α-Aminoazoles/azines: key reaction partners for multicomponent reactions

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Aromatic α-aminoazaheterocycles are the focus of significant investigations and exploration by researchers owing to their key role in diverse biological and physiological processes. The existence of their derivatives in numerous drugs and alkaloids is due to their heterocyclic nitrogenous nature. Therefore, the synthesis of a structurally diverse range of their derivatives through simple and convenient methods represents a vital field of synthetic organic chemistry. Multicomponent reactions (MCRs) provide a platform to introduce desirable structure diversity and complexity into a molecule in a single operation with a significant reduction in the use of harmful organic waste, and hence have attracted particular attention as an excellent tool to access these derivatives. This review covers the advances made from 2010 to the beginning of 2020 in terms of the utilization of α-aminoazaheterocycles as synthetic precursors in MCRs.

1 Introduction

Aromatic 2-aminoazaheterocycles (AAHs) are an important group of chemicals occurring widely in nature. They are organic molecules having an amino group attached to a carbon adjacent to the ring nitrogen in aromatic systems. Recently, this class of compounds has attracted significant attention due to their presence in a large number of natural and synthetic compounds possessing pronounced features of biological and pharmacological interest. The nitrogenous bases of nucleic acids, i.e., adenine, guanine and cytosine, and the vitamin thiamine are well-known aromatic AAHs found in nature and make up essential molecules required for the proper physiological and biochemical function of living systems. Besides these widespread compounds, nitrogen-containing heterocycles also have been discovered as part of numerous alkaloids isolated from various natural sources. Lophocladiine, a bioactive alkaloid with an AAH core structure, was isolated from the marine red alga Lophocladia sp. collected in the Fijian Islands and observed to exhibit cytotoxicity to the NCI-H460 human lung tumor and MDA-MB-435 breast cancer cell lines.1 The hybrid pyrrole-imidazole alkaloids (PIAs) are an important family of alkaloids, acting mainly as a fish feeding deterrent agent, which are comprised of hundreds of secondary metabolites isolated exclusively from marine sponges. Oroidin was the first isolated PIA and considered to be the biogenetic precursor of all the others due to its simple, achiral and monomeric structure.2 Recently, two PIAs, 15'-oxoadenoseptrin and decarboxyagelamadin C, were isolated from tropical sponge Agelas

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sceptrum from Plana Cays (Bahamas) by J. Muñoz and M. Köck.\(^3\)

Besides natural sources, a considerable number of synthetic AAH-containing compounds with promising bioactivities also exist. In this context, a novel 1,3,5-triazine-2-amine derivative \(1\) was found to show the highest affinity to histamine H4R, with good selectivity over histamine H3R and classified as an antagonist based on the cAMP accumulation assay results.\(^4\) M. V. N. Rodrigues et al. described 3-nitrobenzoyl 9-deazaguanine, LSPN451 as a potential xanthine oxidase inhibitor, which acts as a broad-spectrum chemotherapeutic agent for gout, cancer, inflammation and oxidative damage.\(^5\)

Compound 2 was shown to possess antitumor activity, targeting subunit EZH2 methylates of PRC2, a multi-subunit methyltransferase involved in the epigenetic regulation of early embryonic development and cell growth (Fig. 1).\(^6\)

Structurally, these amino heterocycles can be considered as the dinitrogen analogs of carboxylic acids and esters in which the carbonyl, \(\text{C} = \text{O}\), and hydroxyl, \(\text{OH}\), groups are replaced by azomethine, \(\text{C} = \text{NR}\), and amino, \(\text{NH}_2\), groups, respectively. The cyclic amidine functionality of amino heterocycles is obtained

![Fig. 1 Some important natural and synthetic organic compounds possessing 2-aminoazaheterocyclic structures.](image)

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when the substituents of both the carbon and nitrogen atoms of the azomethine group are replaced by the same and only one five- or six-membered cycle in which both atoms are embedded and the primary amino group is flanked outside the ring known as an exocyclic amino group. Therefore, they display rich chemistry by combining the effect of an azomethine-like C–N double bond with an amide-like C–N single bond having some partial double bond character.

In relation to their utility in the synthesis of various derivatives, aromatic α-aminoazaheterocycles represent important structural motifs for the creation of ring junction nitrogen heterocyclic compounds, and therefore have become promising building blocks for the discovery of novel molecules in the drug and agrochemical industries. They are also the source of important precursors for the production of valuable heteroaromatics such as benzimidazoles, quinazolines and derivatives of substituted imidazoles, pyrimidines, dihydropyridines, etc., which are known to possess robust biological profiles. The methods exploring the reaction of the amidine functionality in α-aminoazaheterocycles have gained immense popularity for obtaining biological leads and exploring drug discovery programs in the past few decades. In most of reactions, they act as 1,3-dinucleophiles and deliver the triad of N–C–N atoms into the ring of the target heterocycle, and hence are widely used in the synthesis of fused pyrimidines and imidazoles constituting the core ring junction structure of several currently marketed drugs. Considering that several natural and biologically active molecules possess nitrogen-fused heterocyclic fragments, they occupy a central place in pharmaceutical and biomedical research. Fig. 2 shows some representative examples of well-known drug and medicinally active compounds prepared as derivatives of α-aminoazaheterocycles.

In the past few decades, the development of processes that allow the formation of several bonds in one operation has greatly overcome the burden to synthetic organic chemists by creating molecular diversity and complexity via the rapid the assembly of simple and readily available substrates. The beginning of the 21st century marked an increase in the interest in multicomponent reactions (MCRs) as a highly impressive tool to access elaborate molecular scaffolds, while combining structural diversity with eco-compatibility to achieve the diversity-orientated synthesis of a variety of molecules, especially bioactive heterocycles. MCRs are now well-established convergent chemical approaches, in which a single operation is sufficient to build one product from the well-defined condensation of three or more reactant molecules with high atom economy and multiple-bond-forming efficiency. With a reduced number of reaction steps and starting from simple, inexpensive starting materials, MCRs render the library production of substantially diverse range of small molecules less costly compared to conventional approaches. Further, the time-consuming isolation and purification of synthetic intermediates are not required, and hence, both the production of waste and expenditure of human labor are significantly reduced, complying with the principles of green chemistry. Their experimental simplicity lies in the fast and elegant access of compounds that allow systematic variations, and consequently they allow the possibility of automatization. Therefore, their extensive application in the synthesis of densely
Some promising and well-established MCRs include the Ugi-4-component condensation, Strecker amino acid synthesis, Hantzsch dihydropyridine synthesis, Biginelli reaction, Mannich reaction, Kabachnik-Fields reaction, Groebke-Blackburn-Bienaymé (GBB) reaction, and Gewald reaction (Fig. 3). The present review is devoted to gathering and generalizing the reported data obtained from a literature survey from 2010 to 2019 and some recently available references from 2020 concerning the application of α-aminoazaheterocycles in MCRs and attempt to fulfil the conception of these reactions. Among the aromatic α-aminoazaheterocycles undergoing MCRs, it has been observed that five-membered (fused or non-fused) azoles are the most studied and frequently employed azaheterocyclic compounds, and V. A. Chebanov’s group covered most of the publications up to 2010 regarding the utilization of azoles in MCRs. Therefore, we incorporate the references starting from 2010.

Although there is a huge variety of five- and six-membered α-aminoazaheterocycles with fused and non-fused structures, fortunately only the simplest of them are reported with their applicability in MCRs as they are readily available and inexpensive. Fig. 4 shows these heterocyclic compounds, which will be encountered in this review frequently. However, only the α-aminoazaheterocycles that are part of a heteroaromatic ring system are covered in this review.

### 2 Classification

The remainder of this review is mainly divided into two sections. The first section deals with the binucleophilic action of the amidine functionality of aromatic AAHs and the second section covers the MCRs involving aromatic AAHs as mononucleophiles. The products resulting from the reaction in which

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**Fig. 3** Some well-known multicomponent reactions.

**Fig. 4** Structure of α-aminoazaheterocycles covered in this review.

**Fig. 5** Classifications of MCRs involving AAHs based on their reaction profile.
AAH exhibits binucleophilic tendency are nitrogen-containing five- or six membered cycles, whereas expected noncyclic structures are obtained when AAH acts as mononucleophiles (Fig. 5). From the viewpoint of biological activity, fused heteroaromatic systems are often of much greater interest than their constituent monocyclic compounds.

Further, the multicomponent treatments of AAH as binucleophile are subdivided into two categories:
(i) AAH as 1,3-binucleophiles (more diverse), and
(ii) AAH as 1,1-binucleophiles (less diverse).

2.1. Aminoazaheterocycles as binucleophiles

Binucleophiles of the amide type are very important reagents in modern heterocyclic chemistry and their reactions with electrophiles are the most widespread and facile synthetic approach to obtain variety of complex heterocyclic systems containing several fused ring junction nitrogen heterocyclic compounds possessing crucial pharmacological characteristics.

2.1.1 As 1,3-binucleophile. A vast number of MCRs have been reported in the literature in the past decade, where both nitrogens of the amidine group of AAH function as nucleophiles. Pyrimidine and imidazole derivatives are the usual structures resulting from these binucleophilic actions and the heterocycles are classed according to their known biological profiles. Therefore, the study of these MCRs is the central principle for the synthetic application of aminoazaheterocycles.

In the formation of compounds containing these core nuclei, AAHs are combined with components that can act simultaneously as an electrophile and nucleophile together with an electrophilic component such as aldehyde and ketone. Based on the type of components that react with AAHs other than aldehydes and ketones, this subgroup is classified as follows.

By definition, active methylene compounds are compounds that possess a methylene group between two strong electron withdrawing groups such as carbonyl, nitrile, and nitro. Because of the strong deactivating nature of these group, the hydrogens of the methylene bridge become acidic in nature, and consequently the methylene carbon acquires nucleophilic character, while the group adjacent to it behaves as an electrophile.

β-Keto/β-dicarbonyl compounds, both non-cyclic and cyclic, are the most investigated components used to explore the 1,3-binucleophilic nature of the amidine functionality of 2-aminoazaheterocycles through MCR chemistry. According to our literature survey, the majority of publications in this review comprise MCRs related to non-cyclic β-keto compounds such as β-ketoesters and β-ketoamides and cyclic β-keto compounds such as cyclohexanedione and analogues, Meldrum’s acid, and 4-hydroxyconamarin. Accordingly, the Biginelli reaction, a three-component reaction (3-CR) that employs β-ketoesters, amines and aldehydes has emerged as a prototype for the construction of dihydropyrimidine scaffolds containing carboxylic ester or carboxamide groups. The versatility of this reaction allows the incorporation of a vast range of substrate molecules including amines, and therefore remains one of the most common reactions studied among chemists utilizing α-aminoazaheterocycles as amine components. A general view of the Biginelli reaction is depicted in Scheme 1.

2.1.1.1 MCRs involving non-cyclic 1,3-dicarbonyl and analogous compounds. The intense research on the Biginelli reaction was witnessed by the fact that the combination of amino azoles such as 2-aminobenzimidazole 3a/2-aminobenzothiazole 3b as amine components with aldehydes 4 and β-ketoesters 5 has been reported with several activators or catalysts. The published articles illustrate that the multicomponent synthesis of benzimidazole or benzothioazole-fused pyrimidines can be conveniently performed in the presence of N,N’-dichloro(2,4,6-trichlorophenyl)urea (CC-2) and N-sulfonic acid based on the polymer support as a solid acid catalyst (SMI-SO₃H), HCl, ZnCl₂, 6H₂O, citric acid, PdCl₂, ZnO NPs, 3D-printed Al₂O₃, H₂BO₃, acetic acid, nano-kaolin/TiO₂/Fe₂O₃, chitosan, Fe₂O₃@SiO₂–TiCl₃ NPs, nano-cellulose/Fe₃O₄, nanoporous sodium montmorillonite clay [Na⁺-MMT]-modified 1-methyl-3-(trimethoxysilyl)propyl)-imidazolium hydrogen sulfate (Na⁺-MMT-[pmim][HSO₄]), etc. A brief description and comparison of the product yield and reaction time of the reported methods for the synthesis of these fused pyrimidine derivatives are shown in Scheme 2. The general mechanism suggested by most authors involves the in situ Knoevenagel condensation reaction between activated aldehydes 4 and β-ketoesters 5, and thereby alkene I is primarily formed. Afterwards, during the Michael addition reaction, 2-aminobenzothiazole/benzimidazole 3 as a Michael donor attacks the alkene in the presence of a catalyst followed by proton transformation to produce intermediate II, which subsequently undergoes intramolecular cyclization with the elimination of a water molecule, resulting in the formation of benzazazole-fused pyrimidine motif 6.

An interesting case was studied by P. K. Sahu and coworkers, where the synthesis of these pyrimidine derivatives was achieved in the presence of a solvent and under solvent-free
conditions using various catalysts. When the condensation among 2-amino benzothiazole \(3b\), aldehydes \(4\) and \(\beta\)-ketoester \(7\) was carried out in the presence of acetic acid as the catalyst and methanol as the solvent at 65 °C, the corresponding products were obtained after 12–20 h. Conversely, the same reaction was completed in 70–120 min when carried out with various metal catalysts under solvent-free conditions. The highest yield was obtained when \(\text{CuCl}_2\) and \(\text{LiCl}\) were used as catalysts, but the
use of LiCl ensured minimum time for completion of the reaction (Scheme 3). The experimental results suggested that the reaction follows different mechanistic routes depending on the type of catalyst. In the presence of acetic acid, 2-amino benzothiazole 3b first reacts with aldehyde 4 to give imine as intermediate III, which then reacts with ethyl acetoacetate 7 to give the final product 9, whereas 2-amino benzothiazole 3b and ethyl acetoacetate 4 first combine in the presence of metal catalysts and resultant intermediate IV adds to the benzaldehyde to give pyrimidobenzothiazole 8 (Scheme 4).

Scheme 3 Synthesis of 4H-pyrimido[2,1-b]benzothiazole derivatives under two different conditions.

Mechanistic path followed in the presence of acetic acid

Mechanistic path followed in the presence of metal catalyst

Scheme 4 Mechanistic routes explaining the formation of 4H-pyrimido[2,1-b]benzothiazoles in the presence of acetic acid and metal catalyst.

Scheme 5 Synthesis of benzothiazolopyrimidine using pyridine under thermal and microwave heating.
Scheme 6  Catalyst-free and solvent-free synthesis of 4H-pyrimido[2,1-b]benzothiazole and 2-oxo-pyrimido[2,1-b]benzothiazole derivatives.

| X      | Reaction conditions       | R¹  | R²     | Time  | Yield   | No. of examples | Reference |
|--------|---------------------------|-----|--------|-------|---------|-----------------|-----------|
| N      | Solvent-free 130–170 °C   | R¹  | R²     | 20–30 min. | 31–80%  | 40              | 35        |
| N      | I₂ (10 mol%), i-PrOH, Reflux | R¹  | R²     | 4 h   | 70 & 94 | 2               | 36        |
| CH     | [Bmim]BF₄, 110 °C         | CF₃ | OEt,   | 6–9 h | 82–92   | 19              | 37        |
| N      |                           | Ph  |        | 7–9 h | 78–89   |                 | 38        |
| N      | Nano-Fe₃O₄@SiO₂-NH₂gallic acid, EtOH, Reflux | R¹  | R²     | 15–20 | 81–90   | 15              | 39        |
| N      | CH₂COOH/HCl, reflux       | Ph  | Ph     | 8 h   | 76–86   | 5               | 40        |
| N, CH  | HCl/EtOH, reflux          |     |        | 8–9 h | 8–60    | 7               | 41        |
| N, CH  | TBBDA (5 mol%), 80 °C      |     |        | 10–80 min | 83–90   | 7               | 42        |

Scheme 7  Three-component synthesis of triazolo/tetrazolo-fused pyrimidines using various catalysts.
Scheme 8  Synthesis of podands containing two terminal tetrazolo[1,5-a]dihydropyrimidine groups.

Scheme 9  Proton acid-catalysed synthesis of thiazolopyrimidines from 2-aminothiazole, ethylacetoacetate and aromatic aldehydes.

| Reaction conditions                      | Time    | Yield (%) | No. of examples | Reference |
|-----------------------------------------|---------|-----------|-----------------|-----------|
| NH$_2$SO$_3$H (30 mol%), EtOH, Reflux    | 1.5 h   | 65–81     | 12              | 44        |
| Nano-Fe$_3$O$_4$@SiO$_2$@SO$_3$, 60 °C | 1.5–2.5 h | 89–95    | 5               | 45        |
| H$_3$BO$_3$/H$_2$O, RT                   | 8–30 min | 80–95    | 12              | 25        |
| AcOH, MW 80 °C                          | 10–30 min | 83–95   | 6               | 26        |

Scheme 10  Synthesis of benzoimidazolo pyrimidine and triazolopyrimidine derivatives based on thiamine hydrochloride (VB1)-catalyzed three-component reaction.
Besides these acid-catalyzed methods, P. K. Sahu et al. adapted the synthesis of benzothiazolopyrimidine 11 starting from a completely different β-dicarbonyl, known as curcumin 10, 2-aminobenzothiazole 3b and aromatic aldehydes 4 using pyridine as a catalyst under thermal heating involving methanol as the solvent as well as microwave irradiation solvent-free conditions (Scheme 5). 11 The synthesis of curcumin derivatives 11 was found to be completed within 18–20 h when carried out under conventional heating. Conversely, the reaction time was significantly reduced to 8–10 min when the same reaction mixture was irradiated with microwaves under solvent-free conditions. Thus, synthesis under microwaves provides a very simple and efficient way to obtain curcumin derivatives in a shorter time with the advantage of reducing environmental pollution by eliminating the use of volatile organic solvents. The detailed mechanistic study shows that the reaction proceeds

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**Scheme 11** Mechanism proposed for VB$_2$-catalyzed synthesis of fused pyrimidines.

**Scheme 12** ZnCl$_2$-catalysed synthesis of benzimidazole/triazole-fused dihydropyrimidinones.

**Scheme 13** Microwave heating-assisted synthesis of azolopyrimidine derivatives.
through a Knoevenagel-type intermediate and follows the path of the usual Biginelli reaction.

A catalyst-free and solvent-free approach based on the Biginelli reaction was developed by F. Chadegani et al., wherein the one-pot three-component reaction between 2-amino-benzothiazole 3b, benzaldehyde derivatives 4 and β-ketoester or β-diketone derivatives (12 or 13) was performed at 60 °C, which afforded the corresponding pyrimido[2,1-b]benzothiazole derivatives 14 in 3–5 h. The same reaction was also studied with malonic acid derivatives as the β-diketo component, and subsequent annulation reactions provided 2-oxo-pyrimido[2,1-b]benzothiazoles 15 with no substitutions at the 2 and 3 positions. The mechanism for the formation of 4H-pyrimido [2,1-b]benzothiazole and 2-oxo-pyrimido[2,1-b]benzothiazole derivatives 15 was the same, except in the latter case, malonates with two properly placed leaving groups (two alkoxy groups) at sufficiently high temperature underwent decarboxylation to afford the final product (Scheme 6).

Simple aminoazoles parallel to benzo-fused aminoazoles have also been found to take part in the Biginelli reaction to generate azole-fused pyrimidine derivatives. However, although the obtained product is slightly less fused, it possesses equivalent biological features. Further among the non-fused aminoazoles, 5-aminotetrazole, 3-aminotriazole, and 2-aminothiazole...
are widely employed in MCRs for the synthesis of various heterocyclic derivatives upon reaction with 1,3-diketocompounds and aldehydes under different conditions. In this context, a catalyst- and solvent-free method was employed by V. L. Gein’s research group for the synthesis of tetrazolo-fused pyrimidines by heating a mixture of acetoacetic esters, 5-aminotetrazole and aromatic aldehydes at 130–170 °C until the evolution of bubbles of gaseous side product ceased. The yield of the products was found to be low in the case of electron-donor substituents in the aldehyde. Conversely, the character of substituents in the acetoacetic esters did not notably affect the yields. Haleel and coworkers developed a protocol for the synthesis of analogues of tetrazolopyrimidine derivatives in the presence of iodine under refluxing conditions. The synthesis was achieved by reacting ethyl acetoacetic esters, 5-aminotetrazole and heteroaryl aldehydes (2-pyridinecarboxaldehyde and 4-pyridinecarboxaldehyde) in isopropanol medium at 82–85 °C in the presence of 10 mol% of catalyst. The same three-component reaction was also established using catalysts such as [bmim][BF₄] as a green ionic liquid, nano-Fe₃O₄@SiO₂–NH-gallic acid and CH₃COOH/HCl, and N,N,N′,N′-tetrabromobenzene-1,3-disulfonamide (TBBDA). E. S. Filatova et al. utilized 3-oxobutanoate-containing polyethers as 1,3-diketocompounds in the reaction with benzaldehyde and 5-aminotetrazole involving polyphosphoric acid as the catalyst to carry out the synthesis of podands bearing two terminal tetrazolo[1,5-a]dihydropyrimidine groups along with byproducts such as podands containing one tetracyclotetrazolo[1,5-a]pyrimidine ring system and a free hydroxy group at the other terminus of the polymer chain. I. Batool and coworkers disclosed a novel multicomponent strategy that affords the synthesis of thiazolopyrimidines through the condensation reaction among 2-aminothiazole, ethylacetoacetate and differently substituted aromatic aldehydes. The reaction, which was catalyzed by sulfamic acid in ethanol under reflux conditions, was established to find potent antidiabetic and antibacterial drugs. Moreover, some reported methods demonstrated their versatility by using both amino azole and its benzo analogues as AAH for the synthesis of the corresponding pyrimidine scaffolds under the same reaction conditions. For example, the thiamine hydrochloride (VB₁) catalyzed synthesis of benzo[4,5]imidazo[1,2-a]pyrimidine and [1,2,4]triazolo[1,5-a]pyrimidine derivatives was developed by heating a reaction mixture containing 2-aminobenzimidazole/3-amino-1,2,4-triazole and ethyl acetoacetate/acetyl acetone in water under refluxing conditions. VB₁ is a nonflammable, inexpensive and non-toxic reagent, which is comprised of a pyrimidine ring and a thiazole ring linked by a methylene bridge. Target compounds were obtained in high yields (80–96%) in 3–6 min with the employment of...
merely 5 mol% of the catalyst. A plausible mechanism illustrating the reaction pathway is summarized in Scheme 11. After the initial formation of benzylidene-type intermediate 28 from the VB$_1$-catalyzed Knoevenagel condensation of dicarbonyl compound 24 and aldehyde 4, a nucleophilic attack from amino azoles 3a and 25 occurs in Michael-type addition manner, followed by intramolecular cyclisation, yielding the desired pyrimidines 26 and 27 after dehydration.

W. Fan et al. utilized 5-hydroxymethylfurfural (HMF) 28 in the multi-component Biginelli reaction with 2-aminobenzimidazole/aminotriazole 3a and 16 and ethyl acetoacetate 5 together with the catalyst ZnCl$_2$ at 80 °C, which led to the generation of dihydropyrimidinones 29 and 30 in moderate to good yields (Scheme 12). The advantage of using HMF lies in the CH$_2$OH motif, which can be functionalized further to the desired target molecules.

I. G. Tkachenko et al. reported a three-component synthesis for the regioselective formation of 4,7-dihydro[1,2,4]-triazolo and 4,7-dihydro[1,2,3]triazolo[1,5-a]pyrimidines 33 involving a reaction between 3-amino-1H-1,2,4-triazole/5-amino-2H-1,2,3-triazole derivatives 31, acetaldehyde 32 and acetylacetone/β-keto esters 12 in water under microwave irradiation. Using ethyl 4,4,4-trifluoro-3-oxobutanoate as the 1,3-dicarbonyl compound under the same reaction conditions, the corresponding 5-hydroxy-4,5,6,7-tetrahydro derivatives 34 were obtained, which failed to dehydrate at the reaction temperature (Scheme 13).

The simplest aldehyde, formaldehyde (in the form of paraformaldehyde) was also effectively incorporated into the structure of azole-fused pyrimidine derivatives. Specifically, S. A. Komykhov et al. reported a method for the preparation of 8 unsubstituted 4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines 36, which presumed the three-component reaction of 3-amino-1,2,4-triazole 25 with paraformaldehyde 35 and different 1,3-dicarbonyl compounds 12 (Scheme 14). This method is highly environment-friendly as no catalyst and organic solvent are required. Comparable yields of the target compounds were isolated by refluxing the starting components in hot water under either conventional heating or microwave irradiation.

In the synthesis of triazole/tetrazole-fused pyrimidine derivatives through the involvement of N-aryl/alkyl acetoacetamides as one component acting as a β-keto compound, Gein et al. made a significant contribution. In this context, a three-component reaction mixture containing N-alkylamides of acetoacetic acid such as N-methyl- or N,N-diethyl-3-oxobutanamide 37, aromatic aldehydes 4 and 5-aminotetrazole 16a was condensed to afford the corresponding N-substituted 7-aryl-5-methyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamides 38. Based on a similar method, the same group also reported the condensation of 3-amino-1,2,4-triazole 25 with N-aryl/alkylamides of acetoacetic acid 37 and aromatic aldehyde 4, which resulted in N$_7$-diaryl-5-methyl-4,7-dihydro-1,2,4-triazolo[1,5-a] pyrimidine-6-carboxamides 39. In both cases, a solventless mixture of starting materials was heated at high temperature.
Scheme 21  Synthesis of 7-(4-nitrophenyl)[1,2,4]triazolo[1,5-a]pyrimidine 69 and 5-alkyl-6-(1-piperidinylsulfonyl)-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine 70 derivatives.

Scheme 22  Synthesis of pyrazolo[1,5-a]pyrimidines 72, 73 and 74 tethered with a sulfone moiety.

Scheme 23  Microwave-assisted synthesis of azole-fused pyrimidine derivatives 78, 79 and 80.
(120–150 °C) for a few minutes, resulting in the synthesis of tetrazolo and triazolopyrimidine rings in high yields, and the formation of product was indicated by the solidification of the mixture together with no further evolution of water vapor (Scheme 15).

Several other synthetic strategies have also been reported, where triazolopyrimidine derivatives were prepared using N-aryllamides of β-keto acid as the active methylene compound. For example, R. Pada et al. reported a simple method involving heating a DMF solution containing 5-amino-1,2,4-triazole 25, N-aryl acetoacetamides 40 and 4-(phenoxymethyl)benzaldehyde 41 for 15 min under conventional and microwave heating conditions, which afforded the corresponding triazole-fused pyrimidines 42 in 55–78% yield. The same approach in the same year was developed by M. Borisagar’s group with thiophene-2-carbaldehyde 43 as the aldehydic component, and the reaction of the starting materials was carried out under microwave heating. Another similar method under conventional heating of the starting components involving 4-(2,4-dinitrophenoxy)benzaldehyde 45 as the specific aldehyde, 5-amino-1,2,4-triazole 25 and N-aryl substituted acetoacetamides 40 was demonstrated by P. D. Fadadu et al. in DMF solvent. Following these results, Kavadia and coworkers explored 2-bromopyridine-4-carbaldehyde 47 as an aldehydic component in an analogous methodology. The approach utilized conventional heating conditions for a DMF solution of the three starting reagents to construct the corresponding pyrimidine ring 48. A comparatively longer reaction time (2–4 h) was needed in this strategy to obtain yields in the range of 74–94% (Scheme 16).

J. D. Bhatt and coworkers also contributed to this field by synthesizing pyrazole-linked triazolopyrimidines 51 using two different methods. In the catalyst-free method, the Biginelli-type reaction involving starting materials 25, 49 and 50 was heated conventionally at high temperature (155 °C) in DMF solvent (Scheme 17, Method A). In the other method, the same reaction was performed by heating the starting materials in the presence of triethylammonium acetate (TEAA) under microwave irradiation at 350 W (Scheme 17, Method B). The catalytic efficiency of TEAA was also studied by recovering the catalyst from previous runs up to five successive reaction cycles, which showed that there was a notable decrease in the efficiency of the catalyst only after four successive cycles.

The sugar-catalysed solvent-free one-pot synthesis of [1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide derivatives 53 was accomplished by B. Adrom and co-workers. In this method, a mixture of 3-amino-1,2,4-triazole 25, 4-arydehyde 4 and aceetoacetylactide 52 was heated with maltose as the acidic catalyst at 80 °C under solvent-free conditions (Scheme 18). The reaction was proposed to proceed through the usual pathway, in which the in situ formation of intermediate 54 from acetoacetamide 52 and activated aldehyde 4 occurred followed by nucleophilic attack of 3-amino-1,2,4-triazole 25 in the presence of the catalyst. The resulting species 55 upon cyclisation afforded the desired product.

Owing to the pharmacological properties associated with the numerous derivatives of azole-fused pyrimidines, an extended Biginelli reaction was reported, wherein N-alkyl acetoamide 40 was generated in situ by the reaction of amines 58 with compounds such as diketene 56, and 2,2,6-trimethyl-4H-1,3-

| X    | Y    | Reaction conditions | Time (min) | Yield (%) | No. of examples | Reference |
|------|------|---------------------|------------|-----------|-----------------|-----------|
| NH   | CH   | NH2SO3.H (5 mol%)  | 15-60      | 69-96     | 6                | 9                     |
| NH   | CH   | Li (10 mol%),      | 10-15      | 81-97     | 5                | 14                    |
| NH   | CH   | Silica gel, MW, 120 | 3-6        | 90-95     | 8                | 6                     |
| NH   | CH   | H2SO4.Si (10 mol%) | 20         | 90-95     | 6                | 14                    |
| NH   | CH   | SBA-Pr SO3H,       | 5-15       | 85-96     | 4                | 6                     |
| NH   | CH   | AcOH, 60 °C        | 10-35      | 86-99     | 8                | 10                    |
| NH   | CH   | CNH3, CSMe         | 5-60       | 69-96     | 18               | 18                    |
| NH   | CH   | n-Wo.SO3H, 100 °C  | 12-20      | 90-95     | 10               | 7                     |
| NH   | CH   | Fe(OI)2( Citrate)  | 1.5-4 h    | 79-95     | 10               | 7                     |
| NH   | CH   | DES (KCI Glycerin) | 20-30      | 32-91     | 16               | 7                     |
| NH   | CH   | MnPyrSO3H (10 mol%)| 4-7        | 86-91     | 11               | 78                    |
| NH   | CH   | MnMnSO3H (10 mol%) | 3-5        | 90-97     | 10               | 76                    |
| NH   | CH   | m-Pr SO3H, MW, 100 °C| 15-30    | 82-90     | 10               | 79                    |
| NH   | CH   | RHA (pmm) HSO, 100 °C| 2-5       | 87-93     | 9                | 80                    |
| -    | CH   | CPh                | 30         | 85-90     | 4                | 81                    |
| -    | CH   | No-Np (10 mol%)    | 10         | 85-98     | 8                | 82                    |
| -    | CH   | CN (150 mol%), MW 150 W, 70 °C | 3 | 90-93 | 15 | 83 |
| -    | CH   | MW 150 W, 45 °C    | 1          | 85-94     | 15               | 84                    |
| -    | CH   | Hydroxymelit (Mg- | 40-60      | 80-89     | 2                | 85                    |
| -    | CH   | Chloroan, AcOH     | 60-100     | 81-95     | 5                | 86                    |
| -    | CH   | Naphthene (m-PhSO), | 7-30       | 85-95     | 19               | 87                    |
| -    | CH   | 3exo, EOB, 85 °C   | 35-60      | 78-94     | 7                | 88                    |
| -    | CH   | γ-Fe2O3 (10%)      | 20-50      | 87-94     | 15               | 89                    |
| -    | N    | Catalysed and solvent-free, 160-170 °C | 5-10 | 31-68 | 7 | 90 |
dioxin-4-one 57. For instance, Zeng et al. presented a four-component tandem procedure to prepare a series of dihydrotetrazolopyrimidinyl carbamides 60. N-alkyl acetoamide 40 was generated by stirring a solution containing amines 58 and diketen 56 in ethyl acetate at room temperature for 2 h. Subsequently, the temperature was increased to 78 °C and 5-aminotetrazole 16 and aldehyde 4 were added together with iodine (30 mol%). It was observed that aryl amine did not work given that combining aniline with diketen did not afford the corresponding product even after 24 h. A similar and greener approach was introduced by A. Shaabani et al., in which 2,2,6-trimethyl-4H-1,3-dioxin-4-one 56 was combined with different alkyl amines 58 at 150 °C for the in situ generation of N-alkyl acetoamide 40. The intermediate was then allowed to participate in the MCR with various aldehyde 4 and 3-amino-1,2,4-triazole 16 in the presence of a catalytic amount of p-toluene-sulfonic acid (PTSA) in water for the synthesis of [1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide derivatives 59 (Scheme 19). The synthesis of tetrazolo-fused pyrimidines utilizing pyruvic acid derivatives as the 1,3-dicarbonyl compound was accomplished by V. L. Gein et al. through multicomponent heterocyclisation reactions. In a catalyst-free and solvent-free approach, they performed a three-component condensation reaction between various pyruvic acid derivatives 61 and 63 with 5-aminotetrazole 16a and aromatic aldehydes 4 at 130–150 °C. The corresponding products were obtained in 62–85% yield after 30 min when the evolution of gas ceased and mixture was solidified. The same authors also described a condensation protocol in which diethyl 2-oxobutenedioate sodium salt was in situ converted into diethyl 2-oxobutenedioate 61, which was reacted with aromatic aldehydes 4 and tetrazol-5-amine 16a in acetic acid under reflux conditions for 2 h. Subsequently, the mixture was then kept at room temperature for 24 h and the corresponding diethyl 6-aryl-3,6-dihydrotetrazolo[1,5-a]pyrimidine-4,5-dicarboxylates 62 and 64s were filtered as solid precipitates (Scheme 20). These condensations were assumed to proceed through the initial Knoevenagel condensation.
reaction of aldehydes and pyruvic acid derivatives, and then the as-formed unsaturated intermediate experiences nucleophilic attack from the tetrazolo amine followed by intramolecular cyclisation and dehydration. Moreover, the data before 2015 concerning the application of pyruvic acid in multicomponent heterocyclisation with aminoazoles was compiled and presented in the form of a review titled “Heterocyclization reactions of pyruvic acids and aminoazoles with controlled chemoselectivity” by Y. I. Sakhno et al.65

New pyrimidine nuclei containing scaffolds with increased biological application are the basic demands for the development of new strategies. In this context, sulfonamide-linked pyrimidine derivatives possessing exciting biological properties were prepared by M. A. Kolosov et al. through a three-component condensation protocol. 5-Alkyl-6-(1-piperidinylsulfonfonyl)-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine derivatives 68 were obtained when a mixture containing β-sulfonanamide ketone, aromatic aldehydes 4, and 3-amino-1,2,4-triazole 27 was refluxed in DMF for 3 h (Scheme 21).64 The starting material, 1-(1-piperidinylsulfonyl)acetones 65, was synthesized sequentially from 1-(methylsulfonyl)piperidine undergoing metalation with n-butyllithium, reaction with aliphatic aldehydes, and oxidation of the obtained sulfoalcohols. The interesting feature of the present method is the formation of a different type of heteroaromatic derivative, i.e., 7-(4-nitrophenyl)[1,2,4]triazolo[1,5-a]pyrimidine 68, if 4-nitrobenzaldehyde 66 is employed as the aromatic aldehyde. This heteroaromatization is generally characteristic to 4-nitro derivatives of dicycloazolooazides, and in this case, 4-nitrobenzaldehyde 66 triggered the elimination of the sulfonamide moiety.

Next, the utility of β-ketosulfones as molecular scaffolds for the synthesis of pyrazolo[1,5-a]pyrimidine was described by M. R. Shaabana et al. with the development of one-pot three-component procedures, wherein the reaction between 1-aryl-2-(phenylsulfonyl)ethanone derivatives 69, 3-amino-1,2,4-triazole/2-aminobenzimidazole (3a, 28 and 71) and triethyl orthoformate 70 was carried out at refluxing temperature for 4 h in the presence of piperidine (Scheme 22). Here, triethyl orthoformate seems to act as a methylene-furnishing agent to form the ring structure of the products. The corresponding products 7-aryl-6-(phenylsulfonyl)[1,2,4]triazolo[1,5-a]pyrimidines 72 and 2-aryl-3-(phenylsulfonyl)pyrimidin(1,2-a)benzimidazoles 73 were obtained in 80–83% yield and evaluated for Aurora-A kinase inhibitor activity.65

Furthermore, S. M. Gomha and coworkers also demonstrated the similar utility and greater versatility of the complex β-ketosulfones, 1,5-dimethyl-2-phenyl-4-(2-phenylsulfonyl)acetyl)-1H-pyrazol-3(2H)-one 75. They performed a reaction between dimethylformamide dimethylacetal (DMF-DMA) 76, a methyne-furnishing reagent, various amino azoles (3a, 16a and 77) and β-ketosulfones under microwave irradiation at 150 °C for 12 min to synthesize severalazole-fused pyrimidine derivatives 78, 79 and 80 (Scheme 23).66

2.1.1.2 MCRs involving cyclic 1,3-dicarbonyl and analogous compounds. Cyclic 1,3-dicarbonyl compounds are immensely applied for the synthesis of highly fused pyrimidine systems in Biginelli-type condensation reactions. The pyrimidine nuclei generated as a result of the MCR between cyclic β-dicarbonyl compound, AAH and aldehydes/ketones are fused from both sides, which are known as quinazolinone derivatives. Therefore, MCRs involving cyclic β-dicarbonyl as active methylene compounds in the Biginelli reaction have become a highly explored area.

Furthermore, a number of methods have been reported where triazole and benzimidazolo quinazolinone rings are constructed with the same catalytic system, exhibiting their versatility. In 2010, the use of sulfamic acid as a green and reusable catalyst-based approach was developed by M. M. Heravi et al. for the efficient and convenient one-pot three-component condensation of 2-amino benzimidazole 3/3-amino-1,2,4-triazole 16 as amine sources with dimedone 81 and different aldehydes 4 to afford corresponding triazole/benzimidazoloquinazolinones 82 and 83.67 They also examined the same reaction using indandione instead of dimedone, but the reaction did not proceed beyond the Knoevenagel condensation of indandione and aldehyde. Other strategies to obtain these
quinazolinone systems with catalytic systems include the use of iodine,\(^6\) silica gel,\(^4\) silica-supported sulfuric acid,\(^7\) sulfonic acid-functionalized SBA-15 as a heterogeneous nanoporous solid acid catalyst,\(^8\) acetic acid (performing dual role of acid and solvent),\(^9\) and 1-butyl-3-methylimidazolium bromide ([bmim][Br]).\(^10\)

Nanomaterials supported sulfonic acid was employed by A. Amoozadeh and S. Rahmani as an efficient and recyclable catalyst for the synthesis of benzimidazolinoquinazolinone derivatives based on the three-component reaction between 2-amino-benzimidazole, 1,3-cyclohexandione derivatives and various aldehydes under solvent-free conditions. The products were isolated after 12–20 min in excellent yields.\(^11\) To date, various practical approaches have been developed, wherein the same starting materials are being reacted in the presence of catalysts such as Fe₃O₄@chitosan,\(^12\) Fe₃O₄@clay nanocomposite,\(^13\) choline chloride:glycerol as a deep eutectic solvent,\(^14\) 1-methyl-1-sulfonic acid pyrrolidinium chloride [MPyr(SO₃H)]Cl/4-methyl-4-sulfonic acid morpholinium chloride [MMor(SO₃H)]Cl,\(^15\) Brønsted acidic ionic liquid supported on rice husk ash (RHA-[pmim]HSO₄),\(^16\) montmorillonite KSF as a heterogeneous catalyst,\(^17\) nickel nanoparticles,\(^18\) CAN,\(^19\) microwave irradiation at 150 W,\(^20\) hydrothermal (Mg-Al-CO₃),\(^21\) chitosan,\(^22\) nanosheets AlPO₄(SO₃H),\(^23\) graphene oxide (GO),\(^24\) γ-Fe₂O₃@SiO₂@[bis-APTES]Cl₃ nanoparticles,\(^25\) and catalyst- and solvent-free conditions at 160–170 °C by various research groups. All these methods were proven to be highly efficient, giving the products in excellent yields in a shorter time (Scheme 24).

R. Ghorbani-Vagheia et al. reported the 7-aminonaphthalene-1,3-disulfonic acid-functionalized magnetic Fe₃O₄ nanoparticles (Fe₃O₄@SiO₂@Propyl-ANDSA)-catalyzed one-pot synthesis of tetrahydrotetrazolo[1,5-a]quinazolines/tetrahydrobenzo[h]tetrazolo[5,1-b]quinazolines \(^8\) and \(^8\) by the reaction of 5-aminotetrazole \(^6\) aromatic aldehydes \(^4\) and dimedone/6-methoxy-3,4-dihyronaphtalen-1(2H)-one (81 and 85) at \(100 °C\) in \(H_2O/ EtOH\) medium (Scheme 25).\(^26\)

A closely related structural analogue of dimedone, 2H-thiopyran-3,5(4H,6H)-dione \(^8\), was utilized by S. Shen’s group as 1,3-cyclicdicarbonyl compounds in their two successive

### Scheme 30

**Different methods to synthesize thiazolo[3,2-a]chromeno[4,3-d]pyrimidin-6(7H)-one derivatives**

| Reaction conditions | Time (h) | Yield (%) | No. of examples | Reference |
|---------------------|---------|-----------|-----------------|-----------|
| [Bmim]BF₄ (10 mol%), 100 °C | 2–3     | 85–91     | 27              | 96        |
| SLS (10 mol%), H₂O, RT | 3.5–5   | 81–95     | 15              | 97        |
| L-Proline (10 mol%), H₂O, 70 °C | 3–4     | 80–91     | 15              | 98        |

### Scheme 31

**Sulfamic acid-catalyzed synthesis of fused pyrimidine derivative.**
publications to synthesize a series of novel thiopyran-fused pyrimidine derivatives 88 and 89. In 2011, benzoimidazole and thiopyran-fused novel pyrimidine frameworks were constructed through the MCR between 2-aminobenzothiazole 3a, aryl aldehyde and 2H-thiopyran-3,5(4H,6H)-dione in glacial acetic acid at moderate temperature (50 °C). The reaction proceeded smoothly with aromatic aldehydes, bearing both electron-donating and electron-withdrawing groups, whereas the same reaction with aliphatic and heteroaromatic aldehydes did not afford the expected products. After the successful synthesis of these fused pyrimidine derivatives, they further explored 2H-thiopyran-3,5(4H,6H)-dione 87 in the synthesis of a novel series of tetrazolo[1,5-a]thiopyran[3,4-d]pyrimidine 88 derivatives by the reaction of 5-aminoazotetrazole 16, aryl aldehyde 4 and 2H-thiopyran-3,5(4H,6H)-dione 87 in the presence of PTSA at 30 °C (Scheme 26). Besides PTSA, other Brønsted acidic catalysts such as sulfamic acid, sulfuric acid, hydrochloric acid, and nitric acid and Lewis acidic catalysts such as ferric chloride, ferrous chloride and aluminium chloride were also utilized to optimize the reaction conditions.

Barbituric acid derivatives 90 were explored as cyclic 1,3-dicarbonyl compounds in the reaction with 3-amino-1H-1,2,4-triazoles 27 and aromatic aldehydes 4 by M. H. Abdollahi-Basir and coworkers. This zinc terephthalate metal–organic framework catalyzed one-pot, three-component reaction was conducted under ultrasonic irradiation and solvent-free conditions, affording pyrimido[4,5-d][1,2,4]triazolo[1,5-a]pyrimidinediones 91 with good to excellent yields (Scheme 27). The advantage of using the zinc terephthalate metal–organic framework catalyst is that it can be easily recovered after the reaction is over by simple filtration. The recovered catalyst was used in consecutive runs with no significant decrease in the product yield.

4-Hydroxycoumarine 92 and analogous compounds are interesting cases of 1,3-dicarbonyl-type compounds with which the scope of the Biginelli reaction has greatly been studied for the synthesis of extensively fused pyrimidine structures. Developments in this regard include V. N. Mahire and coworker’s environmentally benign protocol, which afforded chromene fused benzoimidazopyrimidinones 93 via the reaction of 4-hydroxycoumarin 92, aldehydes 4 and 2-
aminobenzimidazole 3a using silane@TiO2 nanoparticles 95 as a heterogeneous catalyst under reflux conditions in ethanol (Scheme 28). The mechanism proposed to explain this conversion starts with the usual Knoevenagel condensation between 4-hydroxycoumarin 92 and benzaldehyde 4 to form a Schiff base as intermediate 94 and it is assumed that silane@TiO2 nanoparticles 95 activate the carbonyl carbon of the aldehyde through hydrogen bonding. Next, 2-aminobenzimidazole 3a reacts with the intermediate 94 through Michael addition followed by cyclization and dehydration to give the desired products (Scheme 29).

A combination of substituted 2-benzothiazole 96 and 4-hydroxycoumarine 97 with different aldehydes 4 was employed by A. V. S. Reddy and Y. T. Jeong to present a versatile one-pot multicomponent approach for the preparation of substituted fused chromenopyrimidine rings 98. In this approach, a mixture of the above-mentioned reactants was condensed in the presence of an ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate. The optimization of the reaction conditions

| Scheme 34 | Solvent-free approaches for the synthesis of 6-aryl-substituted triazoloquinazolindiones. |
|-----------|------------------------------------------------------------------------------------------|

| Scheme 35 | Mechanism proposed by L. Wu et al. to explain the synthesis of substituted triazoloquinazolindiones. |
|-----------|---------------------------------------------------------------------------------------------------|

| Scheme 36 | Synthesis of novel benzothiazole/thiadiazole fused quinazoline-5,14-dione derivatives 109 and 110 under different reaction conditions. |
|-----------|----------------------------------------------------------------------------------------------------------------------------------|

| Scheme 37 | Synthesis of 7-aryl-benzo[n]tetrazolo[5,1-b]quinazoline-5,6-diones 111 under heterogenous catalysis. |
|-----------|---------------------------------------------------------------------------------------------------|
over the reaction mixture of 4-hydroxycoumarin, 4-ethoxybenzaldehyde and 2-aminobenzothiazole under solvent-free conditions revealed that the best result in terms of reaction time and product yield was achieved with 10 mol% of ionic liquid at 100°C. The authors also showed that the ionic liquid can be reused and recycled for at least five consecutive runs without the loss in activity. Conversely, P. K. Sahu catalyzed a one-pot reaction containing an aqueous mixture of the same three components using a surfactant, sodium lauryl sulphate (SLS), at room temperature. The study of the influence of the sodium lauryl sulphate (SLS) micelles and their different concentrations on reactivity showed that the best yield was obtained with 10 mol% catalyst loading in the least time compared to the other surfactants and catalysts. P. K. Sahu et al. developed a mild and efficient variant of the above-mentioned protocol, wherein the reaction involving the same three-components was catalyzed by the L-proline in water. A brief summary regarding the reaction conditions, reaction time, range of the product yields, etc. is given in Scheme 30.

An interesting strategy in which the ester linkage of 4-hydroxycoumarine is opened upon the sulfamic acid-catalyzed reaction of 4-hydroxycoumarin, aromatic aldehydes and 3-amino-1H-1,2,4-triazole was reported by M. M. Heravi and coworkers. The resulting compound is the simple triazolopyrimidinone derivatives. When the authors performed this one-pot three-component reaction with 2-aminobenzimidazole, an usual chromene-fused benzimidazolopyrimidinone was obtained (Scheme 31). Based on the proposed mechanism, the lactone carbonyl group of intermediate, which is formed as a result form the combination of 4-hydroxycoumarin and aldehyde, is prone to attack by the nucleophilic nitrogen of 3-amino-1H-1,2,4-triazole or 2-aminobenzimidazole. 4-Hydroxy-1-phenylquinolin-2(1H)-one, a structural variant of 4-hydroxycoumarine, was used in the Biginelli reaction together with aryl aldehydes and aminotriazole/aminobenzimidazole by Mourad et al. under the classical and microwave heating. Around 7–21 h was required to complete the reaction when a DMF solution of all the starting materials was allowed to stir under classical heating, whereas microwave heating triggered the same reaction to completion within 5 min (Scheme 33). Besides the advantageous reduction in reaction time in the latter case, the yields of products were also observed to be greatly enhanced to an excellent level.

Naphthoquinones, which possess a cyclic β-keto structural unit, constitute a major class of naturally occurring compounds with potential medicinal properties. L. Wu et al. employed this precursor in the MCR synthesis of various structurally diverse quinazolinedione derivatives under different catalytic systems. The three-component coupling of aldehyde, 2-hydroxy-1,4-naphthoquinone and 3-amino-1,2,4-triazole was achieved in the presence of sulfamic acid under solvent-free conditions to produce a novel series of 6-aryl substituted triazoloquinazolindione derivatives in good yields and high regioselectivity. In another paper published in the same year, they demonstrated nano n-propylsulfonated γ-Al2O3 as an efficient and reusable catalyst to promote the same conversion. Both solvent-free approaches provided excellent yields of the

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**Scheme 38** Microwave-assisted synthesis of 13-aryl-13H-benzo[2,3-b]quinazoline-5,14-diones.

**Scheme 39** Solvent-free synthesis of a novel series of tanshinone I derivatives having an azacyclo ring.

**Scheme 40** Synthesis of pyrazolo[3,4-b][1,8]naphthyridine and pyrazolo[3,4-d]pyrimido[1,2-a]pyrimidine derivatives and.
products within 1–2 h of heating (Scheme 34). The common mechanism based on the proposed synthetic route is shown in Scheme 35, which follows the sequence of Knoevenagel reaction, Michael addition reaction, intramolecular cyclisation and dehydration in the presence of catalyst to afford compound 107, which is prone to undergo aerial oxidation to give the target compound.

After getting successful results from previous reports, the same authors employed other amino azoles as precursors under modified reaction conditions. A one-pot three-component reaction involving 2-aminobenzothiazole 3b, aromatic aldehydes 4 and 2-hydroxy-1,4-naphthoquinone 105 in the presence of Amberlyst-15 was accomplished under solvent-free conditions to afford the synthesis of novel 13-aryl-13\(H\)-benzo[g]benzothiazolo[2,3-b]quinazoline-5,14-diones 110. They also synthesized a series of novel substituted 5\(H\)-benzo[i][1,3,4]thiadiazolo[3,2-a]quinazoline-6,7-diones 110 in very good yields through the one-pot condensation of 5-substituted-2-amino-1,3,4-thiadiazole 108 with 2-hydroxy-1,4-naphthoquinone 105 and aldehydes 4 in DMF at 130 °C (Scheme 36).

A. Maleki et al. employed a Brønsted acid-functionalized magnetic polymeric nanocomposite, Ba\(_{0.5}\)Sr\(_{0.5}\)Fe\(_{12}\)O\(_{19}\)@PU-SO\(_3\)H, for the synthesis of 7-aryl-benzo[h]tetrazolo[5,1-b]quinazoline-5,6-diones 111 in a deep eutectic solvent (DES) based on choline chloride and urea (Scheme 37). The catalyst was readily recovered from the reaction mixture with the help of an external magnet and could be reused 6 times without significant loss in activity.

C.-T. Ma et al. identified an oxalic acid and proline-based deep eutectic solvent (DES) as an effective catalyst and environmentally benign reaction medium for the one-pot synthesis of 13-aryl-13\(H\)-benzo[g]benzothiazolo[2,3-b]quinazoline-5,14-diones 112 via the microwave-assisted three-component reaction between aromatic aldehydes 4, 2-aminobenzothiazole 3b and 2-hydroxy-1,4-naphthoquinone 105 (Scheme 38).

Furthermore, a slightly modified form of naphthoquinone, 3-hydroxy-8-methyl-1,4-phenanthrenequinone 113, was utilized by L. Wu and X. Yang in a three-component coupling reaction with 3-amino-1,2,4-triazole 27 and aldehydes 4. The reaction was carried out in the presence of a catalytic amount of p-TsOH under solvent-free conditions to produce a novel series of tan shinone I derivatives 114 having an azacyclo ring with good yields and high regioselectivity (Scheme 39).

P. T. Patil et al. reported the synthesis of novel pyrazolo[3,4-b][1,8]naphthyridine 118 and pyrazolo[3,4-d]pyrimido[1,2-a]

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### Table: Reaction conditions

| Reaction conditions       | Time    | Yield (%) | No. of examples | Reference |
|---------------------------|---------|-----------|-----------------|-----------|
| EtOH-AcOH, MW, 150 °C     | 5 min.  | 41–78     | 18              | 109       |
| H\(_2\)O, MW, 120 °C      |         | 38–72     | 15              |           |
| H\(_2\)O-AcOH, MW, 120 °C |         | 37–80     | 13              |           |
| TEA/AcOH(1:2), H\(_2\)O, 50 °C | 2–3 h | 82–90     | 12              | 110       |
| MW, EtOH/AcOH, 80 °C      | 10–15 min. | 70–91   | 19              | 111       |

Scheme 41 Different approaches for the synthesis of imidazo[1,2-a]azine derivatives.
pyrimidine 119 derivatives through an efficient one-pot method. In this method, the reactions between 2-aminopyrimidine/2-aminopyridine 116 and 117, aromatic aldehydes 4 and 3-methyl-1-phenyl-2-pyrazolin-5-one 115 were performed in the presence of 15 mol% phosphorus oxide under refluxing ethanol (Scheme 40). The authors also studied the structure–activity relationship, which showed that the anti-inflammatory activity of product 118 is much better than that of product 119.

A variation to this reaction was investigated by V. A. Peshkov et al., wherein 2-ketoaldehyde is the main component to introduce the deviation in the synthesized product by the involvement of both carbonyl groups, thus providing a novel class of imidazoazine derivatives 3b, 124 and 125. Three different reaction conditions were used to study the scope of the process, where 2-aminooazines 120, 2-oxoaldehydes 121 and cyclic 1,3-dicarbonyl compounds 122 were taken in a combination of two solvents and heated at high temperature under microwave irradiation for 5 min, resulting in the generation of a small library of title compounds and highlighting the possibility of a case-specific approach. The same reactions were also performed in the presence of TEA/AcOH (1:2) by N. Etivand et al. and EtOH/AcOH under microwave irradiation by J. Wang and coworkers (Scheme 41).

K. Meena et al. developed the catalyst-free synthesis of benzo[d]imidazo[2,1-b]thiazoles 131, wherein 2-aminobenzothiazole derivatives 3a and d medoned 81 were combined with arylglyoxal 130 instead of aromatic aldehydes at 80 °C in glycerol. The same starting materials were also ground at room temperature in glycerol. All the reactions were completed in ~30 min (Scheme 42).

A lemon juice-mediated ecofriendly one-pot three-component approach for the synthesis of diverse pharmaceutically important tricyclic fused imidazoles 134 tethered with aryl and various cyclic 1,3-dicarbonyls was developed by A. Saha and coworkers. This metal-free strategy involved reactions between arylglyoxals 132 and N-alkyl-4-hydroxyquinolone/4-hydroxy coumarin 133 with 2-aminobenzothiazoles/2-aminobenzimidazoles 3 using lemon juice as a natural acid catalyst under refluxing temperature giving the products in good to excellent yields (Scheme 43).

Scheme 42  Synthesis of benzo[d]imidazo[2,1-b]thiazole derivatives 131 via ecofriendly methods.

Scheme 43  Lemon juice-mediated synthesis of tricyclic fused imidazoles 134.

Scheme 44  Synthesis of novel benzo[g]thiazolo[2,3-b]quinazolin-4-ium hydroxide derivatives.
A. Nouri et al. developed a novel approach for the synthesis of benzo[g]thiazolo[2,3-b]quinazolin-4-ium hydroxide derivatives 135 using aryl glyoxal monohydrates 132 instead of aldehyde in a triethylamine and p-toluenesulfonic acid system-catalyzed one-pot, three-component reaction with 2-hydroxy-1,4-naphthoquinone 105 and 2-aminothiazole/2-aminobenzothiazole 3b under H₂O/acetone (2:1) at room temperature (Scheme 44). Instead of using arylglyoxals directly, A. Jana et al. utilized aryl acetylenes and aryl methyl ketones for the in situ generation of arylglyoxals and developed a metal-free I₂/DMSO-based oxidation–cyclization protocol for the synthesis of medicinally important structures having 2-arylbenzo[d]imidazo[2,1-b]thiazoles linked with a barbituric acid moiety. These three-component reactions were performed between 2-aminobenzothiazole derivatives 3b, barbituric acid derivatives 136 and aryl acetylenes/aryl methyl ketones 137 and 138 at 110 °C under microwave heating. Mechanistically, aryl acetylenes 137 and aryl methyl ketones 138 under the reaction conditions generate arylglyoxals, which are then reacted with 2-aminobenzothiazole derivatives and barbituric acid derivatives. Consequently, a series of benzothiazole-fused imidazoles 139 and 140 was prepared in good yield (Scheme 45).

When aldehydes are replaced by ketones such as isatin, acenaphthoquinone and related compounds in three-component reactions were performed between 2-aminothiazole derivatives 3b, barbituric acid derivatives 136 and aryl acetylenes/aryl methyl ketones 137 and 138 at 110 °C under microwave heating. Mechanistically, aryl acetylenes 137 and aryl methyl ketones 138 under the reaction conditions generate arylglyoxals, which are then reacted with 2-aminobenzothiazole derivatives and barbituric acid derivatives. Consequently, a series of benzothiazole-fused imidazoles 139 and 140 was prepared in good yield (Scheme 45).
component Biginelli-like condensation reactions, a pyrimidine scaffold with spiro linkage results in 143. This was exemplified by Y. Dai et al. through an efficient one-pot strategy, where isatin 142 was mixed with 5-aminotetrazole 16 and dimedone 81 in the presence of a super acid catalyst ([MeC(OH)2]+ClO4−) in an aqueous medium.116 The spiro-tetrazoloquinazolinones 144 were also synthesized by M. Shen’s group, wherein the same combination of reactants was treated in PEG-H2O medium together with PTSA as the catalyst.117 Both procedures were conducted under refluxing temperature (80 °C) and exhibit a great level of tolerance for isatin (Scheme 46).

In the first step of the mechanistic route described by Y. Dai et al., the condensation of isatin and dimedone was proposed to give intermediate 145, which is then attacked by 5-aminotetrazole to provide intermediate 146. This intermediate 147 in the study by M. Shen et al. was achieved through addition of isatin to the condensed intermediate 147 formed from 5-aminotetrazole and dimedone. The final product is obtained from the intramolecular condensation and cyclisation of the intermediate 146 with the loss of a water molecule (Scheme 47).

P. Maloo’s group reported a straightforward novel multi-component route to access spiro-benzimidazoquinazolinones 150, 151 and 152.118 It involves a one-pot three-component reaction of acenaphthoquinone/isatin 148 and 142, 1,3-diketone 81 and 2-aminobenzimidazole 3a in ethanol at 160 °C using 180 W power microwave irradiation. An attractive feature of this method is the utilization of 1,3-indanedione 149 as an active methylene compound for the construction of the corresponding fused spiropyrimidine ring 151 in 72% yield under mild and operationally simple conditions (Scheme 48). The computational study provided insight into the mechanistic aspects of the reaction. The mechanism proposed by the authors to explain this reaction is based on two paths, A and B. In path A, the Knoevenagel condensation of dimedone and
isatin generates intermediate 153, which undergoes reaction with 2-aminobenzimidazole 3a in two possible ways via the Knoevenagel-Michael-imine route (path A1) or Knoevenagel-imine-Michael route (path A2). In path B, enamine 154 is generated through dimeredone 81 and 2-aminobenzimidazole, which upon condensation with isatin in the Knoevenagel fashion, generates intermediate 155, followed by intramolecular Michael addition to furnish the final spiro product (Scheme 49).

Next, sulfamic acid-catalysed spiro analogue derivatives with fused heterosystems were prepared by A. K. Arya and M. Kumar using isatin instead of aldehyde via a three-component domino reaction. This method involves heating a reaction mixture containing isatin 142, various cyclic 1,3-diketones 122 and 2-aminobenzimidazole 3b in aqueous medium in the presence of 10 mol% sulfamic acid at 80 °C for 12-55 min to afford the corresponding spiroheterocycles 157 (Scheme 50). 119

A similar strategy utilizing 1H-indazole-3-amine 158 instead of 2-aminobenzothiazole 3b in a one-pot three-component condensation with 4-hydroxy-2H-chromen-2-one 92 and isatin 142 was developed by A. M. Jadhav et al. in the presence of acetic acid in EtOH for the rapid synthesis of novel spiro[chromeno[40,30:4,5] pyrimido[1,2-b]indazole-7,30-indoline]-20,6(9 H)-dione derivatives 159 (Scheme 51). 120

A series of novel spirooxindole-O-naphthoquinone-tetrazolo[1,5-a]pyrimidine hybrids 160 was synthesized and evaluated as potent antitumor agents by L. Wu and coworkers. The synthesis of these ternary hybrid molecules was carried out through the condensation reaction between 2-hydroxy-1,4-naphthoquinone 105, isatin 142 and 5-aminotetrazole 16 in the presence of acetic acid under reflux conditions (Scheme 52). 121

Y. K. Tailor et al. Presented an efficient and environmentally benign domino protocol for the synthesis of structurally diverse...
spiroheterocycles 164, 165 and 166 spiroannulated with 1,3,4-thiadiazolo[3,2-a]pyrimidine, involving the three-component reaction of 2-amino-1,3,4-thiadiazole 161, isatin 142/N-methyl-4-piperidone 163/1,2-acenaphthylenedione 148 and carbonyl compounds 162 catalyzed by magnetically recoverable and reusable nanocrystalline sulfated zirconia (Fe₃O₄@ZrO₂/SO₄²⁻) under solvent-free conditions with grinding at room temperature (Scheme 53). K. Verma et al. developed a domino protocol to construct spiroannulated pyrimidophenazines 174, 175 and 176. The synthesis of these hybrid molecules with advantageous heterocyclic substructures involves the four-component reaction of 2-hydroxynaphthalene-1,4-dione 105, benzene-1,2-diamine 171, cyclic ketones (163, 173 and 148) and 2-aminoazines 172 in the presence of erbium-doped TiO₂ NPs as a recyclable and reusable
Scheme 55  Three-component synthesis of 7-unsubstituted 4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines 177 and 178.

| X   | Reaction conditions                        | Time   | Yield (%) | No. of examples | Reference |
|-----|-------------------------------------------|--------|-----------|-----------------|-----------|
|    |                                           |        | 180       | 181             |           |
| S  | TBAHS (30 mol%), Ethylene glycol, 120 °C   | 1–2 h  | 68–       | 8               | 2         | 126 |
| S  | FeF₃ (10 mol%), 100 °C                    | 0.5 h  | 70–97     | 8               | 18        | 127 |
| S  | C/TiO₂-SO₃-SbCl₂ (0.1 g), 90 °C          | 1–3 h  | 85–93     | 13              | 5         | 128 |
| S  | Hydrotalcite (Mg-Al-CO₃), 70 °C         | 40–60 min | 65–89 | 8               | 2         | 85  |
| S  | Chitosan, AcOH, 60-65 °C                | 60–100 min | 74–92 | 8               | 2         | 86  |
| NH | Nano-Fe₃O₄@SiO₂@SO₃, 60 °C              | 1.5–3 h | 83–96     | 15              | 2         | 45  |
| S, NH | Graphite oxide, solvent free, 60 °C | 20–45 min | 83–96     | 14              | 6         | 129 |

Scheme 56  Some reported methods for the synthesis of substituted benzothiazole/thiazole fused pyrimidines.
heterogeneous acid catalyst under refluxing ethanol (Scheme 54). The doping of TiO$_2$ with erbium was found to enhance the catalytic efficiency of TiO$_2$, facilitating the reaction to provide the products with comparatively better yields.

Formaldehyde equivalents, dimethoxy $N,N$-dimethylmethaneamine (DMF-DMA), provide less substituted fused quinazolinone rings, as shown in the approach developed by C.-B. Zhang and coworkers. In their reactions, cyclohexane-1,3-

| X  | Reaction conditions                     | Time (min) | Yield (%) | No. of examples | Reference |
|----|----------------------------------------|------------|-----------|-----------------|-----------|
| CH | [Bmim]BF$_4$ (15 mol%), Grinding, rt  | 10–20      | 71–92     | 9               | 16        | 130 |
| N  | TFA:DIPEA (1:1), MW 90 °C              | 15–42      | 60–98     | 12              | 3         | 131 |
| CH | Nafion-H, PEG-400, 50 °C              | 30–50      | 85–94     | 17              | 16        | 132 |
| N  | PEG-400, MW 110 °C                    | 15–30      | 92–98     | 16              | 10        | 133 |
| CH | $(\gamma$-Fe$_2$O$_3$@Ph-PMO-NaHSO$_4$) 100 °C | 10–40     | 85–96     | 3               | 19        | 134 |

Scheme 57 Proposed reaction pathway to explain the synthesis of benzothiazolopyrimidines.

Scheme 58 Some reported methods for the synthesis of tetrazolo/triazolo fused pyrimidines.
dione 81 and DMF-DMA 76 were mixed and heated at 60 °C. After the mixture was completely homogenized, 3-amino-1,2,4-triazole 25 was added and then the reaction temperature was increased to 105 °C. After a few minutes, the solidified mixture was cooled and diluted with propan-2-ol to obtain the final product 178 with 91% yield. The utilization of DMF-DMA as an aldehydic component in the three-component reaction with aminotriazole and dimedone was also illustrated by A. A. Petrov and A. N. Kasatochkin. The reaction, which was performed in xylene under reflux, was shown to proceed via the generation of enamino ketone 179 and the corresponding pyrimidine ring was formed regioselectively by examining the mixture with high-resolution mass spectrometry (Scheme 55).

2.1.1.3 MCRs involving both cyclic and non-cyclic 1,3-dicarbonyl and analogous compounds. A significant number of methods are also available utilizing both cyclic 81 and non-cyclic 1,3-diketones 12 for the synthesis of pyrimidine moieties catalyzed by numerous catalytic systems. L. Nagarapu et al. developed a tetrabutylammonium hydrogen sulfate (TBAHS)-catalysed protocol for the synthesis of substituted benzothiazolopyrimidine derivatives 180 and 181 via a one-pot, three-component condensation reaction of 2-amino-benzothiazole 6 with substituted benzaldehydes 4 and cyclic 81 and non-cyclic 12 β-dicarbonyl derivatives in ethylene glycol. TBAHS acts as an acidic phase-transfer catalyst. Other catalysts have also been used to explore this methodology such as FeF3, SbCl5 grafted over sulfonic acid-functionalized carbon@titania composites (C/TiO2-SO3-SbCl5), Mg-Al-CO3 hydroxalite, chitosan in 2% acetic acid, nano-Fe3O4@SiO2@SO3, graphite oxide (Scheme 56). The mechanism when the reaction is catalyzed using nano-Fe3O4@SiO2@SO3 as proposed by the author is shown in Scheme 57.

3-Amino-1,2,4-triazole/5-aminotetrazole 16 has also been utilized together with cyclic and non-cyclic β-ketocarboxylic acids for the synthesis of various tetrazolo/triazolo-fused pyrimidine moieties 182 and 183. K. Kumari et al. demonstrated a three-component reaction, wherein a mixture containing 3-amino-1,2,4-triazole 17, aromatic aldehyde 3, dikedone/ethyl acetoacetate 83 and 4 was ground using an agate mortar in the presence of [Bmim][BF4]. The TFA : DIPEA (1 : 1)-catalysed version of this protocol was developed by C. Raju et al. utilizing 5-aminotetrazole instead of 3-amino-1,2,4-triazole in a reaction with aromatic aldehyde and dimedone/ethyl acetoacetate, and the synthesized tetrazole-fused compounds were evaluated for their antimicrobial and antioxidant activity. Similarly, other catalysts such as Nafion-H122, PEG-400123 and NaHSO4 immobilized on core/shell phenylene-bridged periodic mesoporous organosilica magnetic nanoparticles (γ-Fe2O3@Ph-PMO-NaHSO4)124 were used (Scheme 58).

A synthetic approach for densely functionalized tetrahydroindazolo[3,2-b]quinazoline 185 and 186 catalyzed by iron fluoride under ultrasonication in solvent-free conditions was developed by V. V. Shinde and Y. T. Jeong by utilizing 1H-indazole-3-amines 184, cyclic 81 and acyclic 1,3-dicarbonyl compounds 12 and various aldehydes 4 as starting components (Scheme 59). This reaction was completed in a short time and it possesses advantages in comparison to the conventional heating such as good to excellent yields, easy work-up procedure, and avoiding the use of solvent and column chromatographic purification of products.
A straightforward and green route to 4-aryl-3,4-dihydro-1H-pyrimido[1,2-a]benzimidazole derivatives 188, 189 and 190 was accomplished in excellent yields via the reaction of aryl aldehyde 3, 1,3-dicarbonyl compounds 187, 81 and 12 and 2-aminobenzimidazole 3a in ionic liquid, [bmim][BF₄], by C. Yao and coworkers. At high temperature, the three-component reaction with 2,2-dimethyl-1,3-dioxane-4,6-dione 187 yielded pyrimidone ring as the final product through sequential Knoevenagel condensation, Michael addition, intramolecular cyclization and elimination reaction sequence (Scheme 60). During intramolecular cyclisation, the temperature plays a key role in rearranging the cyclized structure into a thermodynamically more stable product upon the elimination of acetone and carbon dioxide as gaseous side products.

An interesting protocol developed by M. Beerappa and K. Shivashankar revealed that benzyl halide can be used as an aldehydic precursor to construct triazolo/benzimidazo quinazolinones 192, 193 and 194 via MCRs. This method involves the one-pot three-component reaction between 2-amino benzimidazole/3-amino-1,2,4-triazole 3a and 25, dimedone/ethylacetoacetate 81 and 5 and various benzyl halides 191 in the presence of trimethyl amine N-oxide as a catalyst under
refluxing ethanol (Scheme 61). Mechanistically, the reaction proceeds through the cascade of in situ oxidation of benzyl halides into benzaldehydes by trimethyl amine N-oxide, Knoevenagel condensation between aldehyde and β-dicarbonyl compound, and finally Michael addition followed by cyclization and dehydration (Scheme 62).

2.1.1.4 MCRs involving malonitrile and analogous compounds. Azaheterocycle condensed pyrimidine systems have also been synthesized using nitrile group-activated methylene

| Reaction condition | Time (min) | Yield (%) | No. of example | Reference |
|--------------------|------------|-----------|----------------|-----------|
| NaOH (20 mol%), EtOH, Reflux under conventional heating | 30 | 60–85 | 13 | - | 138 |
| NaOH (20 mol%), EtOH, Ultrasonic waves at 25–30 °C | 60 | 67–90 | - | - | - |
| H₃BO₃ (20 mol%), CTAB (15 mol%), H₂O, 60 °C | 20 | 80–96 | 11 | - | 139 |
| DBU (100 mol%), EtOH, Reflux | 20 | 82–92 | 16 | - | 140 |
| [H₂-DABCO][H₂PO₄]₂, 100 °C | 30–75 | 90–96 | 10 | - | 141 |
| [H₂-DABCO][ClO₄]₂, 100 °C | 25–60 | - | - | - | - |
| γ-Fe₂O₃@SiO₂@[Bis-APTES]Cl₂ NPs, 90 °C | 20–50 | 86–95 | 12 | - | 89 |
| RHA-[pmim]HSO₄, 100 °C | 2–5 | 88–93 | - | 10 | 80 |
| PEG-400:H₂O (4:1), Reflux | 6–8 h | 72–86 | 7 | - | 142 |
| Na⁺-MMT-[pmim]HSO₄, 100 °C | 87–95 | - | 22 | 31 |
| [H-pi]HSO₄ (3.5 mol%), 100 °C | 85–97 | - | 12 | 143 |

Scheme 63 Synthesis of multi-substituted [1,2,4]-triazolo-[4,3-a]-pyrimidines.
compounds such as malonitrile and alkyl cyanoacetate. K. Ablajan et al. described a method involving the synthesis of 5-amino-7-aryl-7,8-dihydro[1,2,4]triazolo[4,3-a]pyrimidine-6-carbonitrile derivatives 195 and 196 via the one-pot reaction of 3-amino-1,2,4-triazole 25, malononitrile 194 and aryl aldehydes 4 in the presence of 20 mol% NaOH in ethanol under conventional heating or ultrasonic irradiation. It was observed that the replacement of NaOH by triethyl amine, L-proline or acetic acid did not yield the product under both heating conditions. This purine analogue containing triazolopyrimidines with a bridgehead nitrogen was also achieved with same combination of reacting components using catalysts such as boric acid (H3BO3) in aqueous micellar,139 DBU,140 [H2-DABCO][H2PO4]2 or DABCO[ClO4]2,141 γ-Fe2O3@SiO2@[Bis-APTES]Cl2 nanoparticles,138 Brønsted acidic ionic liquid supported on rice husk ash (RHA-[pmim]HSO4),80 polyethylene glycol (PEG-400) in water,142 nanoporous sodium montmorillonite clay ([Na+]-MMT)-modified 1-methyl-3-(trimethoxysilylpropyl)-imidazolium hydrogen sulfate ([Na+]-MMT-[pmim]HSO4),31 and 1,4-piperazinium hydrogen sulfate ([H-pi]HSO4). A brief summary of the information regarding the reaction conditions, reaction time, yield of product, etc. of the reported methods is shown in Scheme 63.

S. Nalawade and coworkers reported a method to achieve the regioselective synthesis of pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate 198 by the reaction of ethylcyanoacetate with substituted benzaldehyde 4 and 2-aminobenzothiazol 3b in ethanol under microwave irradiation operating at 640 W.144 These one-pot three-component reactions were completed within a few minutes, affording the desired products in good to excellent yields. A newly modified form of the cyano group 197-bearing active methylene compound was prepared and utilized in the MCR synthesis of thiazolo[3,2-a]pyrimidine derivatives 199 by A. S. Abd El-All’s group. N-(4-(1H-Benzol[d]imidazol-2-yl)phenyl)-2-cyanoacetamide 199 was prepared by mixing ethyl cyanoacetate with 4-1H-benzol[d]imidazol-2-yl]benzenamine in refluxing ethanol. The newly synthesized cyanoacetamide was then reacted with 2-aminothiazole 22 and aromatic aldehyde 4 in the presence of glacial acetic acid under reflux conditions to afford the corresponding thiazole ring-fused pyrimidine derivatives (Scheme 64).

Novel tricyclic pyrimido[1,2-b]indazole-3-carbonitrile derivatives 200 containing both biologically active pyrimidine and
Scheme 66  Synthesis of triazole and benzimidazole-fused spiro derivatives under microwave and conventional heating.

Scheme 67  Synthesis of two different products under microwave and conventional heating.

Scheme 68  Synthesis of various tetrahydropyrimidines depending upon the structure of acetones used.
Indazole templates were synthesized via the three-component reaction of 1H-indazol-3-amine 184, aldehydes 4, and malononitrile 194 catalyzed by the base di-n-butylamine (DBA) in ethanol. This group-assisted-purification (GAP) chemistry process follows a proposed mechanism, as shown in Scheme 65.

E. S. Gladkov et al. reported the synthesis of spiro derivatives of pyrimidine by methods involving a three-component reaction under microwave and conventional heating. The triazole and benzimidazole-fused spiro derivatives of pyrimidine were prepared by mixing cyclohexanone 201 with malononitrile 194 and 5-amino-1,2,3-triazole/2-aminobenzimidazole 25, 202 and 3a using 10 mol% trimethylamine in ethanol (Scheme 66).

### 2.1.1.5 MCRs involving acetone and analogous compounds

The Biginelli-like three-component condensation following an unexpected alternative direction leading to a tetrahydropyrrolopyrimidine ring was investigated by N. Yu. Gorobets et al. using 3-amino-1,2,4-triazole 25, acetone 206 and different salicylic aldehydes 207. The tendency of giving two different products 209 and 210 when the combination of reactants was treated at different temperatures made this technique interesting. The presence of an ortho-hydroxyl group in the benzaldehyde was observed to take part in the formation of an oxygen bridge under microwave heating of an ethanolic solution containing the reactants at 150 °C. Conversely, no oxygen bridging occurred at the moderate temperature even after 16 h (Scheme 67).

In both cases, the formation of products was achieved in the presence of HCl as the catalyst and the reaction proceeded via imine intermediate 208 formed from the aldehyde and the exocyclic amino group instead of the endocyclic nitrogen of 3-amino-1,2,4-triazole.

![Scheme 69](image)  
**Scheme 69** Solvent-free synthesis of dihydrotetrazolo[1,5-a]pyrimidines and bis-dihydrotetrazolo[1,5-a]pyrimidine.

![Scheme 70](image)  
**Scheme 70** Proposed mechanistic pathway to dihydrotetrazolo[1,5-a]pyrimidines.

![Scheme 71](image)  
**Scheme 71** Synthesis of [1,2,4]triazolo[1,5-a]pyrimidines and pyrimido[1,2-a]benzimidazole derivatives.
The versatility of the method was demonstrated by employing various ketones such as butan-2-one 213, 3-methylbutan-2-one 214, 4-methylacetophenone 212 and ethyl acetoacetate 4. Under similar reaction conditions, butan-2-one 213 afforded a mixture of three isomers 216, 217 and 218 in a ratio of 3 : 3 : 1 with total yield of 42%. The NOESY correlation technique was used to determine the structure of 217 and 218 diastereoisomers and correlations between the protons of the aryl ring and methyl group at position 13 were observed in of case 218 only. The corresponding bridged compounds constructed with 3-methylbutan-2-one 214 and 4-methylacetophenone 212 were isolated upon precipitation in poor yields of 25% and 21%, 219 and 220, respectively, due to the incomplete reaction. Next, an equimolar mixture of ethyl acetoacetate 5 with 3-amino-1,2,4-triazole 25 and salicylic aldehyde acetoacetate 221 in absolute ethanol (instead of methanol to avoid transesterification) and HCl solution in dioxane resulted in the formation of dihydroxy derivative 221. The relative configuration 5R,6S,7S at the stereocenters of 221 was assigned by NMR. During NMR measurement in DMSO-d$_6$ solution, diastereoisomer 222 with the 5R,6R,7S configuration was detected due to the isomerization of 221. Further, the regio- and stereoselective formation of spirotriazolopyrimidine 223 was observed with 71% yield when 3-acetyl-dihydrofuran-2(3H)-one 215 was used in the present Biginelli-like multicomponent reaction (Scheme 68).

Methyl ketones work analogously to β-dicarbonyl compounds in the MCR but have less acidic protons compared to the latter due to the presence of only one electron-withdrawing keto group. R. Ghorbani-Vaghei et al. developed a series of tetrazole-fused pyrimidine derivatives utilizing acetophenone 225, 5-amino-1,2,4-triazolopyrimidine 16 and various aromatic aldehydes 4. Condensation of these reactants at 80 °C under solvent-free conditions together with N$_2$N$_2$N'$N'$-tetrabromobenzene-1,3-disulfonamide (TBBDA) 224 as a catalyst afforded 5,7-diaryl-4,7-dihydrotetrazolo[1,5-a]pyrimidines 227. They also reported the synthesis of novel bis-dihydropyrazolo[1,5-a]pyrimidines 228 via the reaction of diacetylpyridine 226 with 2 equivalents of each aldehyde 4 and 5-amino-1,2,4-triazolopyrimidine 16 under the optimized reaction conditions (Scheme 69). The plausible mechanism as suggested by the authors for this reaction is shown in Scheme 70, where bromine atoms are detached in situ from TBBDA 224 as bromonium ions and act as the oxidant in the reaction medium.

H. M. E. Hassaneen and T. A. Farghaly also explored acetoephone derivatives in a one-pot three-component reaction with 2-aminobenzimidazole/3-amino-[1,2,4]triazole 3a and 25 and aromatic aldehyde 22. The reaction mixture was taken in aqueous medium together with H-ferriterie zeolite as a catalyst and heated under reflux conditions for 8–15 min, affording a novel series of [1,2,4]triazolo[1,5-a]pyrimidines 232 and pyrimido[1,2-a][benzimidazole derivatives 231]. A different methyl ketone-linked compound, 3-acetyl-1-(4-fluorophenyl)-5-phenyl-1H-pyrazole-4-carbonitrile, was synthesized and utilized by K. A. Ali et al. as one of the MCR components for the synthesis of novel substituted pyrimidine scaffolds. This component was mixed with benzaldehyde and 2-aminobenzimidazole/3-amino-[1,2,4]triazole in DMF solvent under reflux to afford 1-(4-fluorophenyl)-5-phenyl-3-(4-phenyl-1,4-dihydropyrimido[1,2-a][benzimidazol-2-yl]-1H-pyrazole-4-carbonitrile/1-(4-fluorophenyl)-3-(5,8-dihydro-5-phenyl-[1,2,4]triazolol[4,3-a]pyrimidin-7-yl)-5-phenyl-1H-pyrazole-4-carbonitriles 233 and 234 (Scheme 71).
V. Pogaku et al. developed a one-pot three-component approach to synthesize novel pyrazole-linked triazolopyrimidines as a potent \(\alpha\)-glucosidase inhibitor by performing a reaction using acetophenone derivatives 206, 3-methyl-1-phenyl-5-(1H-1,2,4-triazol-1-yl)-1H-pyrazole-4-carbaldehyde 234 and 4H-1,2,4-triazol-3-amine 25 as starting materials. This piperidine-catalyzed reaction was executed in DMF under reflux conditions to afford the target products 235 with 74–88% yield (Scheme 72).\(^{151}\)

\(N,N\)-Dimethylformamidemethylacetal 76, a formaldehyde analogue, was employed in place of substituted aromatic aldehyde by L. Suresh and coworkers to achieve fused tetrazolo[1,5-a]pyrimidine derivatives 236.\(^{152}\) The multicomponent condensation of 5-aminotetrazole 16, dimethylformamidemethylacetal 76 and acetophenones 206 was carried out in the ionic liquid 1-butyl-3-methylimidazolium hydrogen sulfate \([bmim]\) \(\text{HSO}_4\) at 70 °C. The formation of tetrazolo[1,5-a]pyrimidine 236 was proposed to proceed through \(\alpha,\beta\)-unsaturated ketone intermediate 237a generated \textit{in situ} from the ionic liquid-supported condensation of acetophenone 206 and \(N,N\)-dimethylformamidemethylacetal 76. This intermediate is then attacked by 5-aminotetrazole 16 followed by the subsequent loss of dimethyl amine to form another \(\alpha,\beta\)-unsaturated ketone intermediate 237b. The final step involves the keto-enol tautomerism of this intermediate, followed by cyclization \textit{via} the elimination of a water molecule (Scheme 73).

The green carbocatalyst graphene oxide (GO) was employed by S. Kundu and B. Basu in a one-pot multi-component approach for the synthesis of biologically important 3-sulfenylimidazo[1,2-a]pyridine scaffolds 239.\(^{153}\) The present method involves a reaction between 2-aminopyridine 117, acetophenones 206 and various thiols in the presence of GO and NaI (as the additive) at 80 °C under aerial conditions. The reactions are believed to proceed \textit{via} a selective and tandem manner involving an Ortoleva–King-type intermediate 238 and the catalyst GO was found to be recyclable with appreciable conversions (Scheme 74).

2.1.1.6 MCRs involving cyclohexanone and analogous compounds. A. A. Matveeva reported the synthesis of linearly structured azoloquinazolines with an admixture of isomers with angular ring fusion by the treatment of 3-amino-4H-1,2,4-triazole/5-amino-1H-tetrazole with \(\alpha,\beta\)-unsaturated ketones of...
cyclohexanone series. The extension of this reaction to ylide-
necyclohexanone analogues with a greater alicycle size (C7 and
C8) was not satisfactorily achieved due to their low yields.154

After two years, the possibility of using three-component
cyclocondensation for the synthesis of tetrazolopyrimidines
annulated by C6 to C8 carbocycles was studied. The reactions
were carried out by refluxing a solventless equimolar mixture of
5-amino-1H-tetrazole 16, aldehyde 4, viz. furfural and benzal-
dehyde, and ketone 201, viz. cyclohexanone, cycloheptanone,
and cyclooctenone, for 40–50 min, resulting in the formation of
cyclanotetrazolopyrimidines 240 in moderate yields (Scheme
75).155 The regiospecificity of the reaction was confirmed by the
1H NMR spectra of the reaction mixture, where only signals
corresponding to linearly fused carbo- and heterocycles in the
tetrazolocyclanopyrimidines appeared. No signal was detected
for the angular regioisomer.

Next, the same researcher described the synthesis of two
isomers of linearly fused pyrimidine derivatives with a Cn–Cn
 cycloalkene ring fused at the C5–C6 bond, differing by the
position of the double bond in the cycloalkene ring.156 In this
method, a more nucleophilic aminoazole, 4H-1,2,4-triazol-5-
amine 25, was heated with equimolar amounts of
benzaldehyde/furfural 4 and cycloalkanone 201 (C6–C8) under
refluxing conditions (Scheme 76). Phenyl(furyl)-substituted
linearly fused cycloalkatriazolopyrimidines 241 and 242 con-
taining a common double bond to the cycloalkene and tetra-
hydropyrimidine rings were obtained as the major isomers
together with a minor isomer having a C4–C5 double bond. The
position of the C=C double bond in the minor isomer was
determined using 1H COSY and 1D NOESY data.

Following the above results, subsequently they performed
a three-component condensation reaction between 5-
a mixture of linearly and angularly fused isomeric hexahydro-triazoloquinazolines was found to be linearly fused and consistent with previous reports. An analogous reaction with 3-amino-4H-1,2,4-triazole afforded a mixture of linearly and angularly fused isomeric hexahydro-triazoloquinazolines.

E. M. H. Abbas et al. developed an approach where dimethylformamide-dimethylacetal (DMF-DMA) was utilized as an alternative to formaldehyde in the MCR synthesis of novel poly-heterocyclic ring systems. Various azole-fused pyrimidine systems were obtained by the component reactions between benzothiopyran-4-ones and aminooxazoles and DMF-DMA. The Groebke–Blackburn–Bienaymé (GBB) reaction was developed independently in 1998 by three research groups, viz. Katrin Groebke (Switzerland), Christopher Blackburn (Cambridge, USA) and Hugues Bienaymé (France). The vast utility of this reaction is evidenced by the number of subsequent publications and by the multiple-thousand-member focused libraries of fused aminoimidazoles that have been successfully synthesized by the use of this reaction. More precisely, this is one of the most efficient methods to achieve imidazoheterocyclic scaffolds, which are recognized as a privileged structure for novel synthetic drug molecules. The GBB reaction is a four-centre three-component method, which basically involves the treatment of an aldehyde with an azine/azoles and isonitrile in the presence of a suitable catalyst either under solvent or solvent-free conditions under microwave irradiation as the heat source. The reaction proceeds through the initial formation of a Schiff base via the condensation of aldehyde and amine. The Schiff base, possessing both an electrophile and nucleophile, undergoes nonconcerted [4 + 1] cycloaddition with the isonitrile, which

![Scheme 79](image_url) Iodine-catalyzed synthesis of various azole fused pyrimidines.

![Scheme 80](image_url) Synthesis of novel tetrazolo-fused pyrimidines under microwave heating.

In continuation of these developments, G. P. Kantin and M. Krasavin demonstrated an acid-catalysed MCR synthesis of a series of novel tetrazolo-fused pyrimidines. A reaction mixture containing 2-amino[1,2,4]triazole and aromatic aldehyde was heated under microwave irradiation at 130 °C using hydrochloric acid as a catalyst. The reaction was carried out with 2 equivalents of aromatic aldehyde as the aldehydic component together with 2-aminoenidazole and 1-ethyl-4-piperidone, it yielded a mixture of an intermediate and the final product. The intermediate was then transformed into the final pyrimidine derivative via in situ oxidation (Scheme 79).

2.1.1.7 MCRs involving isonitrile and analogous compounds (Groebke–Blackburn–Bienaymé reaction). The Groebke–Blackburn–Bienaymé (GBB) reaction was developed independently in 1998 by three research groups, viz. Katrin Groebke (Switzerland), Christopher Blackburn (Cambridge, USA) and Hugues Bienaymé (France). The vast utility of this reaction is evidenced by the number of subsequent publications and by the multiple-thousand-member focused libraries of fused aminoimidazoles that have been successfully synthesized by the use of this reaction. More precisely, this is one of the most efficient methods to achieve imidazoheterocyclic scaffolds, which are recognized as a privileged structure for novel synthetic drug molecules. The GBB reaction is a four-centre three-component method, which basically involves the treatment of an aldehyde with an azine/azoles and isonitrile in the presence of a suitable catalyst either under solvent or solvent-free conditions under microwave irradiation as the heat source. The reaction proceeds through the initial formation of a Schiff base via the condensation of aldehyde and amine. The Schiff base, possessing both an electrophile and nucleophile, undergoes nonconcerted [4 + 1] cycloaddition with the isonitrile, which
behaves as a vinylidene carbenoid, to give the intermediate. A subsequent prototropic shift generates the final fused 3-aminoimidazoles. Earlier published reviews illustrate multicomponent reactions based on the GBB reaction leading to the synthesis of fused imidazole derivatives and their importance in the drug discovery program. In this review, we cover the recently developed GBB methods that have not been covered before. S. Keshipour and coworkers used a $p$-TSOH/ZnCl$_2$ catalyst.

| Reaction conditions | Time | Yield (%) | No. of examples | Reference |
|---------------------|------|-----------|----------------|-----------|
| PTSA (5 mol%), ZnCl$_2$ (5 mol%), MeOH, Reflux | 48 h | 78–87 | 17 | 163 |
| HClO$_4$ (5 mol%), MeOH, RT | 4–24 h | 30–80 | 16 | 164 |
| NH$_4$Cl (100 mol%), PhMe, Reflux | 12–24 h | 65–93 | 12 | 165 |
| Choline chloride/Urea (DES) 80 °C | 40–120 min | 77–94 | 20 | 166 |
| HCl/dioxane, MeCN Reflux | 2–6 h | 15–90 | 37 | 167 |
| Gla, AcOH (20 mol%), MeOH, 70 °C | 2 h | 67–92 | 20 | 168 |
| β-CD-SO$_3$H (10 mol%), EtOH or MeCN, 80 °C | 1 h | 88–96 | 23 | 169 |
| Yb(OTf)$_3$ (2.5 mol%), MW, 160 °C | 5 min | 94–99 | 25 | 170 |
| In(OTf)$_3$ (15 mol%), EtOH, 80 °C | 5–45 min | 52–76 | 26 | 171 |
| In(OTf)$_3$ (10 mol%), PhMe, 80 °C | 45 min | 83–96 | 20 | 172 |
| InCl$_3$ (1 mol%), CH$_2$COOH MeOH, MW, 85 °C | 1 h | 70–93 | 18 | 173 |
| P$_2$O$_5$/SiO$_2$, MeOH, 70 °C | 5–6 h | 70–86 | 12 | 174 |
| Calix[n]arenes-SO$_3$H, H$_2$O, RT | 3–4 h | 75–96 | 13 | 175 |
| Cu(OTf)$_2$ (10 mol%) CuOTf·C$_6$H$_6$ (10 mol%), PhMe, 120 °C | 2 h | 33–77 | 31 | 176 |
| EESA (0.1 mol%), EtOH, 35 °C | 35 min. | 80–90 | 6 | 177 |
| Visible light (24 W CFL) | 2–3 h | 82–98 | 22 | 178 |
| ZrCl$_4$ (10 mol%), PEG-400, 55–75 °C | 2–4 h | 47–79 | 15 | 179 |

Scheme 81  Reported GBB methods utilizing various catalysts.
Fig. 6 Various derivatives of aminoazaheterocycles, aldehydes and isocyanides used in the GBB reaction.

Scheme 82 Catalyst-free microwave-assisted GBB reaction.

Scheme 83 Reaction mechanism to explain the synthesis of GBB product.
A catalytic system to carry out the GBB reaction, which took 48 h to complete. A comparatively shorter reaction time was taken by the methods catalyzed by HClO$_4$, NH$_4$Cl, urea-based/choline chloride system, HCl/dioxane, glacial acetic acid, β-cyclodextrin-SO$_3$H, Yb(OTf)$_3$, In(OTf)$_3$, InCl$_3$, P$_2$O$_5$/SiO$_2$, calix[n]arenes-SO$_3$H, Cu(OTf)$_2$, CuOTf-$C_8$H$_{16}$, electrostatically enhanced sulfuric acid (EESA), visible light (24 W CFL), and ZrCl$_4$. A brief summary regarding the reaction conditions, time, yields, etc. is shown in Scheme 81 (Fig. 6).

A series of twenty-three novel unsymmetrical bis-heterocycles having either imidazo[2,1-b]thiazole 262 or benzo
imidazo[2,1-b]thiazole frameworks bound with chromone, quinoline or julolidine was obtained in good to excellent yields (82–97%) by an acid-free GBB reaction under microwave-heating conditions (Scheme 82). The density functional theory (DFT) approach was used to study the mechanism of this reaction (via concerted or non-concerted pathways) with the PCM(Toluene)[M06-2X/6-311+G(d,p)//M06-2X/6-311G(d)] level of theory and it was observed that only the non-concerted pathway is followed. The mechanism starts with the condensation of 2-aminoazoles with aldehyde to form an imine intermediate. Subsequently, the reaction can follow concerted and non-concerted pathways. Concerted pathway A involves the [4 + 1] cycloaddition between imine and isocyanide followed by a prototropic shift to give imidazo[2,1-b]thiazole-chromone. In non-concerted pathway B, the nucletophilic addition of isocyanide to imine takes place to form nitrilium ion, which undergoes sequentially a 5-exo-dig cyclization and a prototropic shift to generate the target product (Scheme 83).

A concise one-pot three-component cascade approach was reported by G. Martinez-Ariza et al. to achieve biologically important imidazo[1,2-a]heterocycles and via the reaction of 2-aminothiazole/2-aminopyridine and two equivalents of each aldehyde and acetyl cyanide in the presence of calcium chloride at 140 °C (Scheme 84).

A. Sagar et al. developed an interesting one-pot GBB double annulation cascade process to synthesize diverse dihydroisoquinoline (DHIQ) salts, and in this catalyst- and solvent-free protocol, a reaction mixture containing various heteroaromatic amines, 2-(2-bromoethyl)benzaldehyde derivatives, and isocyanides.

Scheme 87  Proposed mechanism involving a reactive cyclic iminium-induced GBB double annulation cascade route.

Scheme 88  DABCO-catalyzed synthesis of various 3-amino-2-carboxyethyl-linked fused imidazoles.

Scheme 89  Synthesis of imidazo[1,2-a]pyridin-3-amines through GBB 3-CR condensation/deprotection protocol.
was heated at 80 °C for 10–20 min, leading to the construction of two privileged heterocyclic rings (Scheme 86). Mechanically, the formation of pyridoimidazo-DHIQ salts 274–277 starts with the reactive cyclic iminium ion 277a generated in situ from heteroaromatic amines and 2-(2-bromoethyl)benzaldehyde derivatives, which undergoes [4 + 1] cycloaddition with isocyanides (Scheme 87).

Furthermore, a chemoselective Strecker–Ugi-type reaction was developed by S. K. Guchhait and V. Chaudhary, wherein TMSCN 279, a isonitrile equivalent, ethyl glyoxalate 278 and 2-aminopyridine/2-aminobenzothiazole 117 and 3b were combined in a DABCO-THF solvent system under microwave irradiation and maintained at 120 °C (Scheme 88). Various 3-amine and 2-carboxyethyl functionalized N-fused imidazoles were proposed to be obtained through a reaction pathway involving the desilylative activation of TMSCN in DABCO-THF. Its flexibility for various derivatives of 2-aminopyridine/2-aminobenzothiazole 280 and 281 and the incorporation of ethyl glyoxalate as a viable aldehyde substrate make this method a very important Strecker–Ugi reaction using TMSCN 279.

R. C. Cioc et al. reported a similar reaction, which describes the application of trityl isocyanide, as new isonitrile equivalent in a combinatorial approach for the first time. The Strecker reaction of 6-chloro-2-aminopyridine 282 with trityl isocyanide 283 and aldehyde 4 under the reaction conditions exclusively provided α-amino nitrile over the imidazo[1,2-a]pyridine 285 (Scheme 89). Application of the optimized Strecker protocol to a series of 2-aminopyridines and aromatic/aliphatic aldehydes showed that the cyclization to the GBB products 284 is favored. The success of this strategy relies on the fate of the nitrilium ion intermediate 286, which should undergo

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**Scheme 90**  Fate of nitrilium ion intermediate in the Ugi, Strecker and GBB reactions.

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**Scheme 91**  Behaviour of 3-amino-5-methylisoxazole and 5-amino-N-aryl-1H-pyrazole-4-carboxamides in multicomponent reactions.

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**Scheme 92**  GBB reaction with 5-amino-N-aryl-1H-pyrazole-4-carboxamide under two different conditions.
intramolecular trapping by the pyridine nitrogen rather than fragmentation. Significant fragmentation of the nitrilium ion (GBB product/Strecker product ratio = 5 : 1) was also observed for the electron-deficient 5-fluoro-2-aminopyridine. The detritylation of the GBB products was observed to be facile with 3 equivalents of TFA at 65 °C.

They also performed a reaction in which all three pathways, Strecker, Ugi and GBB, are possible to investigate which product predominates. Accordingly, Ugi 4-CR with 5-fluoro-2-aminopyridine, pivalaldehyde, acetic acid, and trityl isocyanide was performed under the optimized conditions. Based on the NMR analysis, the selective formation of the GBB product clearly indicated the complete predominance of this pathway as no evidence of the Strecker and Ugi products was found. As expected, the addition of an external nucleophile (acetate) did not compete with the intramolecular trapping of the nitrilium ion by the pyridine nitrogen, even though it is relatively electron deficient. Furthermore, the mild activation of the imine by a carboxylic acid instead of a strong Bronsted acid (possibly through hydrogen bonding rather than protonation) completely suppressed the nitrilium ion fragmentation towards the Strecker product 289 (Scheme 90).

Scheme 93 Synthesis of structurally diverse spiroheterocycles.

Scheme 94 Synthesis of spirooxindoles via GBB and Pictet–Spengler reaction.
The well-known aminoazoles, 3-amino-5-methylisoxazole 291 and 5-amino-N-aryl-1H-pyrazole-4-carboxamides 287, were studied by M. V. Murlykina et al. as amine components in the Ugi and GBB multicomponent reactions (Scheme 91). Particularly, 5-amino-N-aryl-1H-pyrazole-4-carboxamide 287 reacted as 1,3-binicuclophile with aromatic aldehydes 4 and alkylisocyanides 292 with the formation of 3-(alkylamino)-N,2-diaryl-1H-imidazo[1,2-b]pyrazole-7-carboxamides 294 (GBB reaction) (Scheme 92). In contrast, 3-amino-5-methylisoxazole 291 acted as a primary amine in the Ugi four-component reaction with aromatic aldehydes 4, phenylpropionic acid and tert-butylisocyanide 292, giving N-(1-arylethyl-2-(tert-butylamino)-2-oxo)-N-(5-methylisoxazol-3-yl)-3-phenylpropiolamides 293.

Y. K. Tailor et al. presented a modified form of the isocyanide-based GBB protocol, wherein aldehyde is replaced with ketones such as isatins 142 and cyclic carbonyl compounds 173 and 300. The synthesis of structurally diverse spiroheterocycles 301, 302 and 303, spiroannulated with imidazothiazole and imidazothiadiazole was achieved by the three-component reaction between 2-aminobenzothiazole/2-aminocarbonyl compounds and imidazothiadiazole 3a and 299, cyclohexyl/tert-butyl isocyanides 261 and isatins/cyclic carbonyl compounds in the presence of TiO2 nanoparticles using an ethanol/water solvent system at 90 °C (Scheme 93).

The same authors recently developed an interesting and diversity oriented synthetic strategy for spirooxindoles spiroannulated with imidazo[4,5-c]isoquinolines 306, imidazo[4,5-c][2,7]naphthyridines 307 and imidazo[4,5-b]thieno[2,3-d]pyridines 308. This isocyanide-based multicomponent reaction involves GBB followed by the Pictet–Spengler reaction. A reaction mixture containing 2-aminobenzothiazole/2-aminocarbonyl compounds in aqueous medium (Scheme 94).

B. Yang et al. developed a novel one-pot three-component protocol for biologically and pharmaceutically important tetracyclic-fused imidazo[1,2-a]pyridines 308. This method involves the GBB coupling of 2-aminopyridines 117, various isatins 142 and isocyanides 261 in the presence of HClO4 followed by a retro-aza-ene reaction and subsequent intramolecular nucleophilic reaction (path a) in butanol medium under reflux conditions to afford the title products in moderate yields (Scheme 95). The formation of benzodiazepine-fused imidazo[1,2-a]pyridine (through path b) was not observed, which may be due to the strain of the seven-membered ring.

An ultrasound-assisted GBB reaction-based protocol was recently developed by M. A. Claudio-Catalan and coworkers to synthesize bound-type fused bis-heterocycle imidazo or benzo[d]imidazo[2,1-b]thiazoles and benzo[d]imidazo[2,1-b]thiazoles 309, 2-chloro-3-formylquinoline 311, isocyanides 261 and aromatic/heteroaromatic aldehydes 304, 43 and 305 was treated with 10 mol% para-toluene sulfonic acid-modified TiO2 nanoparticles in aqueous medium (Scheme 94).

The formation of benzodiazepine-fused imidazo[1,2-a]pyridine (through path b) was not observed, which may be due to the strain of the seven-membered ring.

An ultrasound-assisted GBB reaction-based protocol was recently developed by M. A. Claudio-Catalan and coworkers to synthesize bound-type fused bis-heterocycle imidazo or benzo[d]imidazo[2,1-b]thiazoles and 1,5-disubstituted tetrazole (1,5-DsT)-containing quinoline moiety 312. This solvent- and catalyst-free approach utilizes 2-aminothiazoles/2-amino-benzothiazoles 309, 2-chloro-3-formylquinoline 311, isocyanides 261 and trimethylsilylazide 311 under mild green conditions to generate two types of fused heterocycles in one step, which proceeds through the GBB reaction/ SNAr/ring-chain azido-tautomerization strategy (Scheme 96). The synthesized compounds were also evaluated for antibacterial and antiamoebic activities against various Gram-positive and Gram-negative bacteria.

2.1.1.8 MCRs involving alkynes and analogous compounds. Organic compounds containing acetylene bonds adjacent to

![Scheme 95](image1)

Synthesis of tetracyclic-fused imidazo[1,2-a]pyridines via sequential GBB, retro-aza-ene and intramolecular nucleophilic reaction pathways.

![Scheme 96](image2)

Ultrasound-assisted synthesis of imidazo[2,1-b]thiazoles and benzo[d]imidazo[2,1-b]thiazoles.
a carbonyl group are considered excellent precursors for multicomponent cascade reactions because these compounds provide a key electrophilic site for a variety of nucleophiles. Among them, acetylenic esters have attracted significant attention given that their two carboxylate groups enhance their electrophilicity to a great level.

In organic synthesis, the application of aldehydes, amines and alkynes for the MCR synthesis of propargyl amines is termed $A^3$-coupling. Cascade processes involving cyclization by the Cu(i)-activated triple bond in propargyl amine afford versatile molecular complex compounds. Significant work has been reported based on multicomponent cascade reactions involving the $A^3$-coupling of 5/6 membered 2-aminoazaheteroaromatic compounds with aldehydes and alkynes through 5-exo-dig/6-endo-dig cycloisomerization. A general and highly efficient method for the synthesis of imidazopyridine derivatives was reported by N. Chernyak and V. Gevorgyan using the copper-catalyzed three-component coupling of 2-aminopyridines with aryl/heteroaryl/alkyl aldehydes and terminal alkynes through 5-exo-dig cycloisomerization using $\text{CuCl}$ and $\text{Cu(OTf)}_2$. The employment of 2-aminoquinoline and 2-aminoisoquinoline as coupling partners in this transformation led to imidazoquinoline and imidazoisoquinoline frameworks in good yields. Similarly, P. Liu et al. reported a novel three-component reaction towards the synthesis of imidazo[1,2-$a$]pyridines, which was independently developed based on $\text{CuSO}_4$/TsOH-catalyzed three-component reaction using 2-aminopyridines, aldehydes and alkynes through 5-exo-dig cycloisomerization. S. K. Guchhait et al. explored the catalytic efficiency of a mixed Cu(i)–Cu(II) system by partial reduction of in situ-generated CuSO$_4$

| Path | Reaction conditions | Time (h) | Yield (%) | No. of examples | Reference |
|------|---------------------|----------|-----------|-----------------|-----------|
| a    | CuCl (5 mol%), Cu(OTf)$_2$ (5 mol%), PhMe, 120 °C | 12–16 | 44–92 | 22 | 190 |
|      | CuSO$_4$ (10 mol%), PTSA (10 mol%), PhMe, Reflux | 18 | 46–68 | 24 | 191 |
|      | CuSO$_4$.5H$_2$O (15 mol%), D-Glucose (30 mol%) EtOH, Reflux | 10–16 | 45–82 | 24 | 192 |
| b    | Cul (15 mol%), Ag$_2$CO$_3$ (15 mol%) MeCN, Reflux | 5–8 | 51–73 | 22 | 193 |
|      | CuSO$_4$.5H$_2$O (20 mol%), PTSA (10 mol%), PhMe, 120 °C | 8 | 60–93 | 23 | 194 |

Scheme 97  Cu-catalyzed synthesis of substituted imidazoles and pyrimidines via 5-exo-dig and 6-endo-dig-cyclisation, respectively.
with glucose in ethanol (non-anhydrous) under open air in the A3-coupling of various 2-aminoazaheteroaromatic compounds with aldehydes and alkyne through an MCR cascade reaction. The corresponding fused imidazoles were generated via 5-exo-dig cyclosomerization and prototropic shift (Scheme 97, path a).⁹²

Conversely, A. Kumar and coworkers demonstrated an efficient regioselective cascade synthesis of pyrimidine ring 315 (ref. 193) via a transition-metal (copper/silver) catalyzed 6-exo-dig cyclization reaction. Herein, the coupling between 2-amino benzimidazole 120, aldehydes 4, and alkyne 313 was carried out, leading to the formation of propargylamine intermediate 315a, which regioselectively undergo 6-exo-dig cyclization through intramolecular N–H bond activation-mediated C–N bond formation. A recent report on the synthesis of nitrogen ring junction pyrimido-indazoles via 6-exo-dig cyclization was published by J. Palaniraja et al., wherein the A³ coupling reaction between 1H-indazol-3-amine, aromatic aldehydes and alkynes was achieved in the CuSO₄-PTSA catalytic system. Conversion to the highly functionalized pyrimido[1,2-b]indazoles proceeded through 6-exo-dig cyclization (Scheme 97, path b).³⁹⁴ Fig. 7 shows the structure of various 5/6 membered 2-aminoazaheteroaromatic compounds, aldehydes and alkynes frequently employed in these cascade reactions.

Next, facile access to various fused pyrimidine and azoles such as 2,3-, 2,4-disubstituted pyrimido[1,2-a]benzimidazoles, and 3-disubstituted imidazo[2,1-b]benzothiazoles was described by J. Wu et al. via reactions between heterocyclic azoles 3, aldehydes 4 and alkycarboxylic acids 316.³⁹⁵ The CuI and K₂CO₃-catalyzed MCR synthesis of pyrimido[1,2-a]benzimidazoles and imidazo[2,1-b]benzothiazoles proceeds through a 6-exo-dig and 5-exo-dig cyclization, respectively (Scheme 98).
W. Sun et al. reported a one-pot multicomponent protocol utilizing magnetic Cu\(^{0}\)@HAP@\(\gamma\)-Fe\(_2\)O\(_3\) hybrid to catalyze the synthesis of imidazo[1,2-\(a\)]pyridine derivatives \(117\) from 2-aminopyridine derivatives \(117\), aldehydes 4/glyoxylic acids \(321\), and alkynes/alkynyl carboxylic acid \(317\). This method involves combining 2-aminopyridine derivatives either with a mixture of aldehydes with alkynes or with glyoxylic acids and alkynyl carboxylic acid together with 10 mol\% catalyst in isopropanol at 100 °C (Scheme 99). The magnetic nanocatalyst could be easily separated from the reaction mixture using an external magnet and reused up to three runs with a slight loss in activity.

An interesting multicomponent approach to access imidazole-derived heterocycles \(322b\) was reported by X. Li et al. through an oxidative cascade reaction.\(^{197}\) This Cu(OTf)\(_2\) and Li\(_2\)CO\(_3\)-catalyzed reaction was conducted using terminal alkyne \(313\), 2-amino N-heterocycle \(120\), benzyl/allylic bromide \(322a\) and TEMPO (as an oxidant) in toluene under an oxygenated environment at 100 °C (Scheme 100). After 10 h, the target products, densely functionalized imidazo-fused heterocycles \(322b\), were obtained in moderate to good yields.

Furthermore, the novel synthesis of dimethyl 4,5-dihydro-5-aryl[1,2,4]triazolo[1,5-\(a\)]pyrimidine-6,7-dicarboxylates \(324\) was reported by B. Karami and coworkers through the one-pot condensation of 3-amino-1H-1,2,4-triazole \(25\), dimethyl acetylenedicarboxylate \(323\), and aryl aldehydes 4 using silica sodium carbonate as a solid base catalyst (Scheme 101).\(^{198}\)
nitrobenzaldehyde 68 and methyl acrylate 325 and subsequent addition of 2-aminobenzimidazole 3a.

In this sequential three-component reaction, 1,4-dioxane/H2O (1:1) as a reaction medium, and three equivalents of methyl acrylate 325 were used for smooth access to Baylis–Hillman alcohol 326. Afterwards, three equivalents of 2-aminobenzimidazole 3a was added for the subsequent tandem Michael addition and cyclization process, affording the final saturated pyrimidinone ring derivative 327 (Scheme 102).

A fused heterocyclic ring possessing three nitrogen atoms was synthesized by R. Moradivalikboni through an MCR. The catalyst benzene sulphonamide dibromide was synthesized and employed in the one-pot condensation of 2-amino thiadiazol 328, aromatic aldehydes 4 and acetic acid 329 in toluene under reflux conditions, which afforded thiadiazole-fused triazine derivatives 330 in excellent yields (Scheme 103).

A unique approach to benzothiazole-fused imidazoles 332 was developed by S. G. Balwe and Y. T. Jeong via the iron-catalyzed three-component cascade coupling of 2-amino benzothiazole 3b, aldehydes 4 and nitroalkane 331 in air. The mechanistic aspect of this unprecedented formation of fused imidazoles includes a sequential aza-Henry reaction and subsequent intramolecular cyclization, followed by denitration. A variety of substituted benzo[d]imidazo[2,1-b]thiazole 332 was obtained after 6–8 h in excellent yields (Scheme 104).

M. W. Powner et al. proposed a totally different type of three-component pathway to access novel pyrimidine scaffolds 336 in aqueous media. The interesting feature of this approach involves the in situ generation of 2-aminothiazole 22 from β-mercaptop-acetaldehyde 333 and cyanamide 334 in water at neutral pH, which then undergoes a three-component reaction

Scheme 103 Synthesis of thiadiazolotriazine derivatives using benzene sulphonamide dibromide as a catalyst.
with 4-amino-imidazole 5-carboxamide 335 and various aldehydes 4 in water at pH around 5.0 under an argon atmosphere (Scheme 105).

D. N. Lyapustin et al. employed morpholino-nitroalkenes 337 in a reaction with aminoazoles 16 and aromatic aldehydes 4 to report the multicomponent synthesis of 4,7-dihydro-5-R-7-aryl-6-nitroazolo[1,5-a]pyrimidines 338. The reaction was performed with 1.5 equivalents of boron trifluoride etherate in butanol at 120 °C for 1.5–6 h.\textsuperscript{203} The proposed pathway for this multicomponent transformation involves the conversion of morpholino-nitroalkenes 337 into the corresponding nitroalkynes 337a under the effect of catalyst, followed by the formation of azolyl-nitroalkene 337b (Scheme 106).

2.1.2 Aromatic α-aminoazaheterocycles as 1,1-binucleophiles. MCRs involving aromatic 2-aminoazaaromatic heterocycles as 1,1-binucleophiles are based on the participation of the exocyclic NH\textsubscript{2}-group exclusively. The usual products of these multicomponent interactions are five/six membered nitrogen-containing heterocycles having azaheterocycles as a substituent. The literature reveals that β-dicarbonyl compounds, organic anhydrides especially isatoic anhydride, alkyl acetylene dicarboxylate, mercaptoacetic acid, etc. have been employed to study the MCRs of this category.

2.1.2.1 MCRs involving β-dicarbonyl compounds. Dimedone, Meldrum’s acid, 1,3-indanedione, and barbituric acid and its N,N-dialkyl derivatives are the frequently used β-dicarbonyl compounds in MCRs as they possess acidic hydrogens between two strong electron withdrawing group. M. Kumar’s group conducted significant research on exploring MCRs involving these β-dicarbonyl compounds, AAHs and aldehydes/ketones, where the 1,1-binucleophilic reactivity of AAH is necessary. They synthesized diverse benzo/thiazolyquinoline-2,5-diones 341 and their spiro analogues 342 upon the one-pot four-component combination reaction of Meldrum’s acid 339, 2-aminobenzothiazoles 340, dimedone 81 and isatin/carbonyl compound (aldehydes and ketones) 142/4 in the presence of sulfamic acid (Scheme 107).\textsuperscript{204}

The plausible mechanistic path as suggested by the authors involves the initial Knoevenagel condensation reaction between Meldrum’s acid 339 and carbonyl compound 4 and 142 followed by nucleophilic attack by dimedone 81, leading to the generation of a linker between two β-dicarbons. The intermediate formed after the addition of 2-aminobenzothiazole 340 to the
dimedone ring with the removal of a water molecule undergoes intramolecular attack by the exocyclic amino group of benzo-thiazole at the carbonyl group of Meldrum’s acid, which further on heating rearranges to the final heterocyclic product 342 with the elimination of carbon dioxide and acetone as gaseous side products (Scheme 108).

On a similar basis, they described a diversity oriented synthetic protocol to access unsymmetrically annulated 1,4-
dihydropyridine spiroheterocycles via the four-component domino reaction of 2-aminobenzothiazoles, isatin and two different cyclic β-diketones using the Brønsted acidic imidazolium salt 3-methyl-1-(butyl-4-sulfonyl) imidazolium hydrogen sulphate (SFIL) as an ionic liquid in aqueous medium (Scheme 109, Method A). It was reported that the presence of the ionic liquid/water combination is crucial as the reaction medium for the formation of the target compound as no progress in the reaction was detected in the absence of both entities even after heating the reacting components for a long time. However, the yield of the products was dependent on the ratio of ionic liquid and water employed. Optimization of the ionic liquid/water ratio demonstrated that the best result was achieved with a 1:1 ratio in terms of yield.

Method A

Method B

| Method | R | R¹ | Reference |
|--------|---|----|-----------|
| A      | Me, i-Pr, X = H, 2-Cl, 4-Cl | | 208 |
| B      | X = O, S | | 209 |

Scheme 110 Microwave-assisted catalyst-free synthesis of substituted isoindolinones.

Scheme 111 Two different methods to synthesize polysubstituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones through a three-component condensation reaction.
and reaction time. Easy separation of the ionic liquid after completion of the reaction led to its reuse for at least five cycles without any appreciable loss in activity. After two years, the same group demonstrated a modified version of this approach, where a heteroaromatic aldehyde replaces isatin and the corresponding non-spiroheterocyclic ring was constructed in the presence of an organic catalyst. Structurally diverse unsymmetrically annulated 1,4-dihydropyridines 343 were obtained when an ethanolic solution of 2-aminobenzothiazole 344, thiophene-2-carbaldehyde 43 and various cyclic β-dicarbonyl compounds 122 was heated under reflux conditions in the presence of l-proline as an organocatalyst for 15–38 minutes. For the construction of these fused heterosystems, they utilized a variety of cyclic β-dicarbonyl compounds 122 except Mel-drum’s acid 339, which usually undergoes decomposition at moderate temperature, leading to the elimination of a small molecule and the formation of one-sided fused pyridine derivatives (Scheme 109, Method B).

An interesting and catalyst-free method was developed by K. V. Sashidhara et al. to carry out the one-pot synthesis of substituted isoindolinones 348 utilizing dimedone 81 as a 1,3-dicarbonyl component, various AAH, and formylbenzoic acid 346. In this method, three different types, namely C–C, C–N, and C–S bonds, are formed in a single operation upon heating an ethanolic mixture of reacting components under microwave irradiation. The postulated mechanism starts with the in situ formation of imine from 2-formylbenzoic acid 346 and AAH 347 (Scheme 110). The Michael addition product formed after nucleophilic attack of the enol form of diketone on imine undergoes intramolecular nucleophilic cyclization of the amine in the subsequent step, leading to the desired isoindolinone 348.

Pyruvic acid and its derivatives also function as active methylene compounds in the reaction, where AAH acts as a 1,1-binucleophile, and the article concerning this was published by S. V. Ryabukhin and coworkers, which revealed the parallel synthesis of a series of 3-hydroxy-1,5-dihydro-2H-pyrrol-2-one derivatives 350. Pyruvic acid derivatives 349 were allowed to undergo a three-component condensation with aromatic

| X   | Reaction conditions                                               | Time    | Yield (%) | No. of examples | Reference |
|-----|------------------------------------------------------------------|---------|-----------|-----------------|-----------|
| S   | Al(H2PO4)3 (16 mol%), 100 °C                                     | 13–20 min | 79–86     | 6               | 210       |
| S, NH | H3PO4-Al2O3, 120 °C                                               | 8–16 min | 80–93     | 13              | 211       |
|     | Cellulose-SO3H (4 mol%), 100 °C                                  | 3–20 min | 85–96     | 12              | 212       |
| S   | Zr(HSO4)4 (20 mol%), 80 °C                                       | 30–60 min| 80–92     | 11              | 213       |
| S, NH | Fe3O4@SiO2-imid-PMA8 H2O:EtOH (1:3(v/v), Reflux                  | 1.5–4 h  | 87–95     | 8               | 214       |
|     | Fe3O4@SiO2-imid-PMA8 EtOH, Ultrasonic irradiation, RT            | 8–35 min | 87–95     |                 |           |

Scheme 112  Synthesis of 3-(2′-benzothiazolyl)-2,3-dihydroquinazolin-4(1H)-ones under different reaction conditions.
aldehydes and various 2-aminoaza aromatic heterocycles. This transformation was performed under two different reaction conditions, namely Me$_3$SiCl as the reaction promoter in DMF and acetic acid as the reaction medium (Scheme 111, Method A). It was observed that the use of Me$_3$SiCl in DMF is suitable in terms of providing the corresponding products in 73–93% yield compared to 38–73% in the case of the reaction in acetic acid. In 2014, an analogous reaction was performed with methyl 2-heteroylpyruvates, 2-aminothiazole and substituted aldehydes by V. L. Gein et al. to access 5-aryl-4-(2-heteroyl)-3-hydroxy-1-(2-thiazolyl)-3-pyrrolin-2-ones. The reaction mixture containing the starting materials was heated in acetic acid under reflux for 5–10 min. Given that the authors utilized a selected number of starting components, a few examples were possible by various permutations and combinations (Scheme 111, Method B).

2.1.2.2 MCRs involving organic anhydrides. Organic anhydrides such as isatoic anhydride and acetic anhydride were also explored in this category of reactions by several research groups, wherein these anhydrides undergo the loss of small molecules, viz., carbon dioxide and acetic acid, at moderate temperature. H. R. Shaterian et al. described a one-pot three-component cyclocondensation reaction between isatoic anhydride, 2-aminobenzothiazole and aldehydes, leading to the formation of quinazolinone derivatives. The reaction, which was catalyzed by a heterogeneous catalyst, [Al(H$_2$PO$_4$)$_3$], under thermal solvent-free conditions, worked well with a variety of aryl aldehydes, including those bearing electron-withdrawing and electron-donating groups such as OMe, Cl, Br, and NO$_2$, and the desired compounds were obtained in good to excellent yields. Conversely, aliphatic aldehydes could not be incorporated in the product under the same reaction conditions. The same research group further explored this method, where the synthesis of these pyrimidine-type heterocyclic compounds was carried out by employing alumina-supported phosphoric acid and cellulose-supported sulfonic acid as solid heterogeneous catalysts under solvent-free conditions. It was also demonstrated that all the solid acid catalysts could be recycled and reused for at least three times without any significant loss in yield.
activity. An analogous method was reported by L. Wu, where condensation of the starting materials was effected using Zr(HSO₄)₄ as an acid promoter under solvent-free conditions. M. Esmaeilpour et al. developed an efficient Fe₃O₄@SiO₂-imid-PMA nanocatalyst for the synthesis of quinazolinone derivatives by the condensation of isatoic anhydride with 2-aminoazaaromatic heterocycles and aldehydes under ultrasonic irradiation or reflux conditions. A brief comparison of the reported methods in terms of reaction time and yields is shown in Scheme 112.

According to the authors, these methods follow a common mechanistic pathway, in which an acid–base interaction between catalyst and isatoic anhydride is suggested as the initial step to generate reactive intermediate 352a, which undergoes nucleophilic attack on the carbonyl carbon by AAH 3. Intermediate 352c obtained after the decarboxylation of 2-amino-N-substituted-amide 352b reacts with the activated carbonyl group of aldehydes 4 to form imine intermediate 352d with the removal of a water molecule. Intramolecular nucleophilic attack of the amide nitrogen on the activated imine carbon leads to the cyclized structure, which then affords the desired quinazolinone derivatives 352 through a 1,5-proton transfer rearrangement reaction (Scheme 113).

In contrast to the acid-catalyzed reactions discussed above, a catalyst-free approach for the synthesis of these heterocyclic compounds was developed by J. M. Khurana and S. Kumar. The strategy involved heating a mixture containing the starting materials in water–ethanol 1 : 1 (v/v) system at 80 °C for 30 min. The corresponding products, 2,3-dihydro quinazolin-4(1H)-ones 354, were produced with excellent yields in the range of 81–94%. The versatility of this methodology can be inferred from the smooth incorporation of a range of aromatic, aliphatic and heteroaromatic aldehydes 4, as well as substituted and unsubstituted isatoic anhydrides 353 in the multi-component condensation reaction (Scheme 114).

A relevant but less saturated quinazolinone ring was constructed by A. Khalaft-Nezhad et al. through a different method, which employed acetic anhydride 355, anthranilic acid 356 and...
various AAH $347$. The use of anthranilic acid plays a crucial role in this three-component reaction as it possesses the desired amino functionalities at the ortho position, which is essential for the cyclisation step in quinazolinone ring formation. In the presence of a catalytic amount of titanium dioxide nanoparticles, the condensation reaction among the starting components under thermal and solvent-free conditions for 8–10 h afforded quinazolinone derivatives $357$ bearing different azaheterocycles (Scheme 115). $216$ Nano-TiO$_2$ exhibited recyclable property and this property did not fade up to four consecutive runs.

S. Koroji et al. developed a microwave-assisted silica sulfuric acid-catalyzed one-pot synthesis of novel 3-{benzo[$d$]thiazol-2-yl}-2-alkyl or 3-{2-benzimidazolyl}-2-alkyl quinazolin-4(3H)-one $360$. This three-component reaction was performed by heating a solventless mixture of 2-aminobenzothiazole/2-aminobenzimidazole $3$, anthranilic acid $359$, and orthoesters $358$ under microwave irradiation operating at 600 W (Scheme 116). $217$

### 2.1.2.3 MCRs involving dialkylacetylene dicarboxylate (DAAD) substrate.

Aromatic aminoazaheterocycles also act as 1,1-binucleophiles in various reported methods, where dialkylacetylenedicarboxylates are used as one of the participating components in the MCR. Accordingly, M. Aary-Abbasinejad and coworkers discovered a new and efficient one-pot synthesis of polysubstituted pyrrole derivatives via the triphenylphosphine-
promoted three-component reaction between dialkylacetylenedicarboxylates 362, aryglyoxals 361 and 2-aminothiazole/2-aminobenzothiazole 22/3b. The reactions were performed in dichloromethane at room temperature under neutral conditions, affording pyrrole derivatives with good yields in 24 h. The mechanistic route to the highly substituted pyrrole derivative was suggested to start with the formation of phosphorane, a phosphorus ylide, from triphenylphosphine, DAAD and 2-aminothiazole/benzothiazole, and in a subsequent step, it was assumed that the ylide reacts with aryglyoxal in a Wittig manner to afford intermediate 363. The final pyroles 364 and 365 were achieved by the intramolecular cyclisation of intermediate 363 followed by dehydration (Scheme 117).

M. A. Ghasemzadeh et al. developed an inexpensive and green protocol to access polyfunctionalized 2-pyrrolidinones 367 via a four-component reaction using a heterogeneous magnetic nanocatalyst. When a solvent-free mixture containing 2-aminobenzothiazole 3b, dimethyl acetylenedicarboxylate 323, aromatic aldehyde 4 and piperidine/morpholine 366 was heated in the presence of Fe₃O₄/L-arginine nanoparticles at 80 °C, 2-pyrrolidinones 367 were obtained in excellent yields (Scheme 118). As a magnetic nanocatalyst, Fe₃O₄/L-arginine can be easily retrievable, and therefore reusable for many times.

H. Gao et al. developed a method involving an intermediate, also known as a Huisgen 1,4-dipole after the name of the scientist who first described it, formed by the addition reactions of nitrogen-containing heterocycles to electron-deficient alkynes. The applicability of this intermediate was shown by synthesizing functionalized 2-pyrrolidinones 368 and morpholinium/piperidinium 2-pyrrolidinon-3-olates 369 via the four-component reaction of 2-aminobenzothiazole 3b, aromatic aldehydes 4, acetylenedicarboxylate 362 and piperidine/morpholine 366. Firstly, the Huisgen 1,4-dipole is obtained by mixing acetylenedicarboxylate 362 and piperidine/morpholine 366 at room temperature in ethanol, and then the

Scheme 120 Proposed mechanism for the formation of pyrrolidinones.

Scheme 121 Synthesis of novel functionalized dihydroimidazo[2,1-a]isoquinolines and dihydroimidazo[2,1-a] quinolines.
reaction is further conducted with the remaining reactants toward the target compounds at moderate temperature. The reaction was stirred for two days to get both products in satisfactory yields. Moreover, the acid catalyst PTSA was required for the synthesis of morpholinium/piperidinium 2-pyrrolidinon-3-olates, showing the path-dependent nature of the reaction (Scheme 119).

The mechanism proposed by the authors to explain the reaction pathway is based on the initial formation of 1,3-dipolar intermediate 368a from secondary amine and DAAD and imine intermediate 368b from aldehyde and 2-amino-benzothiazole 3b. Intermediate 368c formed by the nucleophilic addition of 1,3-dipolar intermediate 368a to imine 368b experiences intramolecular nucleophilic attack from the amino group to carbonyl carbon, which produces polysubstituted pyrrolidinone ring 368. The enamine functionality of pyrrolidinone undergoes hydrolysis in the presence of PTSA to yield pyrrolinedione 368d, which rearranges through keto-enol tautomerism to the more stable enol-form, connecting both the ester and amide groups. Being acidic in nature the hydroxyl proton of the enol form is deprotonated by piperidine in solution to give piperidinium 2-pyrrolidinon-3-olate 369 as the final product (Scheme 120).

A closely related reaction based on the use of the 1,3-dipolar intermediate, which allows the construction of a fused imidazole ring, was reported by S. Arab-Salmanabadi and coworkers. Their approach gave a way to access a series of novel functionalized quinolones and isoquinoline-fused dihydroimidazoles 372 and 373 in excellent yields via the three-component reaction of isoquinoline 370 or quinoline 371 derivatives, DAAD 362 and 2-aminobenzothiazole 3b in dichloromethane at ambient temperature under catalyst-free conditions. The plausible rationalized path deduced to explain the product formation was assumed to begin with the formation of the zwitterionic intermediate or 1,3-dipolar intermediate 373a from isoquinoline 371 and DAAD 362. A proton from the amino group of 2-aminobenzothiazole 3b is then transferred to neutralize the negative charge of the zwitterion. Amide ion 373b formed from 2-aminobenzothiazole 3a adds to the isoquinolinium 373c system to generate intermediate 373d, which upon cyclisation and subsequent removal of alcohol affords the desired five-membered nitrogen-containing heterocycles 373 (Scheme 121).

A totally different approach for the synthesis of seven-membered nitrogen-containing heterocycles involving a 1,3-dipolar intermediate was described by K. Ramesh et al., in which dimethyl/diethyl acetylenedicarboxylate 362, 2-
aminopyridine 117 and 2,5-dimethoxytetrahydrofuran 374 were mixed in neutral water. Various cyclodextrins such as α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, 2-hydroxy propyl β-cyclodextrin and methyl-β-cyclodextrin were examined for their efficiency as promoters. However, the corresponding azepine 375 rings were formed in excellent yields with β-cyclodextrin (β-CD) and expensive γ-cyclodextrin (γ-CD), which were discarded as the reaction promoter. This approach was not extended to other AAH as use of 2-aminobenzothiazole 3b instead of 2-aminopyridine 117 did not yield any product. Further, only a small loss in activity of β-CD was observed after three successive runs, which indicated its recyclable and reusable nature as the reaction promoter (Scheme 122). The formation of substituted azepine 375 in the presence of β-CD was evidently suggested by authors through the inclusion complex between 2-aminopyridine 117 and β-CD, which was facilitated by the hydrophobic environment of the cyclodextrin. The primary and secondary-OH groups of CDs help in stabilizing the carbanion of 1,3-dipolar-type intermediate 375a, which further attacks 2,5-dimethoxytetrahydrofuran, leading to the opening of the furan ring. The succeeding step involves intramolecular cyclisation followed by the elimination of an alcohol molecule (Scheme 123).

2.1.2.4 MCRs involving mercaptocarboxylic acid substrates.

Due to the presence of two functional groups on same carbon atom with opposite nature, α-mercaptocarboxylic acid finds extensive application as a prominent precursor in MCRs for the synthesis of thiazolidinone scaffolds. A. Dandia et al. disclosed the ‘on water’ synthesis of a spiro-thiazolidinone ring system using a phase transfer catalyst under ultrasonic waves. This ultrasound-promoted diversity oriented three-component approach was realized using different isatins 142, various aminoazoles 347 and α-mercaptocarboxylic acids 379 with a catalytic amount of cetyltrimethylammonium bromide (CTAB) at 80 °C. After 40–50 min irradiation of the reaction mixture, the corresponding spiro indole-linked thiazolidinone derivatives 380 were obtained in excellent yield (∼90%) (Scheme 124, Method A). The job of this micellar CTAB catalyst is to overcome the hydrophobic effect and increase the ease of solubility of the starting materials. In 2014, CTAB was used as a surfactant by M. Singh et al. to synthesize triazole-linked thiazolidinone hybrids.
In this methodology, isatin was replaced with aromatic aldehydes and the reaction was conducted in aqueous medium employing acetic acid as the organocatalyst. The starting materials, different aldehydes, 3-amino-1,2,4-triazole and \( \alpha \)-mercaptocarboxylic acids were heated in a conventional way and the temperature was maintained at 60°C for 20–35 min (Scheme 124, Method B).

They also assessed the effect of several surfactants on the yield and reaction time of the reaction, but suitable results were given by CTAB for the synthesis of the target compounds.

The mechanistic course of these CTAB-based reactions is shown in Scheme 125. The mechanism starts with the formation of Schiff bases in aqueous micellar medium from heterocyclic amine and carbonyl compounds (aldehydes).

Scheme 126 Construction of non-spiro thiazolidinones and spiro-linked triazole ring.

Scheme 127 Two different methods to synthesize thiazolidinone ring system.

Scheme 128 Microwave-assisted synthesis of chromone-based thiazolidinones.
and isatin), which experience \textit{in situ} nucleophilic attack from the sulfur atom of 2-mercaptocarboxylic acid 379 followed by intramolecular cyclization with the elimination of a water to afford the desired thiazolidinone derivatives 380. All the steps of the reaction sequence in the formation of the triazole-linked thiazolidinone hybrids were triggered by acetic acid, while ultrasonic waves were utilized to promote the synthesis of spiro linked thiazolidinones.

A closely related MCR approach that allows the construction of non-spiro thiazolidinone and spiro triazole rings was described by W. S. Hamama \textit{et al.} under suitable reaction conditions. The MCR for the synthesis of thiazolidinone 383 was conducted by heating 2-amino-1,3,4-thiadiazole 108, a specific aldehyde, 1,3-diphenyl-1H-pyrazole-5-carbaldehyde 382 and mercaptoacetic acid 381 in pyridine at reflux for 19 h.\textsuperscript{226} Conversely, when \textit{p}-methoxybenzaldehyde 384 was used as aldehydic component, while retaining the other two components intact in toluene, the reaction led to the formation of thiazolidinone \textit{via} intermediate 386. The spiro-linked triazole moiety was constituted by refluxing 2-amino-1,3,4-thiadiazole 109, isatin 143 and thiosemicarbazide 387 in an ethanol/acetic acid mixture in a 9 : 1 proportion for 20 h. The formation of spiro compound \textit{via} intermediate 388 is then attacked by thiosemicarbazide 387 and subsequent cyclocondensation affords intermediate 388a, the acetylation of which gives the final product (Scheme 126).

Further progress in the field of utilizing mercaptoacetic acid 381 in the multicomponent synthesis of thiazolidinone ring system 391 was made by D. Kumar and coworkers. They investigated various catalytic potential solid supported protic acids for the one-pot tandem condensation-cyclisation reaction involving benzaldehyde 4, five- or six-membered azaheterocyclic amine 347 and thioglycolic acid 381 (Scheme 127, Method A).\textsuperscript{227} The use of silica gel with a mesh size of 230–400 as a solid support revealed that their relative activity follows the order of HClO$_4$–SiO$_2$ > TfOH–SiO$_2$ > $p$-TsOH–SiO$_2$ > MsOH–SiO$_2$ > HBF$_4$–SiO$_2$ > TFA–SiO$_2$ > HOAc–SiO$_2$. Further, they designed and performed some reactions to make a clear distinction between the superiority of two heterogeneous catalyst systems, HClO$_4$–SiO$_2$ and TfOH–SiO$_2$, which appear closely related in activity order. The superior catalytic power of the former compared to that of the latter in terms of providing product yield was established from two sets of reactions run for 5 h, one with 2-aminopyridine and the other with 2-amino-benzothiazole, while benzaldehyde 4 and mercaptoacetic acid 381 were common to both. With HClO$_4$–SiO$_2$, the products were obtained in 70% and 69% yield in comparison to 52% and 35% yield when TfOH–SiO$_2$ was employed, respectively. In 2016, the

![Scheme 129](image1.png) **Scheme 129** Synthesis of thiazolidine ring-linked indeno[1,2-b]quinoxaline.

![Scheme 130](image2.png) **Scheme 130** Four-component synthesis of tetra-substituted imidazoles under different conditions.

![Scheme 131](image3.png) **Scheme 131** Proposed mechanistic route to tetra-substituted imidazoles.
same reaction, which was catalyzed by ammonium persulfate (APS), was utilized by S. Ebrahimi for the preparation of thiazolidinone ring 390-bearing triazole and p-nitrophenyl substituents via heating a reaction mixture containing 3-amino-1,2,4-triazole, p-nitrobenzaldehydes and mercaptoacetic acid 381 at 90 °C under solvent-free conditions for 60 min (Scheme 127, Method B).

Next, the synthesis of chromone-based thiazolidinone ring 393 was reported in the article published by N. M. Drosos et al., wherein a mixture containing mercaptoacetic acid 379 and its 2-methyl derivative with various 3-formylchromones 392 and 2-aminobenzimidazole 3a was irradiated with microwaves at 100 °C. The corresponding products were obtained after 80 min in moderate to good yields (Scheme 128). They also constructed the same five-membered sulfur-containing ring but with low yield (33–51%) through a two-step synthetic route and a comparison between the two approaches was established.

Recently, R. Singh et al. synthesized new spiro[indeno[1,2-b]quinoxaline-[11,20]-thiazolidine]-40-one 395 via a multi-component approach.230 The reaction between indeno[1,2-b]quinolininone, 2-mercaptoacrylic acid 381 and 2-aminobenzothiazole 3a was conducted in urea-choline chloride 394 as a green deep eutectic solvent using carbon-SO3H as a solid acid catalyst, resulting in the formation of a thiazolidine ring attached to indeno[1,2-b]quinolininone through spiro carbon in 90% yield (Scheme 129). Both the catalyst and DES could be recovered from the reaction mixture quantitatively, and thus reused several times without a significant loss in activity.

2.1.2.5 MCRs involving miscellaneous substrates. In this section, we describe MCRs based on reagents that cannot be categorized in a particular section. The first example includes the synthesis of substituted imidazole derivatives 399 by K. Ramesh et al. through easily available starting materials, benzaldehyde 4, ammonium acetate 397, 2-aminothiazole/2-aminobenzothiazole/2-aminopyridine and benzil 398. This four-component imidazole synthesis was achieved in acetonitrile solvent using a bioglycerol-supported carbon catalyst at moderate temperature (Scheme 130, Method A).

One year later, the same combination of reactants was also utilized by B. Zhao et al. for the ionic liquid-based synthesis of tetrasubstituted imidazole derivatives 396. This 1-butyl-3-methylimidazolium bromide [Bmin]Br-promoted one-pot synthesis of tetraaryl imidazole framework 396 was accomplished by reacting 2-aminothiazole 22, aromatic aldehyde 4, ammonium acetate 397 and benzil 398 at 140 °C (Scheme 130, Method B).

A common mechanism for the synthesis of highly substituted imidazoles 396 is shown in Scheme 131. It was suggested that the reaction proceeds via diamine intermediate 396a, which is formed by the addition of ammonium acetate 397 and heterocyclic amine 347 to the activated carbonyl carbon...
of aldehyde 4. The desired product is obtained from this diamine intermediate 396a, which is condensed with 1,2-diketone 398 with the removal of two molecules of water followed by rearrangement.

M. Kumar et al. synthesized structurally diverse 3-benzothiazolyl-2-styrylquinazolinones through a one-pot three-component sequential synthetic method by taking advantage of ionic liquids in terms of their unique solvating, catalytic and

| Reaction condition                  | Time    | Yield (%) | No. of examples | Reference |
|------------------------------------|---------|-----------|-----------------|-----------|
| SDS (20 mol%), H2O, 100 °C         | 1–3 h   | 71–93     | 16              | 235       |
| NaHSO4·H2O (10 mol%), 100 °C       | 4–30 min| 52–95     | 26              | 236       |
| H2O/HPA (3 mol%), 45 °C            | 1–2 h   | 62–92     | 15              | 237       |
| (RHA)-[pmim]HSO4 100 °C           | 3–5 min | 87–94     | 16              | 238       |
| Hydrotalcite or KOH/MgO, 70 °C     | 2–3.5 h | 72–93     | 11              | 239       |
| Oxalic acid (20 mol%), 80 °C       | 4–30 min| 57–96     | 24              | 240       |
| MPIL B (1 mol%), 45 °C             | 3–10 min| 87–96     | 13              | 241       |
| NH3(CH2)nNH3BiCl3 (0.1 mol%), 100 °C| 7–50 min| 79–99     | 7               | 242       |
| Fe3O4@SiO2-Propyl-Pip-SO2H·HSO4, 100 °C | 5–20 min| 90–98     | 19              | 243       |
| γ-Aminobutyric acid (10 mol%), MW, 100 °C | 5 min   | 87–97     | 15              | 244       |
| Isinglass, 110 °C                  | 85–125 min| 80–95     |                 |           |
| Fe3O4@SiO2-(CH2)2-Urea-SO2H·HCl, 90–95 °C | 15–50 min| 70–96     | 16              | 245       |
| Fe3O4@SiO2-ZrCl2-MNPs, 100 °C      | 7–25 min| 88–95     | 14              | 246       |
| rMGO-Au NPs, 50 °C                 | 25–45 min| 85–88     | 3               | 247       |

Scheme 135 Various reported methods for the synthesis of Betti’s base derivatives.
recycling abilities. Initially, 2-methyl-3,1-benzoxazin-4-one 400 and 2-aminobenzothiazoles 344 were combined with the help of \( \text{SO}_3\text{H-functionalized ionic liquids} \) (SFILs I and II) at 80 °C, and the further addition of aromatic aldehyde 4 was done after 4–7 h when the reaction mixture showed the spot of 3-benzothiazolyl-substituted quinazolinone derivatives 402 on a TLC plate (Scheme 132). The mixture was maintained at 80 °C until the condensation of aldehyde, leading to the benzothiazole and styryl-linked quinazolinones as the final product. The investigation pertaining to the recyclability of SFIL I and II in terms of providing yield and overall reaction time revealed that no appreciable loss in activity there occurred for least consecutive five cycles. The authors also suggested a mechanism to explain the synthesis of 3-benzothiazolyl-2-styrylquinazolinones, as shown in Scheme 133.

The simplest aldehyde, formaldehyde 403, was used in a three-component reaction with 2-aminobenzothiazole 3b and phenol 404 to construct benzothiazole tethered benzoxazine ring 405 by F. Shan and coworkers. The mixture containing the reactants was heated under solvent-free conditions at 120 °C for 2 h to afford the desired product in 16% yield (Scheme 134). The same reaction when carried out with 2-aminothiazole was found to be unsuccessful.
2.2. Aromatic α-aminoazaheterocycles as mononucleophiles

2.2.1 MCRs involving β-naphthol and analogous substrate (synthesis of Betti’s base). The preparation of Betti’s base and its derivatives is an important area in synthetic chemistry because it involves the formation of C–C and C–N bonds under mild experimental conditions. A significant number of approaches have been developed since 2010 based on the use of various types of catalysts together with some catalyst-free methods. The starting materials include compounds possessing a nucleophilic carbon such as naphthols, quinolinols, and indoles, an amine and aldehydes, which when combined lead to Betti’s bases via the formation of a highly reactive intermediate known as o-quinone methides (o-QMs). Moreover, Betti’s base derivatives have also provided convenient access to many useful synthetic building blocks via the amino and phenolic hydroxy functional groups. In 2010, A. Kumar et al. reported a green approach utilizing sodium dodecyl sulfate (SDS) as a mild Brønsted acid, which provides a micellar environment for organic starting materials to help them solubilize in water. This strategy involves heating an aqueous mixture of 2-naphthol and aldehydes 4 and 2-aminobenzothiazole 3b together with 20 mol% of SDS at 100 °C for 1–3 h, resulting in the construction of C–C and C–N bonds. Since then, a number of reactions have been carried out for the synthesis of 1-(benzothiazolylamino)methyl-2-naphthol derivatives based on the same platform with the help of catalysts/promoters such as NaHSO4·H2O,296 heteropolyacid (HPA) as a heterogenous catalyst,297 rice husk ash (RHA)-supported 1-methyl-3-(trimethoxysilylpropyl)-imidazoliun hydrogen sulfate (RHA-[pmim][HSO4]) as an acidic ionic liquid,298 KOH-loaded MgO/hydrotalcite as a basic catalyst,299 oxalic acid as an organocatalyst,300 MPIL B,301 NH3(CH2)3NH3BiCl5,302 Fe3O4@SiO2-Propyl-Pip-SO3H·HSO4,303 γ-aminobutyric acid and isinglass a collagen peptide,304 Fe3O4@SiO2-(CH2)4-urea-SO3H/HCl,305 Fe3O4@SiO2-ZrCl2-MNPs,306 and (rMGO)-Au NPs (Scheme 135). The reaction mechanism for the formation of Betti’s base proceeds though an o-QM intermediate 407a, which is generated from the condensation of 2-naphthol with aldehyde in the presence of a suitable catalyst. Next, a Michael addition reaction occurs, in which 2-aminobenzothiazole 3b in the form of a nucleophile is added to intermediate 407a to afford the final product with the removal of a water molecule as the side product.

Besides these catalytic systems, some interesting and unique feature-embedded catalysts have also been reported to function as reaction promoters. Trichloroisocyanuric acid (TCCA)307 and N-bromosuccinimide (NBS)308 were successfully used to catalyze the three-component synthesis of 1-(benzothiazolylamino)methyl-2-naphthol derivatives. TCCA and NBS undergo in situ release of electrophilic species, Cl+ and Br+ ions, respectively, which make the condensation between 2-naphthol and aldehydes 4 and 2-aminobenzothiazole 3b possible.
and aldehydes 4 easier by increasing the electrophilicity of the carbonyl carbon of the aldehyde (Scheme 136).

P. K. Kalavagunta and coworkers performed the same reaction under catalyst- and solvent-free conditions. Another merit of this approach is that besides simple 2-aminobenzothiazole 3b, it can successfully incorporate a few other derivatives. This simple synthetic procedure was accomplished by maintaining the temperature of the reaction mixture containing 2-aminobenzothiazole 3b, 2-naphthol 406 and various types of aldehydes 3 at around 100–120 °C for 40–50 min (Scheme 137, Method A). The prepared derivatives were screened for their angiotensin-converting-enzyme (ACE) inhibition property and calcium channel blocker (CCB) property. The compounds synthesized using the 4-methoxybenzaldehyde, 2-aminobenzothiazole and 2-naphthol combination and 4-methoxybenzaldehyde, 4-chloro-2-aminobenzothiazole and 2-naphthol combination were found to be active against ACE inhibition and CCB. They further synthesized some more hybrid molecules using the same methodology and identified a novel class of synthetic molecules that do not belong to organochlorides, organophosphates, carbamates, neonicotinoids, and anthranilamides as potent antifeedants and insecticides. In addition, B. Nagaraju et al. also reported a simple and catalyst-free approach, wherein 2-aminobenzothiazoles, 2-naphthol 406

| Reaction conditions       | Time  | Yield (%) | No. of examples | Reference |
|---------------------------|-------|-----------|-----------------|-----------|
| Fe3O4@MCM-48-SO3H,       | 1–3 min | 91–98     | 10              | 256       |
| RT                       |       |           |                 |           |
| Catalyst-free, solvent-free, 125 °C, | 1–6 min | 87–94     | 11              | 257       |
| Montmorillonite K-10 (10 mol%), EtOH, RT | 8–10 h   | 81–93     | 20              | 258       |

Scheme 141  Different methods to synthesize Betti’s base utilizing six-membered heterocyclic amine components.

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| Fe3O4@MCM-48-SO3H,       | 1–3 min | 91–98     | 10              | 256       |
| RT                       |       |           |                 |           |
| Catalyst-free, solvent-free, 125 °C, | 1–6 min | 87–94     | 11              | 257       |
| Montmorillonite K-10 (10 mol%), EtOH, RT | 8–10 h   | 81–93     | 20              | 258       |

Scheme 141  Different methods to synthesize Betti’s base utilizing six-membered heterocyclic amine components.
and various heteroaryl aldehydes 4 and 324 were taken in methanol and heated under reflux to afford a series of novel pyrazole-linked benzothiazole-β-naphthols 409 (Scheme 137, Method B). The synthesized compounds were also evaluated for their cytotoxicity against human cervical cancer cells (HeLa), wherein some derivatives exhibited considerable cytotoxicity with IC50 values ranging between 4.63 and 5.54 μM.

Analogous to 2-naphthol 406, 6-hydroxyquinoline 410 also works as a key component, acting as a carbon nucleophile, in Betti’s base synthesis. P. K. Sahu et al. depicted a clear picture of the reaction profile of 6-hydroxyquinoline 410 and 2-naphthol 406 in the context of utilizing them in the three-component reaction. Their investigation on the modal reaction showed that among the solvents, the reaction proceeded well in water with a significant yield isolated after 8 h without the aid of a catalyst. Furthermore, the solubility of the organic starting materials was enhanced by using surfactants, which allowed the formation of an emulsion between them. Among the surfactants and catalysts used for this purpose, sodium lauryl sulphate (SLS) gave the best result when the reaction was executed using aromatic aldehydes 4, 2-aminobenzothiazole 3b and 2-naphthol/6-hydroxyquinoline 406/410 at room temperature in water. A non-ionic surfactant, Triton X-100, provided a significant yield but required a long time, while cetrimide, also an effective promoter, was not explored as it is expensive and toxic to marine organisms. The usual mechanism of this reaction as described by the authors is shown in Scheme 138.

M. Dabiri’s group utilized 2-hydroxynaphthalene-1,4-dione 105 as a replacement for 2-naphthol 406 in the same reaction to establish a simple route to some novel Betti’s bases. In this approach, 2-aminobenzimidazole 3a and 2-aminopyridine 117 were used as amino components and the three-component...
reaction was catalyzed by InCl₃.²⁵⁴ For the preparation of 3-substituted hydroxy naphthalene-1,4-dione derivatives 412, an assembly of 2-hydroxynaphthalene-1,4-dione 105, aldehydes 4 and 2-aminobenzimidazole 3a or 2-aminopyridine 117 in water was refluxed for 4–6 h in the presence of 20 mol% of InCl₃ (Scheme 139, Method A). Another case wherein 2-aminopyridine 117 and 2-aminopyrimidine 116 act as amine components and kojic acid 413 as an interesting alternative to 2-naphthol 406 together with aldehydes 4 employed in Betti’s reaction was developed by R. Teimuri-Mofrad et al. under ball milling conditions. Ball-milling requires less time as intense grinding of reacting component is carried out under solvent-free conditions, and therefore has attracted significant attention as a green synthetic tool. For the preparation of Betti’s base framework 415 through this one-pot strategy, kojic acid 413, aromatic aldehydes 3 and heteroaromatic amines 347 were ground at room temperature together with a catalytic amount of cerium(III)sulphate.²⁵⁵ Utilization of terephthaldehyde 414 with kojic acid 413 and 2-aminopyrimidine 117 or 2-aminopyridine 116 under the same reaction conditions led to the formation of an interesting compound 416 in which two Betti’s bases were attached through a phenyl ring of 1,4-benzendialdehyde (Scheme 139, Method B).

A reasonable possibility through which the reaction yielded products as proposed by the authors is based on the Mannich reaction. A Lewis acid–base interaction between the catalyst and the oxygen of the carbonyl group of aldehydes 4 was proposed, which increases the electrophilicity of the carbonyl carbon and allows easy nucleophilic attack by the amine 347 component to form imine intermediate 415a. This imine intermediate 415a is then attacked by kojic acid 413 or 2-hydroxynaphthalene-1,4-dione 105 in the subsequent step, leading to the formation of the final product 415 (Scheme 140).

M. Golsheskan and coworkers developed another synthetic route to Betti’s base based on the Mannich reaction utilizing 2-aminopyridine, 2-aminopyrimidine and 2-aminopyridazine as six-membered heterocyclic amine components. The magnetic core was made up of Fe₃O₄ nanoparticles coated by MCM-48 mesoporous silica as a thin layer and the functional groups of sulfonic acid (Fe₃O₄@MCM-48-NaHSO₄) were used as the catalyst to drive the reaction. The stirring of three components, heterocyclic amine 347, aldehyde 4 and 2-naphthol 406, in one pot together with the catalyst at room temperature for 1–3 min was found to be sufficient to provide target products 417 in excellent yields.²⁵⁶ Next, the group of A. Olyaei synthesized
aminonaphthol (Betti’s base) through a similar strategy, in which the same starting materials were heated at 125 °C under catalyst- and solvent-free conditions. In addition, S. Jayashree and K. Shivashankar also performed the same reaction in the presence of montmorillonite K-10 using ethanol as the solvent at room temperature. The reaction conditions, time and range of yields of these methods are summarized in Scheme 141.

A mild, efficient and straightforward method was developed by A. Olyaei and M. Rezaei to synthesize novel bis-Betti’s bases via a pseudo five-component reaction. This one-pot condensation reaction was performed with terephthaldehyde and two molecules of each heteroaryl amines and naphthols in the presence of 10 mol% formic acid under solvent-free conditions at 80 °C (Scheme 142).

The same authors investigated a variation of this reaction, where the aldehyde group of glyoxalic acid was allowed to take part in the three-component Betti’s base synthesis. In this method, a mixture containing heteroarylamines (2-amino-pyrimidine, 2-aminopyrazine, 2-aminopyridine and 2-amino-thiazole), glyoxalic acid and naphthols in water was allowed to interact either at room temperature or under reflux conditions (Scheme 143). A direct consequence of using glyoxalic acid led to the formation of amino acid-type framework. After this method was screened at two temperatures, it was found that the reaction performed at room temperature, which took slightly longer time in some cases, has the advantages of simplicity of the procedure, clean and easy product separation by filtration, whereas sticky mixtures were obtained together with the products on refluxing the reaction mixture. Further, it was also observed that increasing the temperature did not improve the yield of the products significantly. The Mannich-type mechanism was suggested based on the conclusion drawn from two reactions, the reaction of 2-naphthol with glyoxalic acid, which did not yield any condensed product after several hours, and the reaction of heteroaryl-amines with glyoxalic acid, which resulted in an iminoacid intermediate. Hence, it is apparent that the in situ generation of iminoacid from the reaction of amine and glyoxalic acid followed by the reaction with 2-naphthol is the actual route through which α-naphthylglycine is obtained.

In continuation, the same research group published an article wherein indole was demonstrated as an alternative component to naphthols in the three-component synthesis of Betti’s base. The synthesis of α-aminoindoles was achieved through the one-pot coupling reactions of indole, aromatic

![Scheme 149](image)

Methods developed by C. B. Reddy and coworkers to synthesize α-aminophosphonates.

![Scheme 150](image)

Different methods involving dialkylphosphite to synthesize α-aminophosphonates.
aldehydes 4 and heteroaryl amines 347 under catalyst- and solvent-free conditions at 80 °C (Scheme 144, Method A). The precipitation of the products was carried out by adding water and ethanol to the reaction mixture after the reaction was completed. In 2012, S. Ke et al. synthesized some more novel \( \alpha \)-aminoindoles 423 by conducting the same catalyst- and solvent-free reaction with 2-aminopyridine/2-aminothiazole, indole and its \( N \)-methyl derivatives and various aldehydes 4 (Scheme 144, Method B). The reaction was completed in a very short time compared to Method A. Moreover, some of the newly synthesized compounds displayed significant inhibition against cell proliferation.

In 2014, R. Ghorbani-Vaghei et al. performed the same one-pot three-component reaction in the presence of poly(N-bromo-N-ethylbenzene-1,3-disulfonylamide) (PBBS) 424 or \( N,N',N',N' \)-tetramethyltetramethoxyphenylbenzene-1,3-disulfonylamide (TBBDA) 224 under solid-state conditions at room temperature. Both catalysts possess comparable activity in catalyzing this MCR involving six-membered heterocyclic amines 347, aldehydes 4 and indole 422 to afford the final product as \( \alpha \)-aminoindoles 421. The first step of the mechanism proposed for this transformation consists of the reaction between the amine and aldehyde catalyzed by the in situ-generated bromonium ion from TBBDA 224 or PBBS 424, which acts as electrophilic species to give imine as the intermediate. This intermediate then experiences nucleophilic attack by indole, followed by rearrangement to produce the final structure (Scheme 145).

Recently, A. Olyaei et al. developed an efficient and straightforward approach utilizing triethyl orthoformate 70 instead of aldehydes 4 with heteroaryl amines 347 and \( 4 \)-hydroxycoumarin 92 in a three-component reaction to afford novel \((Z/E)-3-\)([heteroaryl]amino)methylene]-chromane-2,4-dione derivatives 425 and 426. This one-pot condensation between the reacting components was conducted in the presence of guanidinium chloride as the organocatalyst under solvent-free conditions (Scheme 146). NMR studies showed that coumarin enamines exist in the ketoenamine tautomeric form and undergo \( Z/E \)-isomerization with respect to the C=C bond in CDCl\(_3\) and DMSO-d6 at room temperature. Furthermore, the synthesized compounds involve intramolecular hydrogen bonds.

2.2.2 MCRs involving trialklyphosphite and analogous substrates (Kabachnik–Fields reaction). The Kabachnik–Fields reaction is an analogue to the three-component Betti’s base reaction except a carbon nucleophilic component is replaced by the substrate acting as a phosphorus nucleophile, because of which \( \alpha \)-aminophosphonates are obtained. According to the literature survey, significant work on the Kabachnik–Fields reaction has been done over the past years given that the products of this reaction represent an important class of bioactive molecules. In this context, M. Lashkari et al. described a \( \alpha \)-aminophosphonate synthesis 428 based on the one-pot condensation reaction among 2-aminobenzothiazole 3b, aldehydes 4, and triethylphosphite 427 in the presence of InCl\(_3\) as a catalyst. This reaction, which was carried out under neat conditions, required heating at 110 °C for 10–16 min, affording the final product in 70–89% yield. The reaction pathway became smooth in the presence of InCl\(_3\) as it facilitates the formation of imine 428a by the condensation of 2-aminobenzothiazole 3b with aldehyde 4, which undergoes the addition of triethylphosphite 427 across the C–N double bond of the activated imine followed by the reaction with water generated during the formation of imine to give \( \alpha \)-amino phosphonates 428 and EtOH (Scheme 147).

In an analogous method, the acidic ionic liquid-mediated reaction among 2-aminopyridine 117, 4-methoxybenzaldehyde 429 and trimethylphosphite 427 was investigated by D. Fang and coworkers, which afforded the corresponding \( \alpha \)-aminophosphonate 430 in 82% yield (Scheme 148). The ionic liquid ([TMPSA][HSO\(_4\)], which catalyzed the reaction, was found to be recyclable and reusable for at least six times without significant decrease in its catalytic activity.

In 2012, C. B. Reddy and coworkers explored the same reaction via a PEG–SO\(_4\)H–catalysed pathway involving 4-(pyridin-4-yl)benzaldehyde 431 as an aldehydic component, 2-aminothiazole 22 and 2-aminobenzothiazole 3b derivatives as heterocyclic amines and triethylphosphite 427. This strategy involves heating the reaction mixture of all the components using toluene as the solvent for 4–6 h in the presence of the required amount of catalyst, which afforded product 432 in 82–89% yield (Scheme 149, Method A). One year later, the same group of researchers developed a microwave-assisted variant of the same three-component reaction under solvent-free conditions in the presence of cupric acetate monohydrate (Cu(OAc)\(_2\).H\(_2\)O) as a catalyst (Scheme 149, Method B).
Following the success of the above-mentioned strategies, the same research reported a nano-titanium dioxide-catalyzed one-pot solvent-free Kabachnik–Fields reaction, wherein trialkylphosphite is replaced by dialkylphosphite. The three-component reaction was conducted using 2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde 434, various heterocyclic amines 347 and dimethyl phosphite 435 at 50 °C for 12–15 min to obtain the novel α-aminophosphonates 433 (Scheme 150, Method A). Recently, they synthesized biologically active α-aminophosphonates 437 by reacting 7-nitro-2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde 436 with heteroaromatic amines 347, 2-amino-6-bromopyridine/2-aminobenzothiazole and dimethyl phosphite 435 in the presence of silica-supported titanium nanooxide (nano-TiO2/SiO2) as a catalyst at 50 °C (Scheme 150, Method B). In addition, C. Sampath et al. also utilized dialkylphosphite 435 to develop a polyethylene glycol (PEG-400)-mediated green protocol, in which diphenyl phosphite 445, glyoxylic acid hydrate 444, and 2-aminopyrazine 443. The corresponding α-diphenylphosphino-N-(pyrazin-2-yl)glycine 446 was achieved in 70% yield when the starting materials were stirred in either methanol or diethyl ether at room temperature (Scheme 152).

2.2.3 MCRs involving active methylene/methyl substrate. Zhang’s group developed the one-pot multicomponent synthesis of chiral β-amino acid derivatives 449 bearing a 1,3,4-thiadiazole moiety on nitrogen via a Mannich-type reaction using a chiral bifunctional organocatalyst. Moderate to excellent enantioselectivities of β-amino acid derivatives were demonstrated by M. V. N. Reddy et al. through the one-pot three-component reaction between one equivalent of each of heterocyclic amine (2-aminopyridine 117 and 2-aminothiazole 22) and triethylorthoformate 439 and two equivalents of diethyl phosphate 440. This pseudo four-component reaction was performed under 1-butyl-3-methylimidazolium chloride ([bmim][Cl]) ionic liquid-mediated ytterbium perfluorooctanoate [Yb(PFO)3]-catalyzed conditions, giving the corresponding aminomethylene bisphosphonates 441 and 442 in good yields (Scheme 151).

Recently, O. S. Soficheva et al. developed an interesting catalyst-free approach based on the three-component condensation of diphenylphosphine 445, glyoxylic acid hydrate 444, and 2-aminopyrazine 443. The corresponding α-diphenylphosphino-N-(pyrazin-2-yl)glycine 446 was achieved in 70% yield when the starting materials were stirred in either methanol or diethyl ether at room temperature (Scheme 152).

![Scheme 153](image1.png) Synthesis of chiral β-amino acid derivatives via Mannich-type reaction.

![Scheme 154](image2.png) Synthesis of hetarylamino-substituted 2,2'-spirobischromanecarboxylates and chromanecarboxylates.
obtained when 2-amino-1,3,4-thiadiazole 108, dimethyl/diethyl malonate 447 and aldehydes 4 were heated in toluene at 60 °C for 4 days using squaramide cinchona 448 alkaloid as a catalyst. As shown in Scheme 153, the mechanism proposed for the transformation starts with the initial formation of imine intermediate 449a from 2-amino-1,3,4-thiadiazole 108 and aldehyde 4. Squaramide 448 is involved in stabilizing the transition state, in which the imine is activated through hydrogen bonding and the enol form of the malonate by the interaction with the basic nitrogen atom of the tertiary amine. The enhanced reaction rate and stereochemical outcome of the reaction were speculated due to this interaction.

Another protocol utilizing an active methylene compound for the synthesis of hetarylamino-substituted 2,2'-spirobischromanecarboxylates 450 and 451 through a pseudo-four-component process under classical Biginelli reaction conditions was developed by J. Světlík and coworkers. This multi-component heterocyclization was carried out with methyl acetoacetate 453, 2-aminobenzothiazole 3b and 2 equivalent of salicylaldehyde 452 together with four drops of concentrated hydrochloric acid in ethanol under reflux (Scheme 154, Method A). The 1H NMR spectrum of the crude product showed that two diastereomers, 450 and 451, were formed, which were easily recognized due to the different positions of their H-4 resonances. Integration of the corresponding signals, being well separated from the rest of the spectrum, allowed the authors to estimate the isomer relation of 450/451 in a ratio 37 : 1, and therefore, the explored multicomponent condensation is highly diastereoselective. In 2016, the same chemists synthesized 4-hetarylamino-substituted chromanecarboxylate derivatives 453 and 454, which require mixing of an ethanolic solution containing one equivalent of each alkyl acetoacetate 453, substituted salicylaldehyde 452 and 2-aminobenzothiazole/2-aminothiadiazole/2-aminothiazoles at room temperature in the presence of a catalytic amount of L-proline for 40–45 h (Scheme 154, Method B).

Next, P. Guo et al. developed a three-component domino reaction utilizing 1,3-dicarbonyl compounds 5 and 81 as the active methylene compounds, six-membered heteroaromatic amines 347 (pyrazin-2-amine 455, pyrimidin-2-amine 456, and pyridin-2-amine 457) and phenylpropiolaldehyde 458 for the formation of unusual furan derivatives 459 and 460. This unprecedented one-pot domino reaction for the construction of C–O and C–N bonds was executed by heating a solution containing the starting components in DMF in the presence of trifluoroacetic acid as a catalyst at 80 °C for 8 h (Scheme 155). The mechanistic insight was gained by performing a controlled experiment, wherein the condensed product, formed by 3-phenylpropiolaldehyde 458 and 1,3-cyclohexanedione 81, was allowed to react with pyrazin-2-amine 455 under the optimized reaction conditions, thereby obtaining the corresponding products.

Scheme 155 Synthesis of unusual furan derivatives via TFA-catalyzed three-component domino reactions.
product in 85% yield. Based on this experiment, a plausible mechanism was proposed, which starts with a TFA-catalyzed Knoevenagel condensation reaction between the 1,3-dicarbonyl compounds and phenylpropionaldehyde. The resulting intermediate under acidic conditions undergoes intramolecular nucleophilic attack of the carbonyl oxygen over the activated triple bond, leading to the formation of a positively charged seven-membered oxygen-containing species, which upon conjugate addition of the heterocyclic amine generates the desired furan derivatives 459 and 460.

By utilizing phenylglyoxal monohydrate 461, R. Khoeiniha et al. demonstrated the efficient and eco-friendly synthesis of novel 4-keto-4,5,6,7-tetrahydrobenzofurans 462 and 463. This catalyst-free one-pot three-component condensation protocol involves the reaction among 2-aminopyridine 117 and 2-aminobenzimidazole 3b derivatives, dimedone 81, and phenylglyoxal monohydrate 461 in water under reflux. With heteroaryl amines such as 3-nitropyridine, 2-amino-4-chloro-6-methylpyrimidine, and 2-amino-4,6-dimethylpyrimidine, open ring products were formed under the same reaction conditions (Scheme 156). Mechanistically, this tandem process sequentially involves an aldol condensation, Michael addition, ring closure, and dehydration reaction.

Recently, the same research group made an extension to the above-mentioned three-component condensation protocol by replacing dimedone 81 with 4-hydroxycoumarine 92, which is allowed to react with phenylglyoxal monohydrate 461, and 2-aminopyrimidine 464/2-aminopyridines 117 in acetonitrile under reflux conditions, giving novel functionalized furo[3,2-c] coumarins. Herein, with heteroarylamines such as 6-methylpyridine, 2-amino-4-chloro-6-methylpyrimidine and 2-amino-4,6-dimethylpyrimidine, heteroarylaminol alklylation of coumarin occurs, which does not undergo closing of the ring to form furan derivatives 465 and 466 (Scheme 157).

Sulfonamide-bearing compound 467 containing a nucleophilic carbon centre adjacent to one carbonyl group as a variant of the β-dicarbonyl compound in terms of its reaction profile was combined with 2-aminopyridine 117 and ethyl orthoformate 70 by O. Yu. Korshunov et al. to synthesize an azomethine-type compound 468. This one-pot three-component reaction was executed in the presence of ethylene glycol (10 mL) at 150 °C until the distillation of ethanol stopped, and then the temperature was increased to 180 °C and maintained for 20 min (Scheme 158). Consequently, azomethyne was precipitated as a solid from the reaction mixture in 48% yield.

Some compounds that are variants of β-dicarbonyl compounds, where the methyl group is activated due to the presence of only one adjacent electron withdrawing group, have also been included in this category of MCRs. For example, acetophenone 206 was used by K. Addadi’s group to synthesize...
β-aminoketone 496 based on a calcium chloride-catalyzed one-pot three-component reaction via the Mannich reaction pathway. This transformation was carried out by heating a mixture of acetophenone 206, 2-aminothiazole 22 and benzaldehyde 4 in ethanol at 60–80 °C for 2 h with one drop of HCl and 1 equivalent of CaCl₂ (Scheme 159). A chiral centre was introduced in the final product, and therefore a racemic mixture of β-aminoketone was obtained, which was resolved with Chiralcel® OD-H column using mobile phases composed of hexane/ethanol or hexane/isopropanol or isopropanol.

Next, R. B. Patil and S. D. Sawant reported the facile and interesting Mannich reaction-based synthesis of β-aminoketones 499, 500 and 501 using 3-acetylcoumarine 497 (an important class of bioactive molecules) as an alternative to β-dicarbonyl. The reaction was performed with an ethanolic solution containing 3-acetylcoumarine, six-membered heteroaromatic amines (2-aminopyridine 117, 2-aminopyrimidine 116, and 2-aminopyridazine 498) and paraformaldehyde 35, which was refluxed together with concentrated hydrochloric acid as the catalyst (Scheme 160). The mixture obtained after 3–4 h was neutralized with aqueous ammonia and then filtered to get the solid products. The yield of the compounds was not mentioned in the research article.

Furthermore, nitromethane as a reacting component in this category of reactions was introduced by H.-X. He and coworkers in a method wherein the cinchona-based squaramide 448-catalyzed one-pot three-component enantioselective aza-Henry reaction was performed with 2-aminobenzothiazoles 3b, aldehydes 4, and nitromethane 502 in toluene at moderate temperature (Scheme 161). The corresponding β-nitro amines...
were obtained after 2 days in 46–90% yield. Some of the derivatives were further used as important intermediates for the two-step synthesis of novel compounds bearing two biologically active heterocycles through palladium-catalyzed hydrogen reduction and subsequent glutaraldehyde addition. Besides, aromatic aldehydes bearing electron-withdrawing and electron-donating substitutions and some substituted 2-amino-benzothiazoles were well tolerated by this aza-Henry reaction and provided products with good enantioselectivities.

2.2.4 MCRs involving miscellaneous substrates. In this section, we group MCRs in which aromatic \( \alpha \)-aminoazaheterocycles show their mononucleophilic nature when undergoing combination with some other substrates, which cannot be included in the above-mentioned categories, and also their reactions cannot be studied under separate headings because of the limited publications available in the literature. Acetylenic esters 362 in a three-component reaction with 2-amino-benzothiazole 3b and various isocyanides 261 at room temperature using dichloromethane as the solvent afforded highly functionalized azadienes 504. This catalyst-free strategy under mild reaction conditions was developed by I. Yavari et al. in 2012 and presented an example in which AAH exhibits an acidic nature.\(^{284}\) The transformation was assumed to take place via the initial formation of 1,3-dipolar intermediate 504a from isocyanide 261 and dialkylacetylene dicarboxylates 362. This in situ-generated intermediate then abstracts a proton from 2-amino-benzothiazole 3b (NH-acidic compound), and the

Scheme 164  Cul-promoted three-component synthesis of isothiourea.

Scheme 165  Acid-catalyzed synthesis of \( N,O \)-acetal derivatives of 2-amino-benzothiazoles.
resulting positive and negatively charged entities combine with each other to give the azadiene (Scheme 162).

In a somewhat related method, where the C-nucleophile (isocyanide) in the previous reaction was replaced by P-nucleophile in the form of triphenylphosphine, M. Anary-Abbasinejad and coworkers performed reactions between triphenylphosphine, dialkylacetylene dicarboxylate 362 and 2-aminothiazole 22/2-aminobenzothiazole 3b under mild conditions to afford phosphorus ylides. These ylides contain a P–C partial double bond and the rotation around which is very slow compared to the NMR timescale at ambient temperature, and thus the E and Z geometrical isomers were identified by 1H and 13C NMR spectroscopy. Mechanistically, this transformation was achieved in a manner similar to the previous reaction except that 1,3-dipolar intermediate 506a results from the initial addition of triphenylphosphine to dialkylacetylene dicarboxylate (Scheme 163).

In 2014, P. Mampuys and coworkers described a copper(I)-catalyzed three-component approach for the synthesis of S-methyl isothiourea by employing thiosulfonates, isocyanides and 5/6 membered heteroaryl amines 347. During the optimization of the reaction conditions, it was observed that the formation of isothioureas occurs even without the aid of a catalyst but with low yield, and the addition of CuI and 4 Å MS to the reaction enhances the product yields to a significant level. The proposed reaction mechanism by the authors involves the CuI-promoted synthesis of the S-methylated tert-butyl isothiocyanate intermediate 508 in the initial step when S-methyl methanethiosulfonate 507 reacts with tert-butyl isocyanide 261. In the next step, heterocyclic amine 347 attacks the intermediate at the imine functionality, which triggers the removal of methanesulfonic acid 508 followed by the proton transformation between the two nitrogen atoms (Scheme 164).

An approach to N,O-acetals was developed by Z. Ji and group via the one-pot condensation of 2-aminobenzothiazoles with aliphatic aldehydes and alcohols. This formic acid/acetic acid-catalyzed strategy illustrated the dual role of the acids, solvent and reactant and offers a smooth way for the transformation. They prepared a library of compounds in two sets. In one set, 2-amino-4-methylbenzothiazole 510 was combined with various aliphatic aldehydes 4 and alcohols. In the other set, 2-aminobenzothiazole 3b and its 4- or 6-substituted derivatives were reacted with formaldehyde 403 and methanol at room temperature. For the synthesized acetals 509 and 510, which require the use of methanol and ethanol as substrates, the corresponding reaction was performed in methanol and ethanol, respectively, while other alcohol-based acetal derivatives were synthesized using tetrahydrofuran (THF) as the reaction medium together with a measured amount of corresponding alcohol (Scheme 165).

Another similar three-component reaction leading to N,O-acetals 511 was reported by Á. Beltránin et al., wherein 2-aminooxazines (2-aminopyridines 117 and 2-aminopyrimidine 464), acetaldehyde 32, and ethanol were allowed to react at room temperature in DCM solvent using 3 Å molecular sieves. The mechanism of this conversion was proposed to rely on the dual role of molecular sieves as a Lewis acid and water sponge. The Lewis acidity of the molecular sieves induces the formation of hemiaminal intermediate 511a from acetaldehyde 32 and amine 117 from which a molecule of water is extruded and fixed into the sieve (acting like a water sponge). The resulting imine 511b is activated through Lewis acidic interaction with the molecular sieves, which experiences O-nucleophilic attack from alcohol to generate acetal derivatives 511 (Scheme 166).

The synthesis of spirooxindole derivatives via a catalyst-free three-component domino protocol was developed recently by N. Kausar and coworkers. This green strategy involves the reaction between 2-aminopyridine/2-aminopyrazine 117 and 464, isatin 142, and 1,3-dicarboxyl compounds 512 in ethyl L-lactate medium at room temperature for 90 min, leading to the formation of spiro derivatives 513 in excellent yields (Scheme 167).

3 Conclusions

Aromatic \( \tau \)-aminoazaheterocycles and their derivatives are widely distributed in nature and have immense importance in various fields, especially in medicine and drug discovery. For the synthesis of their derivatives, multicomponent reactions have been highly accepted as an excellent and multipurpose approach. Thus, we hope that this review will serve to stimulate research in this fascinating and very useful area of organic synthesis.

Conflicts of interest

There are no conflicts of interest to declare.
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