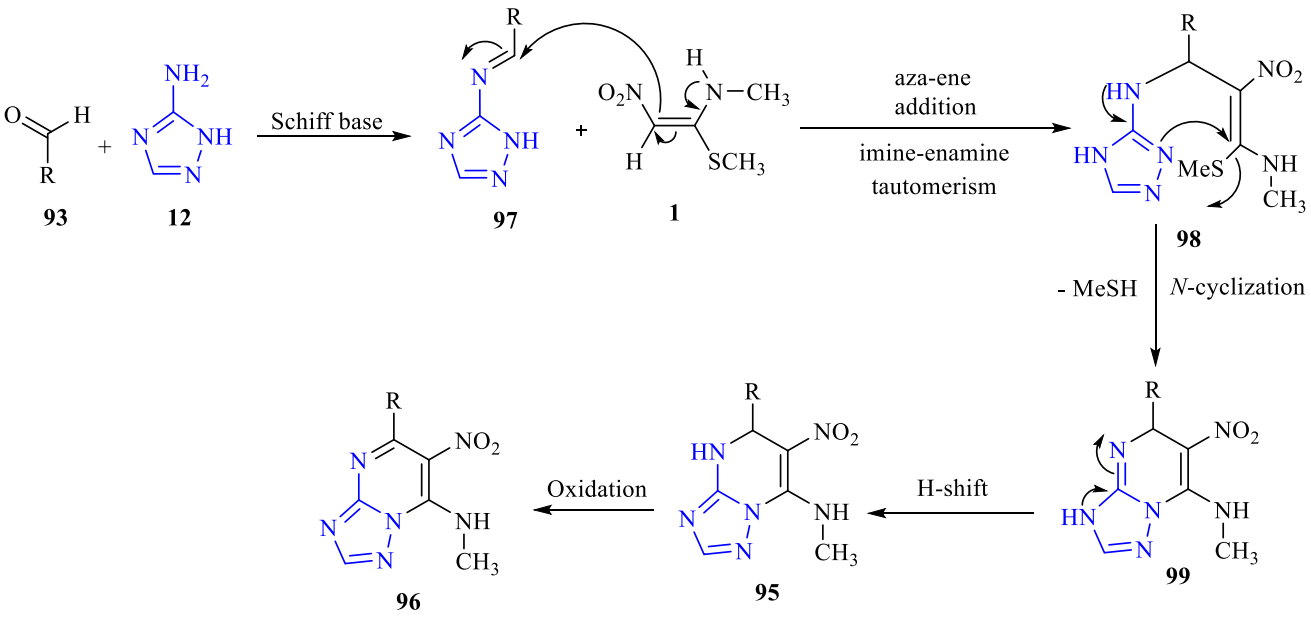


Scheme 36 One-pot procedure for the synthesis of compounds **95** and **96**

98 is generated. Finally, the proton transfer of intermediate **99** led to final compound **95**. In the case of the formation of compound **96**, the generation of these heterocycles can be justified using the oxidation process through the air stream. Indeed, the resonance of the new double bond with low-electron-ring of pyridine leads to the stabilization of product **96**, therefore product **96** tends to oxidize and generate a double bond [75].

Conclusions

1,2,4-Triazole is a significant nitrogen-based heterocycle in the organic chemistry and pharmaceutical field because of its biological activities, potential therapeutic applications and chemotherapeutical values. In this review, we have highlighted some recent synthetic approaches for the synthesis of versatile 1,2,4-triazole heterocycles using 3-amino-1,2,4-triazole. 3-Amino-1,2,4-triazole is an effective mono- or bi-nucleophile in controlled multidirectional reactions that lead to the synthesis of a variety of heterocycles with a high number of heteroatoms. Overall, we hope that this review will assist the chemists in choosing the appropriate methodology for the formation of 1,2,4-triazole based scaffolds and motivate the creation of new synthetic methods in this field.



Scheme 37 Proposed mechanism for the synthesis of expected compounds **95** and **96**

Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests.

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