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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. **Lophocladine**, 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'-oxoadenosceptrin** and **decarbox-yagelamadin C**, were isolated from tropical sponge *Agelas*

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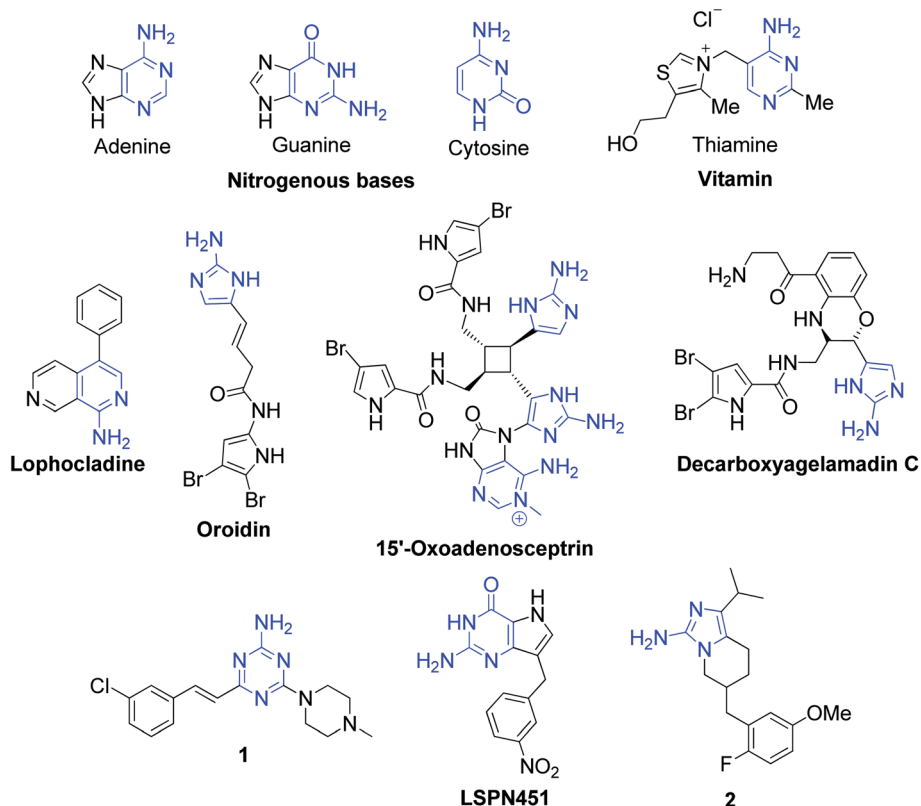


Fig. 1 Some important natural and synthetic organic compounds possessing 2-aminoazaheterocyclic structures.

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, C=O, and hydroxyl, OH, groups are replaced by azomethine, C=NR, and amino, NH₂, groups, respectively. The cyclic amidine functionality of amino heterocycles is obtained



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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.^{7,8} They are also the source of important precursors for the production of valuable hetero-aromatics such as benzimidazoles,⁹ quinazolines and derivatives of substituted imidazoles, pyrimidines, dihydropyridines,¹⁰ *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.¹¹ 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.¹² 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.¹³ Therefore, their extensive application in the synthesis of densely

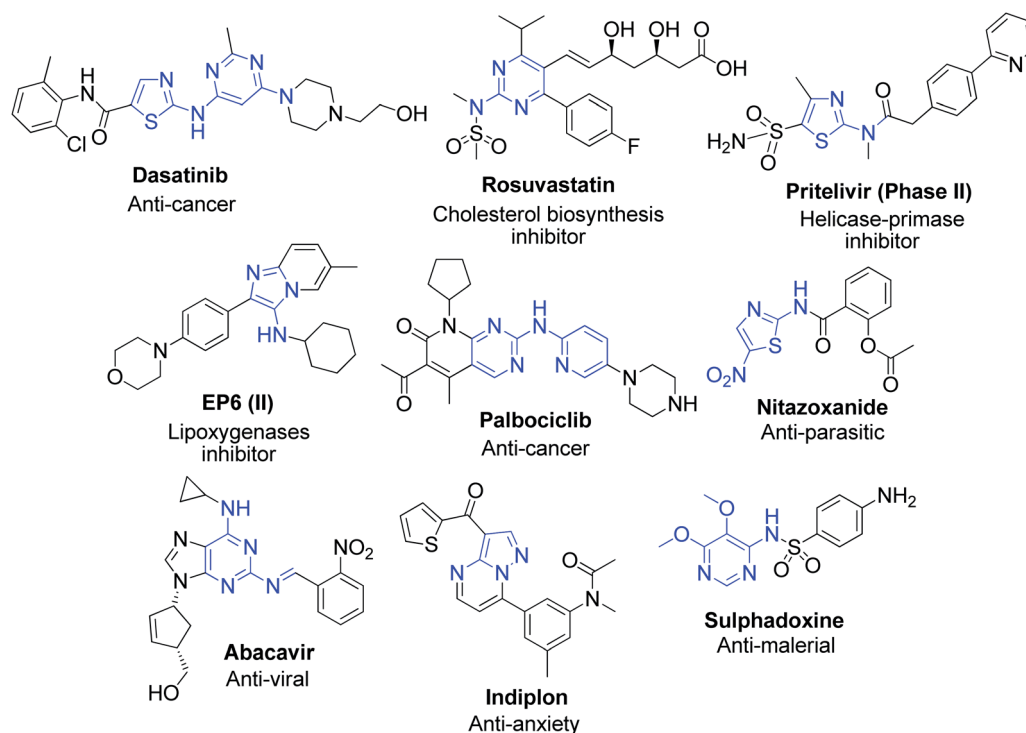


Fig. 2 Some drugs and medicinally active compounds containing 2-aminoazaheterocycles.

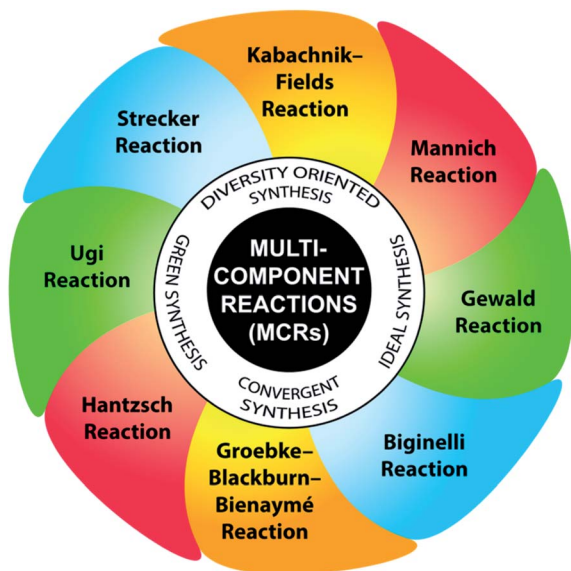


Fig. 3 Some well-known multicomponent reactions.

functionalized molecules with potential bioactivity has undergone explosive growth in recent years. Moreover, their high atom economy, high efficiency, mild conditions, high convergence and concomitant step economy together with their general compatibility with green solvents justify their central place in the toolbox of sustainable synthetic methodologies.¹⁴ 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).¹⁵

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.¹⁶ 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 mono-nucleophiles. The products resulting from the reaction in which

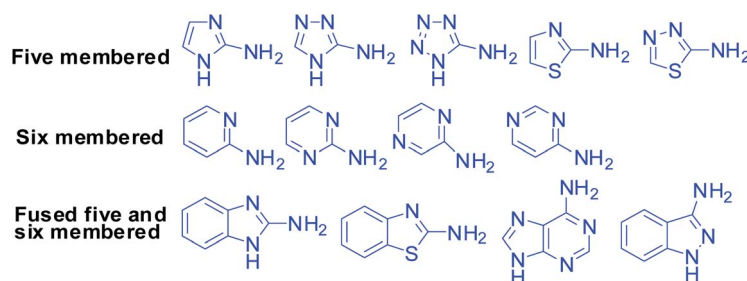


Fig. 4 Structure of α -aminoazaheterocycles covered in this review.

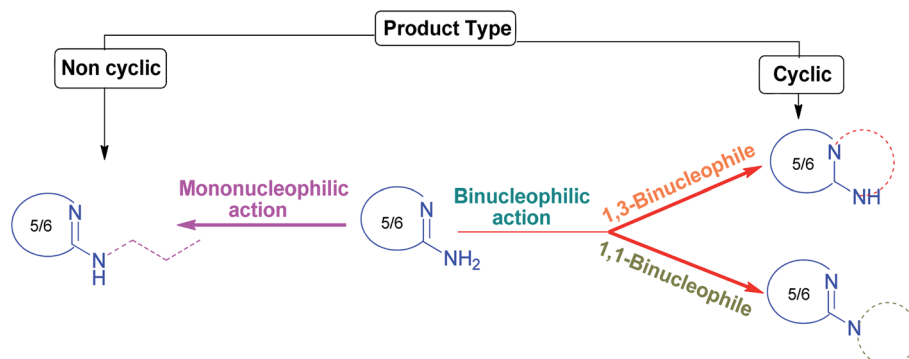
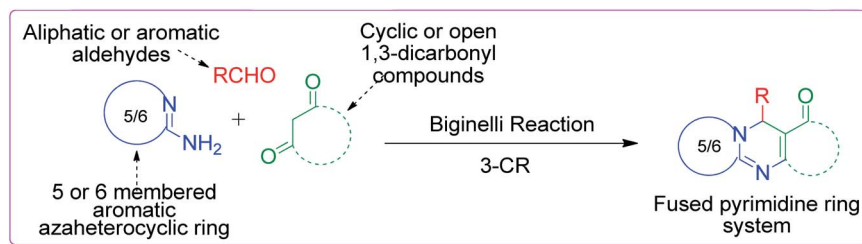


Fig. 5 Classifications of MCRs involving AAHs based on their reaction profile.





Scheme 1 General form of the Biginelli reaction.

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 amidine 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.

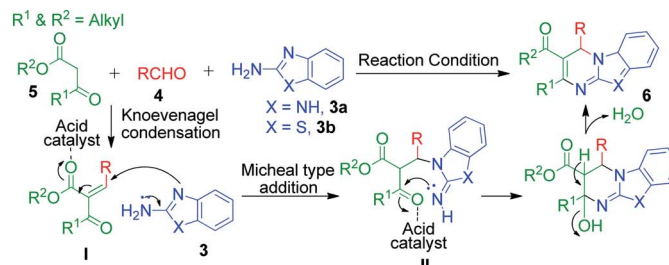
By definition, active methylene compounds are compounds that possess a methylene group between two strong electron withdrawing groups such as carbonyl, nitrile, and nitro. Because of the strong deactivating nature of these group, the hydrogens of the methylene bridge become acidic in nature, and consequently 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-hydroxycoumarin. 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 benzothiazole-fused pyrimidines can be conveniently performed in the presence of *N,N'*-dichlorobis(2,4,6-trichlorophenyl)urea (CC-2)¹⁷ and *N*-sulfonic acid based on the polymer support as a solid acid catalyst (SMI-SO₃H),¹⁸ HCl,¹⁹ ZnClO₄·6H₂O,²⁰ citric acid,²¹ PdCl₂,²² ZnO NPs,²³ 3D-printed Al₂O₃,²⁴ H₃BO₃,²⁵ acetic acid,²⁶ nano-kaolin/Ti⁴⁺/Fe₃O₄,²⁷ chitosan,²⁸ Fe₃O₄@SiO₂-TiCl₃ NPs,²⁹ nano-cellulose/BF₃/Fe₃O₄,³⁰ nanoporous sodium montmorillonite clay (Na⁺-MMT)-modified 1-methyl-3-(trimethoxysilylpropyl)-imidazolium hydrogen sulfate (Na⁺-MMT-[pmim]HSO₄),³¹ 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/benzoimidazole **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 benzoazole-fused pyrimidine motif **6**.

An interesting case was studied by P. K. Sahu and coworkers,³² where the synthesis of these pyrimidine derivatives was achieved in the presence of a solvent and under solvent-free



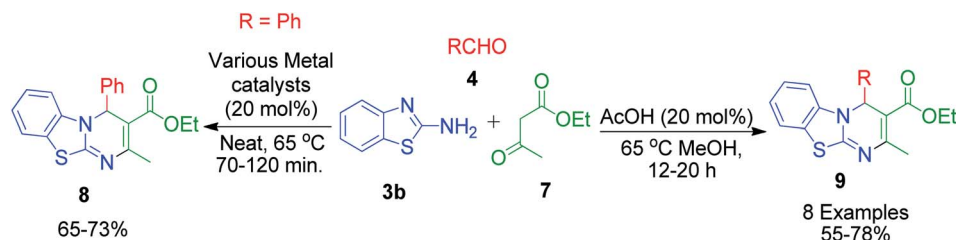
X	Reaction condition	Time	Yield (%)	No. of examples	Reference
NH, S	CC-2 (30 mol%), EtOH, Reflux	5–10 h	55–78	14	17
S	SMI-SO ₃ H, 100 °C	3–4 h	66–76	7	18
S	HCl, MeOH, Reflux	6–12 h	59–83	20	19
NH, S	Zn(ClO ₄) ₂ ·6H ₂ O (2 mol%), MeOH, Reflux	8–12 h	78–89	4	20
NH	Citric acid (260 mol%), EtOH, Reflux	1–1.1 h	85–89	11	21
S	10% PdCl ₂ , Neat, 90 °C conventional heat or MW	20–69 min (Conventional) 3–5 min (MW)	69–79 77–87	12	22
NH, S	ZnO NPs (0.4 mol%), Ball milling, rt	40 min	72–87	20	23
NH	3D printed Al ₂ O ₃ MW, 100 °C	9 min	80	1	24
NH, S	H ₃ BO ₃ /H ₂ O, RT	8–30 min	75–85	13	25
S	AcOH, MW 80 °C	10–30 min	85–93	6	26
S	Nano-kaolin/Ti ⁴⁺ /Fe ₃ O ₄ neat, 100 °C	0.5–3 h	50–98	12	27
S	Chitosan, CH ₃ COOH/H ₂ O, 65 °C	100 min	58–68	4	28
S	Fe ₃ O ₄ @SiO ₂ -TiCl ₃ NPs solvent free, 100 °C	25–150 min	79–90	12	29
S	Nano-cellulose/BF ₃ /Fe ₃ O ₄ solvent free, 100 °C	45–80 min	80–98	12	30
NH	Na ⁺ -MMT-[pmim]HSO ₄ , 100 °C	3–50 min	87–95	22	31

Scheme 2 Three-component synthesis of benzoazole-fused pyrimidine derivatives through the reported acid catalysts.

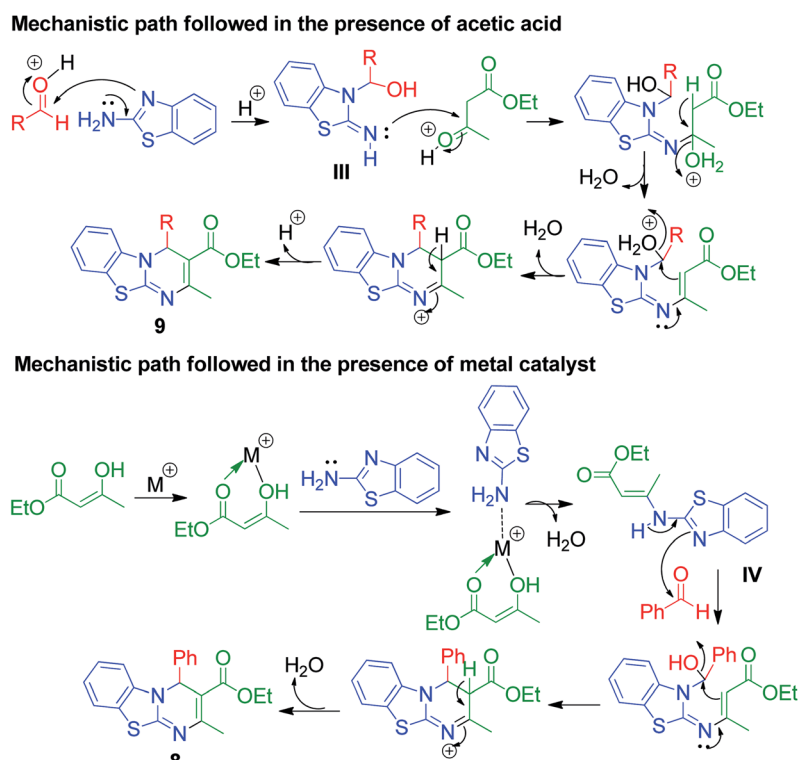
conditions using various catalysts. When the condensation among 2-amino benzothiazole **3b**, aldehydes **4** and β-ketoester **7** was carried out in the presence of acetic acid as the catalyst and methanol as the solvent at 65 °C, the corresponding products

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 CuCl₂ and LiCl were used as catalysts, but the

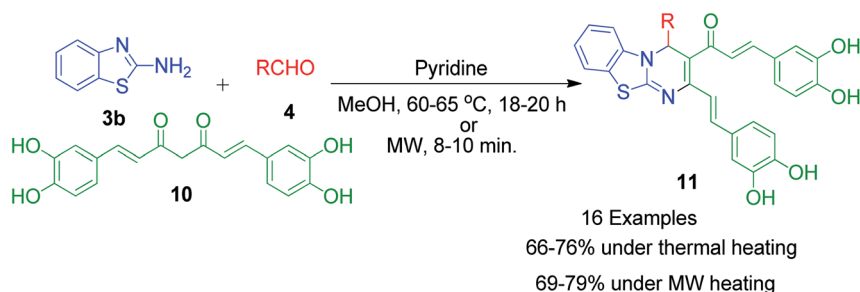




Scheme 3 Synthesis of 4H-pyrimido[2,1-b]benzothiazole derivatives under two different conditions.



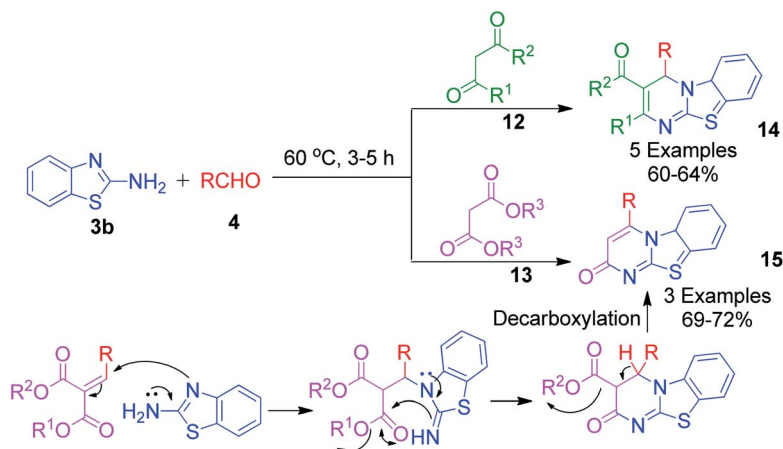
Scheme 4 Mechanistic routes explaining the formation of 4H-pyrimido[2,1-b]benzothiazoles in the presence of acetic acid and metal catalyst.



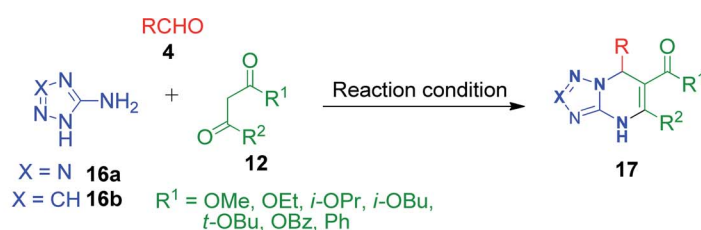
Scheme 5 Synthesis of benzothiazolopyrimidine using pyridine under thermal and microwave heating.

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).



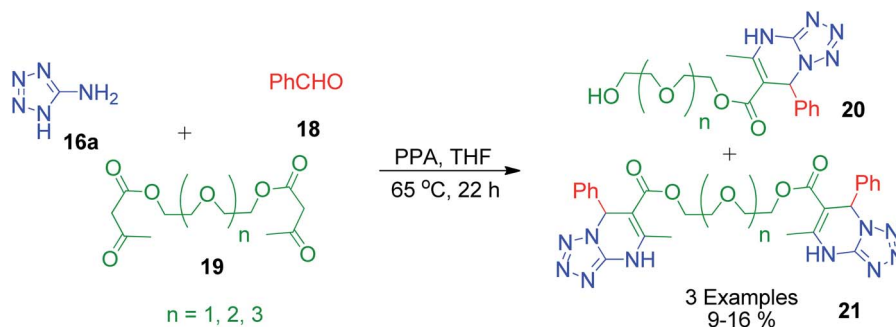
Scheme 6 Catalyst-free and solvent-free synthesis of 4H-pyrimido[2,1-b]benzothiazole and 2-oxo-pyrimido[2,1-b]benzothiazole derivatives.



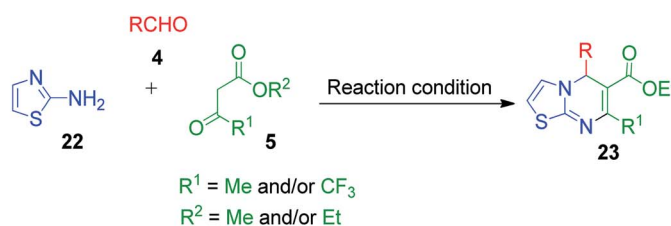
X	Reaction conditions	R ¹	R ²	Time	Yield (%)	No. of examples	Reference
N	Solvent-free 130–170 °C			20-30 min.	31–80%	40	35
N	I ₂ (10 mol%), <i>i</i> -PrOH, Reflux			4 h	70 & 94	2	36
CH	[Bmim]BF ₄ , 110 °C	CF ₃	OEt,	6–9 h	82–92	19	37
N			Ph	7–9 h	78–89		38
N	Nano-Fe ₃ O ₄ @SiO ₂ -NH-gallic acid, EtOH, Reflux			15-20	81–90	15	39
N	CH ₃ COOH/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.



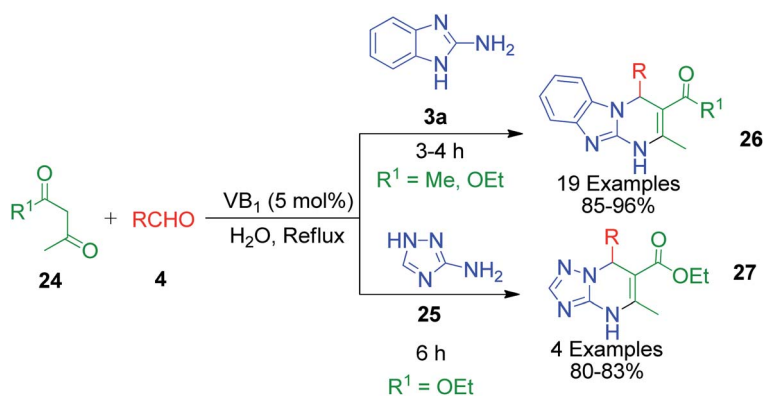


Scheme 8 Synthesis of podands containing two terminal tetrazolo[1,5-a]dihydropyrimidine groups.

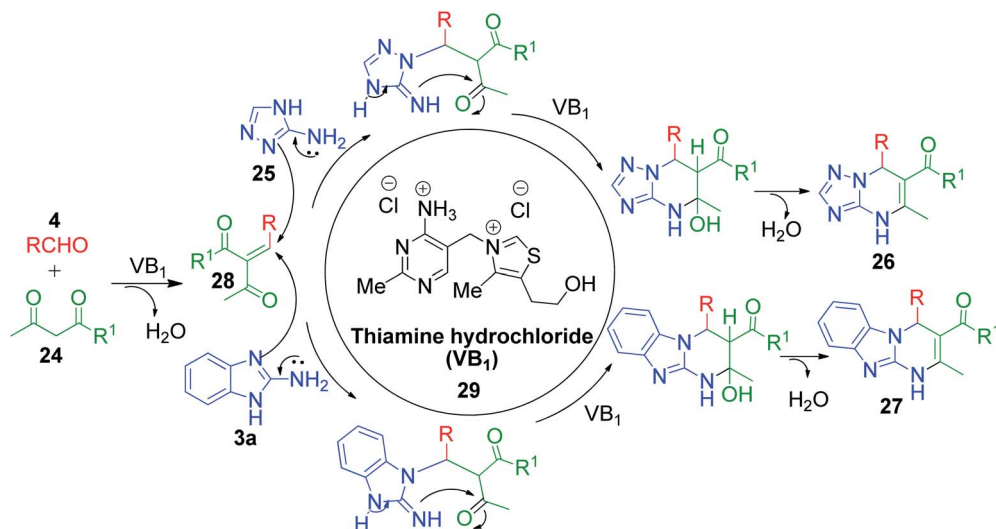


Reaction conditions	Time	Yield (%)	No. of examples	Reference
NH ₂ SO ₃ H (30 mol%), EtOH, Reflux	1.5 h	65–81	12	44
Nano-Fe ₃ O ₄ @SiO ₂ @SO ₃ , 60 °C	1.5–2.5 h	89–95	5	45
H ₃ BO ₃ /H ₂ O, RT	8–30 min	80–95	12	25
AcOH, MW 80 °C	10–30 min	83–95	6	26

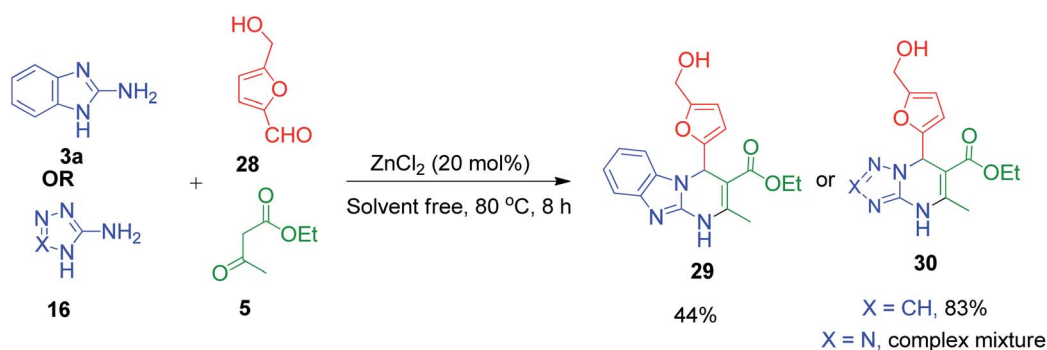
Scheme 9 Protic acid-catalysed synthesis of thiazolopyrimidines from 2-aminothiazole, ethylacetoacetate and aromatic aldehydes.



Scheme 10 Synthesis of benzoimidazolo pyrimidine and triazolopyrimidine derivatives based on thiamine hydrochloride (VB1)-catalyzed three-component reaction.



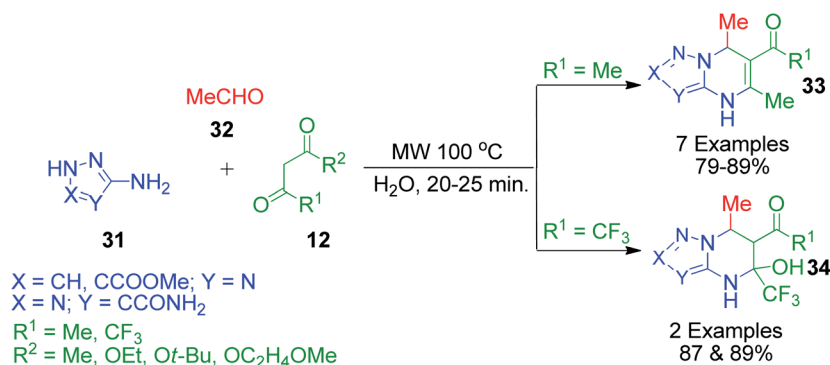
Scheme 11 Mechanism proposed for VB₁-catalyzed synthesis of fused pyrimidines.



Scheme 12 ZnCl₂-catalysed synthesis of benzimidazole/triazole-fused dihydropyrimidinones.

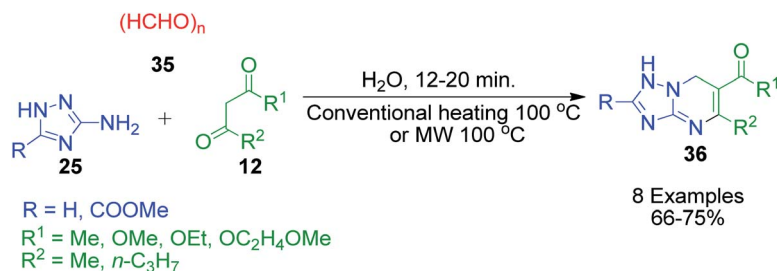
Besides these acid-catalyzed methods, P. K. Sahu *et al.* adapted the synthesis of benzothiazolopyrimidine **11** starting from a completely different β -dicarbonyl, known as curcumin **10**, 2-aminobenzothiazole **3b** and aromatic aldehydes **4** using pyridine as a catalyst under thermal heating involving methanol as the solvent as well as microwave irradiation solvent-free conditions (Scheme 5).³³ 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



Scheme 13 Microwave heating-assisted synthesis of azolopyrimidine derivatives.





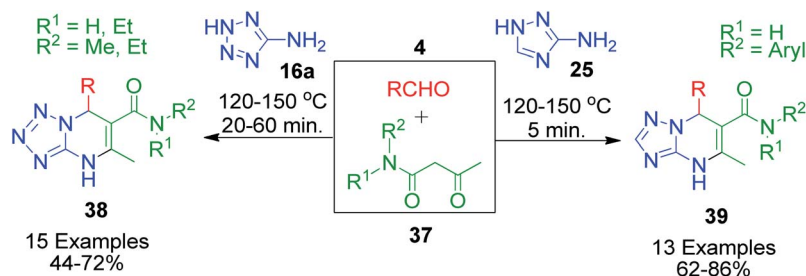
Scheme 14 Conventional heating or microwave heating-assisted synthesis of 7-unsubstituted 4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines 36.

through a Knoevenagel-type intermediate and follows the path of the usual Biginelli reaction.

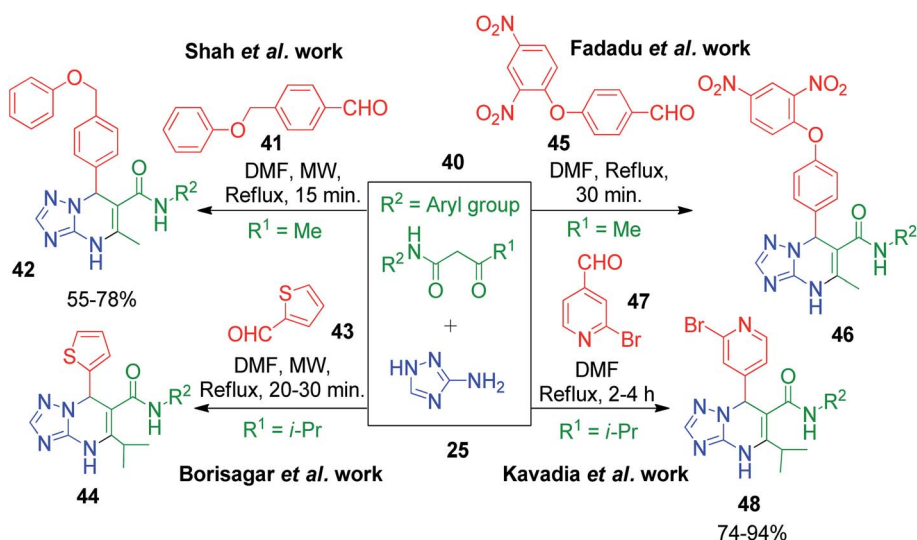
A catalyst-free and solvent-free approach based on the Biginelli reaction was developed by F. Chadevani *et al.*, wherein the one-pot three-component reaction between 2-amino-benzothiazole 3b, benzaldehyde derivatives 4 and β -ketoester or β -diketone derivatives (12 or 13) was performed at 60 °C, which afforded the corresponding pyrimido[2,1-*b*]benzothiazole derivatives 14 in 3–5 h.³⁴ 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 4*H*-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



Scheme 15 Construction of triazolo 39 and tetrazolopyrimidines 38 under solvent-free and catalyst-free conditions.



Scheme 16 Catalyst-free synthesis of various triazolopyrimidine derivatives.

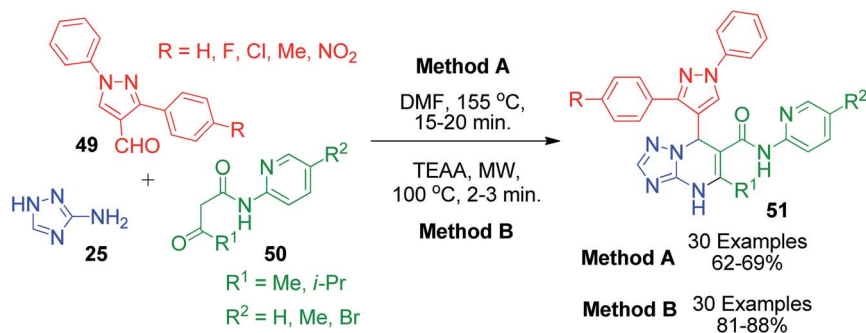
are widely employed in MCRs for the synthesis of various heterocyclic derivatives upon reaction with 1,3-diketocompounds and aldehydes under different conditions. In this context, a catalyst- and solvent-free method was employed by V. L. Gein's research group for the synthesis of tetrazolo-fused pyrimidines 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.³⁵ Haleel and coworkers developed a protocol for the synthesis of analogues of tetrazolopyrimidine derivatives **17** in the presence of iodine under refluxing conditions.³⁶ The synthesis was achieved by reacting ethyl acetoacetic esters **12**, 5-aminotetrazole **16** and heteroaryl aldehydes (2-pyridinecarboxaldehyde and 4-pyridinecarboxaldehyde) **4** 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]⁺[BF][−] as a green ionic liquid,^{37,38} nano-Fe₃O₄@SiO₂-NH-gallic acid³⁹ and CH₃COOH/HCl,⁴⁰ conc. HCl,⁴¹ and *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide (TBBDA)⁴² (Scheme 7).

E. S. Filatova *et al.* utilized 3-oxobutanoate-containing polyethers **19** as 1,3-diketocompounds in the reaction with benzaldehyde **18** and 5-aminotetrazole **16a** involving polyphosphoric acid as the catalyst to carry out the synthesis of podands bearing

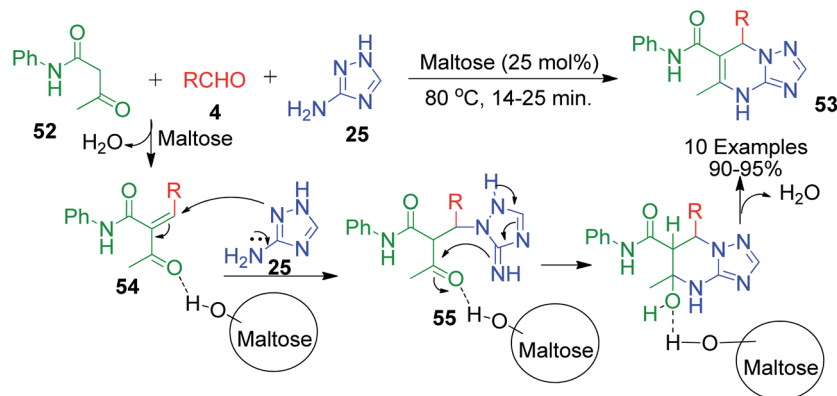
two terminal tetrazolo[1,5-*a*]dihydropyrimidine groups **20** along with byproducts such as podands containing one 4,7-dihydro-tetrazolo[1,5-*a*]pyrimidine ring system **21** and a free hydroxy group at the other terminus of the polyether chain (Scheme 8).⁴³

I. Batool and coworkers disclosed a novel multicomponent strategy that affords the synthesis of thiazolopyrimidines **23** through the condensation reaction among 2-aminothiazole **22**, ethylacetoacetate **5** and differently substituted aromatic aldehydes **4**. The reaction, which was catalyzed by sulfamic acid in ethanol under reflux conditions, was established to find potent antidiabetic and antibacterial drugs (Scheme 9).⁴⁴ This reaction was also performed using nano-Fe₃O₄@SiO₂@SO₃,⁴⁵ H₃BO₃,²⁵ acetic acid,²⁶ *etc.*

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 **26** and [1,2,4]triazolo[1,5-*a*]pyrimidine **27** derivatives was developed by heating a reaction mixture containing 2-aminobenzimidazole/3-amino-1,2,4-triazole **3a** and **25** with various aldehydes **4** and ethyl acetoacetate/acetyl acetone **24** in water under refluxing conditions (Scheme 10).⁴⁶ 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 **26** and **27** were obtained in high yields (80–96%) in 3–6 min with the employment of



Scheme 17 Pyrazole-linked triazolopyrimidines **51** synthesised under conventional and microwave heating.



Scheme 18 Maltose-catalysed solvent-free synthesis of triazolopyrimidine derivatives **53** and its proposed mechanistic route.



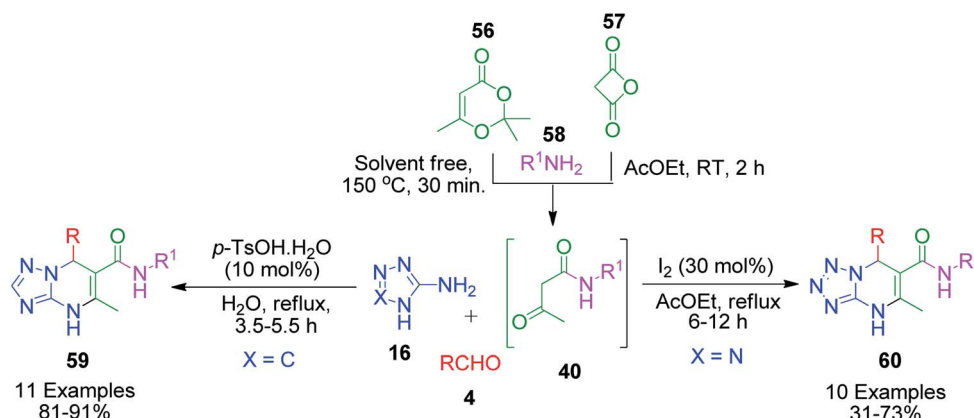
merely 5 mol% of the catalyst. A plausible mechanism illustrating the reaction pathway is summarized in Scheme 11. After the initial formation of benzylidene-type intermediate **28** from the VB₁ **29**-catalyzed Knoevenagel condensation of dicarbonyl compound **24** and aldehyde **4**, a nucleophilic 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 ZnCl₂ 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 CH₂OH motif, which can be functionalized further to the desired target molecules.⁴⁷

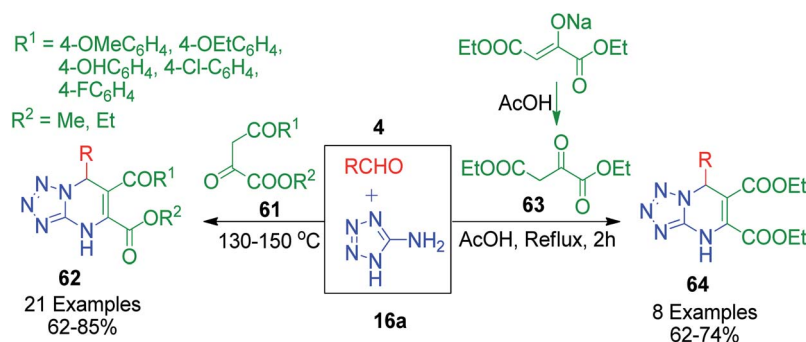
I. G. Tkachenko *et al.* reported a three-component synthesis for the regioselective formation of 4,7-dihydro[1,2,4]-triazolo- and 4,7-dihydro[1,2,3]triazolo[1,5-*a*]pyrimidines **33** involving a reaction between 3-amino-1*H*-1,2,4-triazole/5-amino-2*H*-1,2,3-triazole derivatives **31**, acetaldehyde **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).⁴⁸

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).⁴⁹ 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.

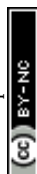
In the synthesis of triazole/tetrazole-fused pyrimidine derivatives through the involvement of *N*-aryl/alkyl acetoacetamides as one component acting as a β -keto compound, Gein *et al.* made a significant contribution. In this context, a three-component reaction mixture containing *N*-alkylamides of 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-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides **38**.⁵⁰ Based on a similar method, the same group also reported the condensation of 3-amino-1,2,4-triazole **25** with *N*-arylamides 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**.⁵¹ In both cases, a solventless mixture of starting materials was heated at high temperature

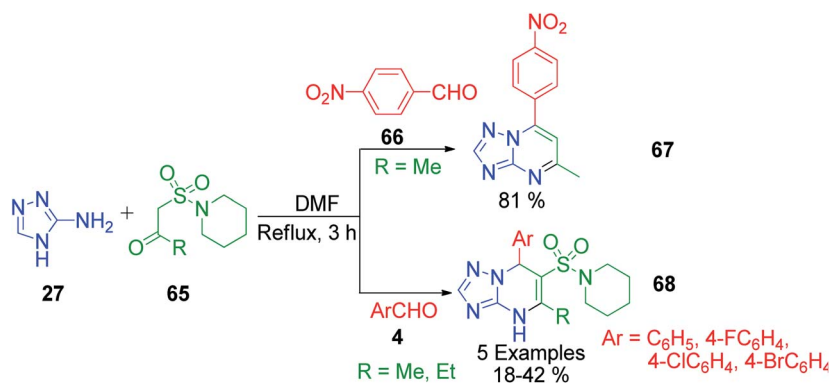


Scheme 19 *In situ* generation of *N*-alkyl acetoamide **60** and its use in the construction of triazole **61** and tetrazole fused pyrimidines **62**.

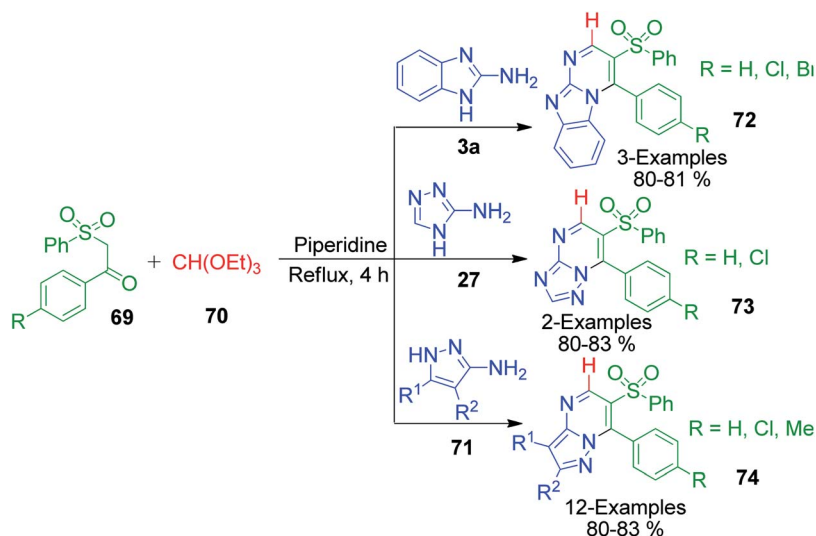


Scheme 20 Synthesis of tetrazolopyrimidines using pyruvic acid and its sodium salt as 1,3-dicarbonyl compounds.

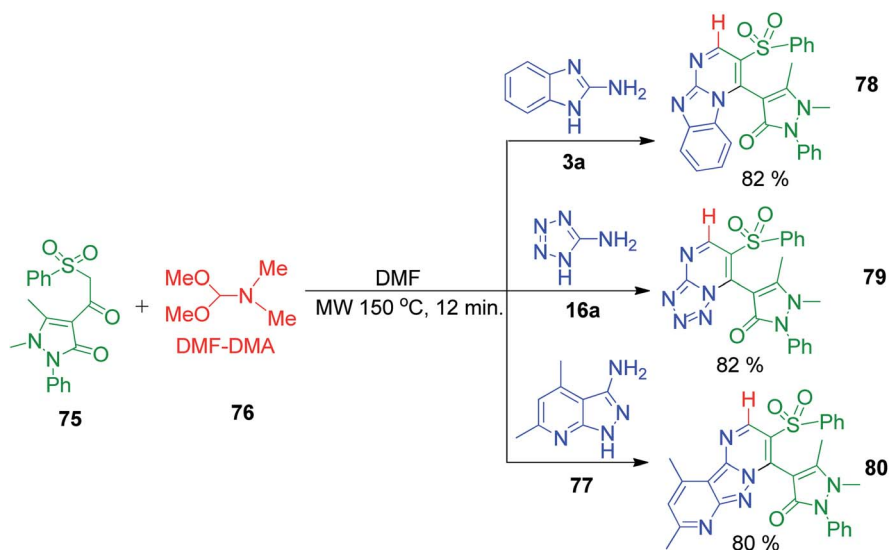




Scheme 21 Synthesis of 7-(4-nitrophenyl)[1,2,4]triazolo[1,5-a]pyrimidine **69** and 5-alkyl-6-(1-piperidynylsulfonyl)-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine **70** derivatives.

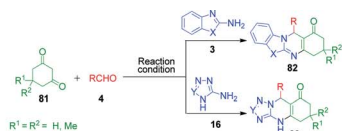


Scheme 22 Synthesis of pyrazolo[1,5-a]pyrimidines **72**, **73** and **74** tethered with a sulfone moiety.



Scheme 23 Microwave-assisted synthesis of azole-fused pyrimidine derivatives **78**, **79** and **80**.





X	Y	Reaction conditions	Time (min)	Yield (%)	No. of examples		Reference
					129	154	
NH	CH	NH ₂ SO ₃ H (5 mol%), MeCN, Reflux	15–60	89–96	6	9	67
NH	CH	I ₂ (10 mol%), MeCN, Reflux	10–15	81–97	5	14	68
NH	CH	Silica gel, MW, 120 °C	3–6	90–95	8	8	69
NH	CH	H ₂ SO ₄ ·SiO ₂ (10 mol%), MeCN, Reflux	20	90–95	6	14	70
NH	CH	SBA-Pr-SO ₃ H, Solvent free, 100 °C	5–15	85–96	4	6	71
NH	CH	AcOH, 60 °C	10–35	86–99	8	10	72
NH, S	CH, CNH ₂ , CSMc	[bmim]Br, 100 °C	5–60	69–96	18	18	73
NH	-	n-WO ₃ ·SO ₃ H, 100 °C	12–20	90–95	10	-	74
NH, S	-	Fe ₃ O ₄ @chitosan EtOH, 40 °C	1.5–4 h	79–95	10	-	75
NH, S	-	Fe ₃ O ₄ @clay H ₂ O, RT	10–15	90–98	10	-	76
NH	-	DES (ChCl:Glycerol) 80 °C	20–30	52–91	16	-	77
NH	-	MPyrnSO ₃ H (10 mol%), 90 °C	4–7	86–91	11	-	78
		MMorSO ₃ H (10 mol%), 90 °C	3–5	90–97			
NH, S	-	Sc(OTf) ₃ (10 mol%), MW, 100 °C	15–30	82–90	10	-	79
NH	-	RHA-[pmim]HSO ₄ , 100 °C	2–5	87–93	9	-	80
-	CH, CPh	Montmorillonite KSF, MeCN, Reflux	30	85–90	-	4	81
-	CH	Ni-Np (10 mol%), MeCN, Reflux	10	85–98	-	8	82
-	CH	CAN (150 mol%), MW 150 W, 70 °C, H ₂ O	3	90–93	-	15	83
-	CH	MW 150 W, 45 °C	1	85–94	-	15	84
-	CH	Hydrotalcite (Mg-Al-CO ₃), 70 °C	40–60	80–89	-	2	85
-	CH	Chitosan, AcOH 60–65 °C	60–100	81–95	-	5	86
-	CH	Nanosheets AlPO ₄ (SO ₃ H), MeCN, 50 °C	7–30	85–95	-	19	87
-	CH	3xGO, EtOH, 85 °C	35–60	78–94	-	7	88
-	CH	γ-Fe ₂ O ₃ @SiO ₂ @ [Bis-APTES]Cl ₂ NPs, 90 °C	20–50	87–94	-	15	89
-	N	Catalyst- and solvent-free, 160–170 °C	5–10	31–68	-	7	90

Scheme 24 Variety of acid catalysts used for the construction of triazolo 82 and benzimidazoloquinazolinone ring 83.

(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*-aryl amides 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-(phenoxyethyl)benzaldehyde 41 for 15 min under conventional and microwave heating conditions, which afforded the corresponding triazole-fused pyrimidines 42 in 55–78% yield.⁵² 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.⁵³ 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.⁵⁴ 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).⁵⁵

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).⁵⁶ 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).⁵⁷ 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.

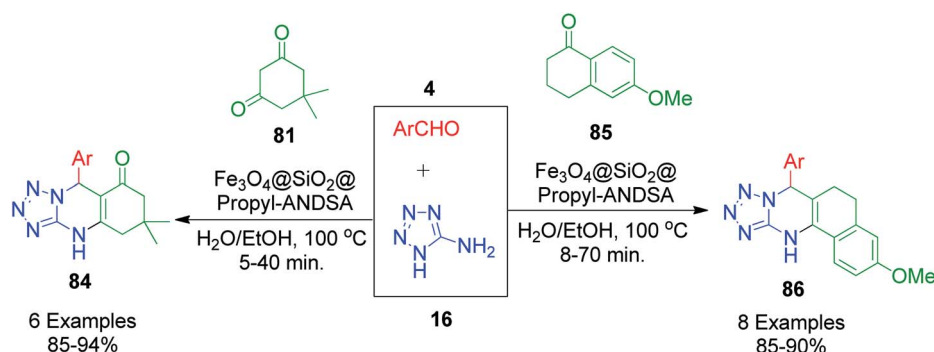
The sugar-catalysed solvent-free one-pot synthesis of [1,2,4] triazolo[1,5-*a*]pyrimidine-6-carboxamide derivatives 53 was accomplished by B. Adrom and co-workers. In this method, a mixture of 3-amino-1,2,4-triazole 25, aryl aldehyde 4 and acetoacetanilide 52 was heated with maltose as the acidic catalyst at 80 °C under solvent-free conditions (Scheme 18).⁵⁸ 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. Maltose, as a carbohydrate, was supposed to promote the reaction through hydrogen bonding.

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-

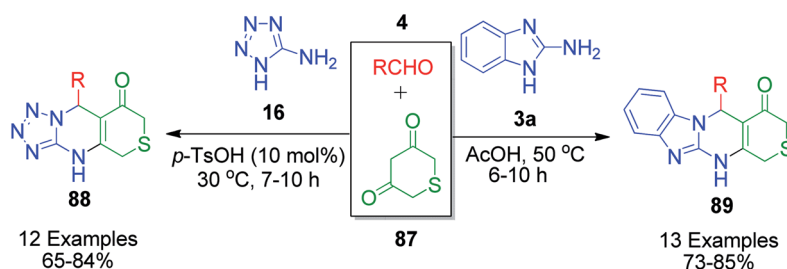


dioxin-4-one **57**. For instance, Zeng *et al.* presented a four-component tandem procedure to prepare a series of dihydrotetrazolopyrimidinyl carbamides **60**.⁵⁹ *N*-alkyl acetoamide **40** was generated by stirring a solution containing amines **58** and diketene **56** in ethyl acetate at room temperature 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 diketene 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-4*H*-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).⁶⁰

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.⁶¹ The same authors also described a condensation protocol in which diethyl 2-oxobutanedioate sodium salt was *in situ* converted into diethyl 2-oxobutanedioate **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).⁶² These condensations were assumed to proceed through the initial Knoevenagel condensation



Scheme 25 Magnetic Fe₃O₄ nanoparticle-catalyzed synthesis of quinazolines derivatives **84** and **86**.



Scheme 26 Synthesis of thiopyran-fused pyrimidine derivatives.



Scheme 27 Synthesis of pyrimido[4,5-*d*][1,2,4]triazolo[1,5-*a*]pyrimidinediones.



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.*⁶³

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-piperidinylsulfonyl)-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine derivatives **68** were obtained when a mixture containing β -sulfonamide 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 dihydroazoloazines, and in this case, 4-nitrobenzaldehyde **66** triggered the elimination of the sulfonamide moiety.

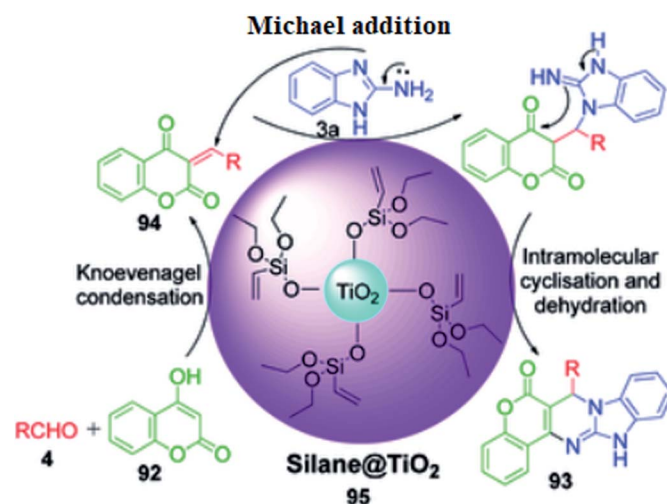
Next, the utility of β -ketosulfones as molecular scaffolds for the synthesis of pyrazolo[1,5-*a*]pyrimidine was described by M. R. Shaabana *et al.* with the development of one-pot three-component procedures, wherein the reaction between 1-aryl-2-(phenylsulfonyl)ethanone derivatives **69**, 3-amino-1,2,4-triazole/2-aminobenzimidazole (**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 methyne-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)pyrimido[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)

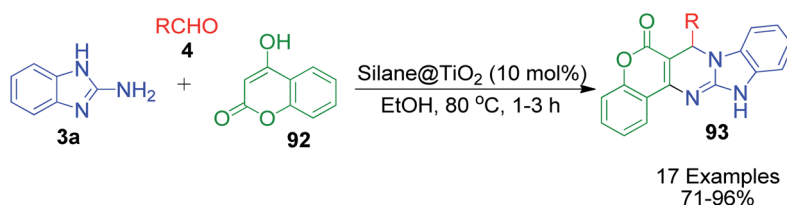
acetyl)-1*H*-pyrazol-3(2*H*)-one **75**. They performed a reaction between dimethylformamide dimethylacetal (DMF-DMA) **76**, a methyne-furnishing reagent, various amino azoles (**3a**, **16a** and **77**) and β -ketosulfones under microwave irradiation at 150 °C for 12 min to synthesize several azole-fused 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.

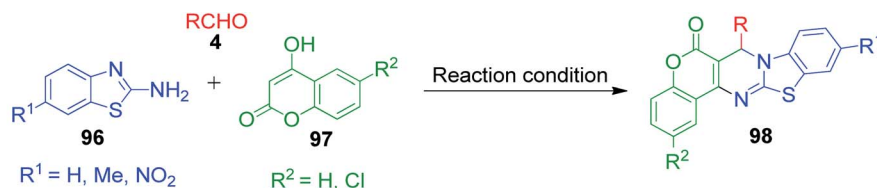
Furthermore, a number of methods have been reported where triazolo and benzimidazolo quinazolinone rings are constructed with the same catalytic system, exhibiting their versatility. In 2010, the use of sulfamic acid as a green and reusable catalyst-based approach was developed by M. M. Heravi *et al.* 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 triazolo/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



Scheme 29 Proposed mechanism for the synthesis of thiazolo[3,2-*a*]chromeno[4,3-*d*]pyrimidin-6(7*H*)-one derivatives **93**.



Scheme 28 Synthesis of thiazolo[3,2-*a*]chromeno[4,3-*d*]pyrimidin-6(7*H*)-one derivatives.



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

Scheme 30 Different methods to synthesize thiazolo[3,2-a]chromeno[4,3-d]pyrimidin-6(7H)-one derivatives 98.

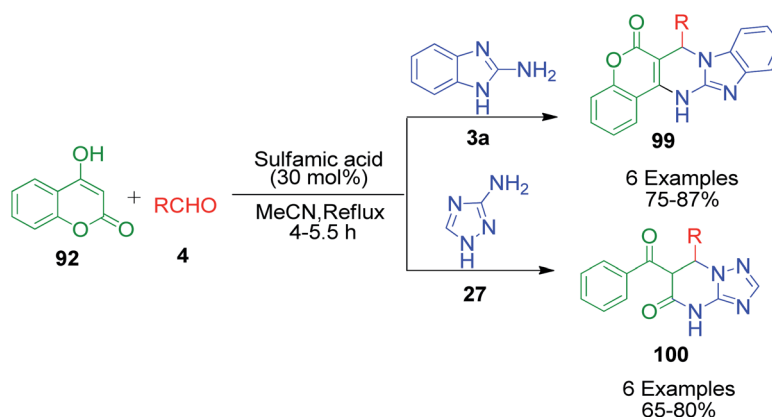
quinazolinone systems with catalytic systems include the use of iodine,⁶⁸ silica gel,⁶⁹ silica-supported sulfuric acid,⁷⁰ sulfonic acid-functionalized SBA-15 as a heterogeneous nanoporous solid acid catalyst,⁷¹ acetic acid (performing dual role of acid and solvent),⁷² and 1-butyl-3-methylimidazolium bromide ([bmim][Br]).⁷³

Nano-WO₃-supported sulfonic acid was employed by A. Amoozadeh and S. Rahmani as an efficient and recyclable catalyst for the synthesis of benzimidazolo quinazolinone 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.⁷⁴ 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,⁷⁵ Fe₃O₄@clay nanocomposite,⁷⁶ choline chloride:glycerol as a deep eutectic solvent,⁷⁷ 1-methyl-1-sulfonic acid pyrrolidinium chloride [MPyrrSO₃H]Cl/4-methyl-4-sulfonic acid morpholinium chloride [MMorSO₃H]Cl,⁷⁸ Sc(OTf)₃,⁷⁹ Brønsted acidic ionic liquid supported on rice husk ash (RHA-

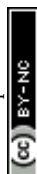
[pmim]HSO₄),⁸⁰ montmorillonite KSF as a heterogeneous catalyst,⁸¹ nickel nanoparticles,⁸² CAN,⁸³ microwave irradiation at 150 W,⁸⁴ hydrotalcite (Mg–Al–CO₃),⁸⁵ chitosan,⁸⁶ nanosheets AlPO₄(SO₃H),⁸⁷ graphene oxide (GO),⁸⁸ γ-Fe₂O₃@SiO₂@[bis-APTES]Cl₂ nanoparticles,⁸⁹ and catalyst- and solvent-free conditions at 160–170 °C⁹⁰ 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 **84** and **86** by the reaction of 5-aminotetrazole **16** aromatic aldehydes **4**, and dimedone/6-methoxy-3,4-dihydropyran-1(2H)-one (**81** and **85** at 100 °C in H₂O/EtOH medium (Scheme 25).⁹¹

A closely related structural analogue of dimedone, 2H-thiopyran-3,5(4H,6H)-dione **87**, was utilized by S. Shen's group as 1,3-cyclicdicarbonyl compounds in their two successive



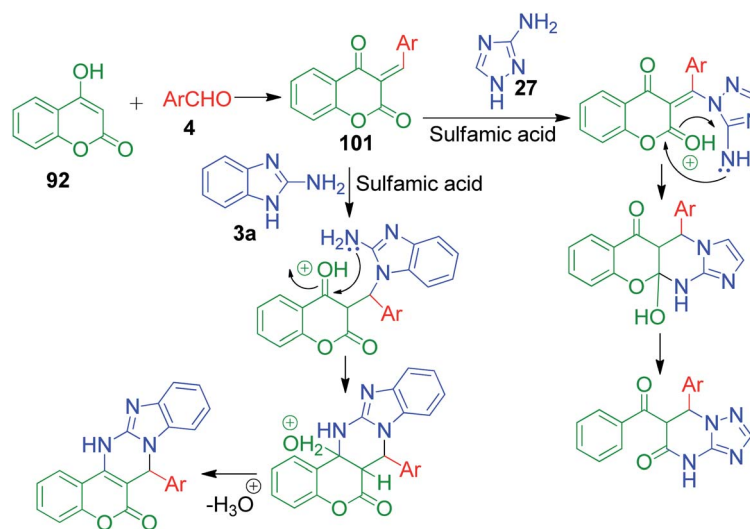
Scheme 31 Sulfamic acid-catalyzed synthesis of fused pyrimidine derivative.



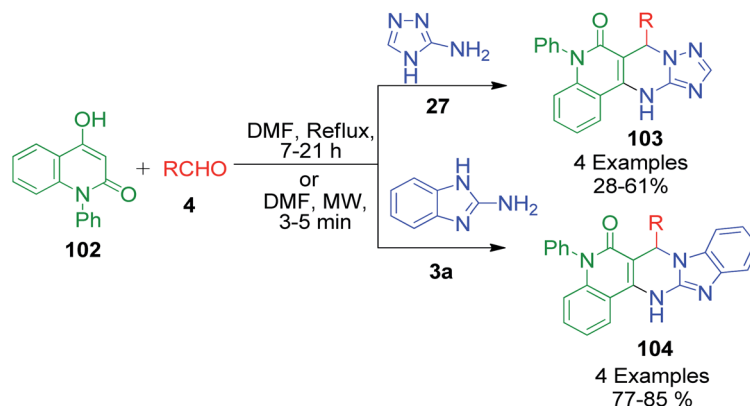
publications to synthesize a series of novel thiopyran-fused pyrimidine derivatives **88** and **89**. In 2011, benzoimidazole and thiopyran-fused novel pyrimidine frameworks were constructed through the MCR between 2-aminobenzothiazole **3a**, aryl aldehyde and 2*H*-thiopyran-3,5(4*H*,6*H*)-dione in glacial acetic acid at moderate temperature (50 °C).⁹² 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 2*H*-thiopyran-3,5(4*H*,6*H*)-dione **87** in the synthesis of a novel series of tetrazolo[1,5-*a*][thiopyrano[3,4-*d*]pyrimidine **88** derivatives by the reaction of 5-aminotetrazole **16**, aryl aldehyde **4** and 2*H*-thiopyran-3,5(4*H*,6*H*)-dione **87** in the presence of PTSA at 30 °C (Scheme 26).⁹³ 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-1*H*-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).⁹⁴ 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-Hydroxycoumarin **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-

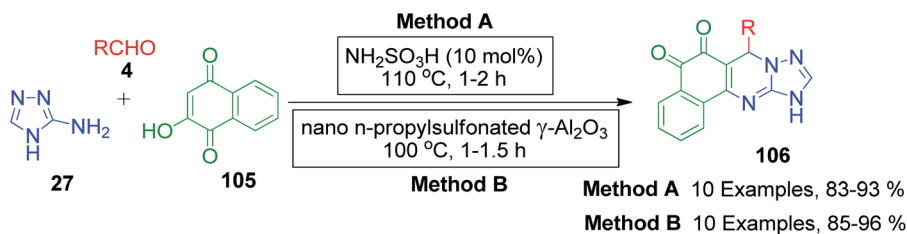


Scheme 32 Proposed pathways to fused pyrimidine derivative.

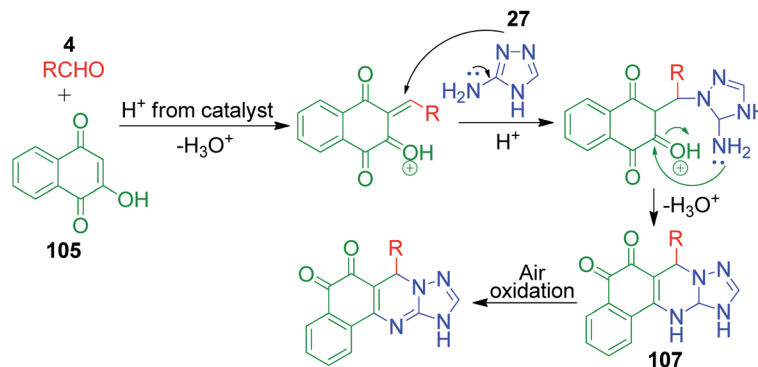


Scheme 33 Synthesis of triazole/benzimidazole-fused pyrimidine derivatives.





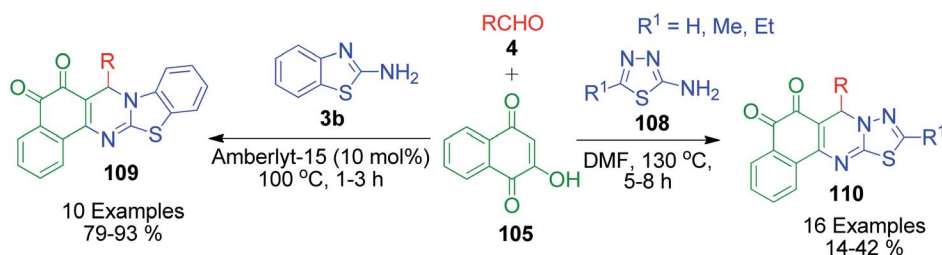
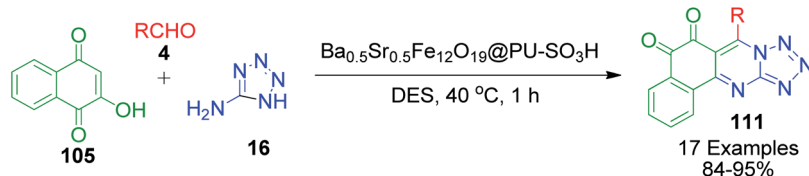
Scheme 34 Solvent-free approaches for the synthesis of 6-aryl-substituted triazoloquinazolidiones.

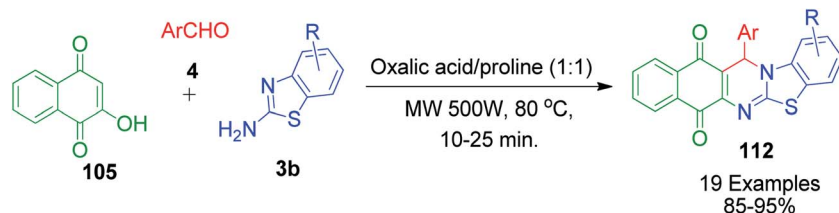
Scheme 35 Mechanism proposed by L. Wu *et al.* to explain the synthesis of substituted triazoloquinazolidiones.

aminobenzimidazole **3a** using silane@TiO₂ nanoparticles **95** as a heterogeneous catalyst under reflux conditions in ethanol (Scheme 28).⁹⁵ 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-amino-benzimidazole **3a** reacts with the intermediate **94** through

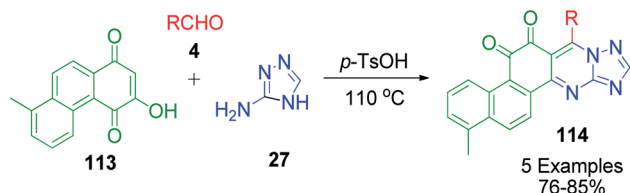
Michael addition followed by cyclization and dehydration to give the desired products (Scheme 29).

A combination of substituted 2-benzothiazole **96** and 4-hydroxycoumarin **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 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[h]tetrazolo[5,1-b]quinazoline-5,6-diones **111** under heterogenous catalysis.



Scheme 38 Microwave-assisted synthesis of 13-aryl-13H-benzo[g]benzothiazolo [2,3-b]quinazoline-5,14-diones **112**.



Scheme 39 Solvent-free synthesis of a novel series of tanshinone I derivatives **115** having an azacyclo ring.

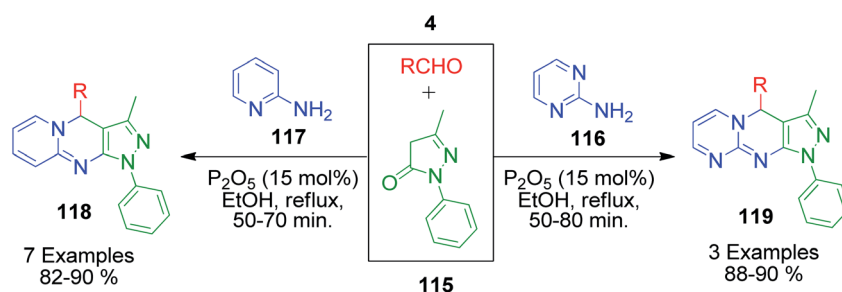
over the reaction mixture of 4-hydroxycoumarin, 4-ethoxybenzaldehyde and 2-aminobenzothiazole under solvent-free conditions revealed that the best result in terms of reaction time and product yield was achieved with 10 mol% of ionic liquid at 100 °C. The authors also showed that the ionic liquid can be reused and recycled for at least five consecutive runs without the loss in activity.⁹⁶ 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.⁹⁷ 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.⁹⁸ 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-hydroxycoumarin **92** is opened upon the sulfamic acid-catalyzed reaction of 4-hydroxycoumarin **92**, aromatic aldehydes **4** and 3-amino-1H-1,2,4-triazole **27** was reported by M. M. Heravi and coworkers. The resulting compound is the simple

triazolopyrimidinone derivatives **100**. When the authors performed this one-pot three-component reaction with 2-aminobenzimidazole **3a**, an usual chromene-fused benzimidazolopyrimidinone **99** was obtained (Scheme 31).⁹⁹ Based on the proposed mechanism, the lactone carbonyl group of intermediate **101**, which is formed as a result from the combination of 4-hydroxycoumarin **92** and aldehyde **4**, is prone to attack by the nucleophilic nitrogen of 3-amino-1H-1,2,4-triazole **27** or 2-aminobenzimidazole **3a** (Scheme 32).

4-Hydroxy-1-phenylquinolin-2(1H)-one **102**, a structural variant of 4-hydroxycoumarin, was used in the Biginelli reaction together with aryl aldehydes **4** and aminotriazole/aminobenzimidazole **27** and **3a** by Mourad *et al.* under the classical and microwave heating.¹⁰⁰ 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 **103** and **104** 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 quinazolinone derivatives under different catalytic systems. The three-component coupling of aldehyde **4**, 2-hydroxy-1,4-naphthoquinone **105** and 3-amino-1,2,4-triazole **27** was achieved in the presence of sulfamic acid under solvent-free conditions to produce a novel series of 6-aryl substituted triazoloquinazolinone derivatives **106** in good yields and high regioselectivity.¹⁰¹ 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



Scheme 40 Synthesis of pyrazolo[3,4-b][1,8]naphthyridine and pyrazolo[3,4-d]pyrimido[1,2-a]pyrimidine derivatives **118** and **119**.

products within 1–2 h of heating (Scheme 34).¹⁰² 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-dione derivatives **109**.¹⁰³ They also synthesized a series of novel substituted 5*H*-benzo[*l*][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).¹⁰⁴

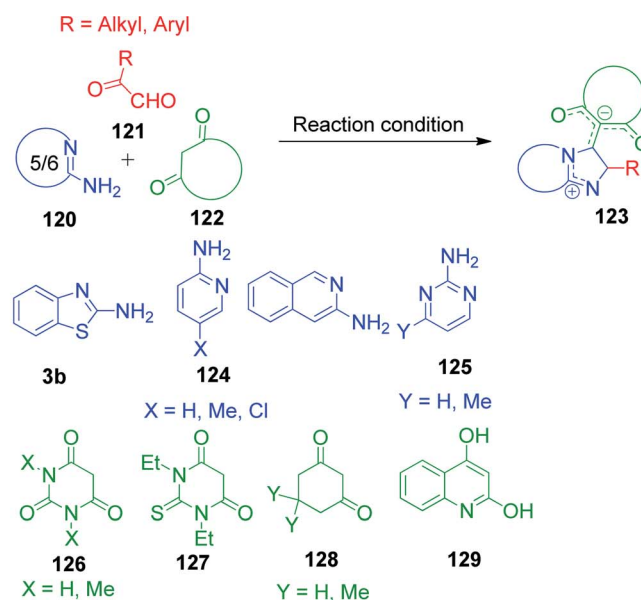
A. Maleki *et al.* employed a Brönsted acid-functionalized magnetic polymeric nanocomposite, Ba_{0.5}Sr_{0.5}Fe₁₂O₁₉@PU-SO₃H, for the synthesis of 7-aryl-benzo[*h*]tetrazolo[5,1-*b*]

quinazoline-5,6-diones **111** in a deep eutectic solvent (DES) based on choline chloride and urea (Scheme 37).¹⁰⁵ 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).¹⁰⁶

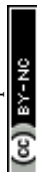
Furthermore, a slightly modified form of naphthoquinone, 3-hydroxy-8-methyl-1,4-phenanthrenequinone **113**, was utilized by L. Wu and X. Yang in a three-component coupling reaction with 3-amino-1,2,4-triazole **27** and aldehydes **4**. The reaction was carried out in the presence of a catalytic amount 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).¹⁰⁷

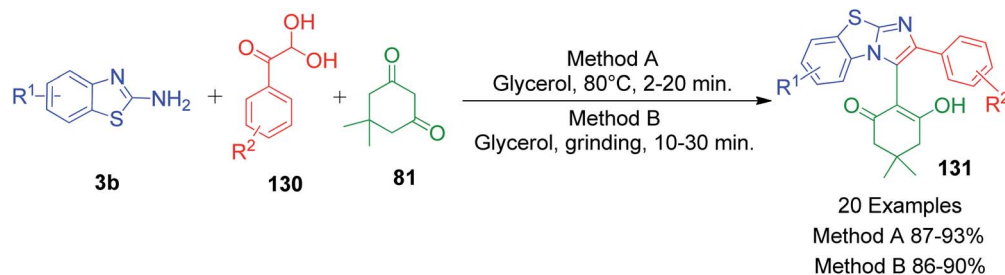
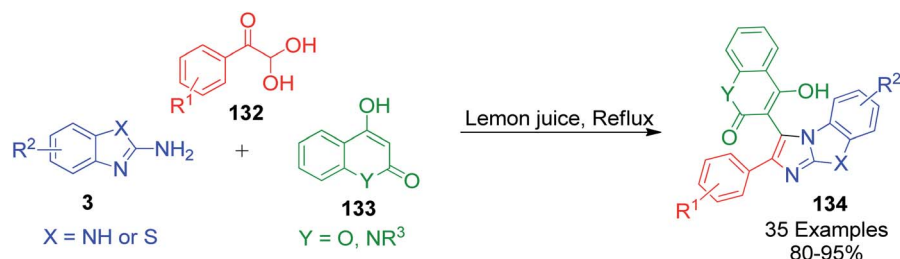
P. T. Patil *et al.* reported the synthesis of novel pyrazolo[3,4-*b*][1,8]naphthyridine **118** and pyrazolo[3,4-*d*]pyrimido[1,2-*a*]



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.



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**.

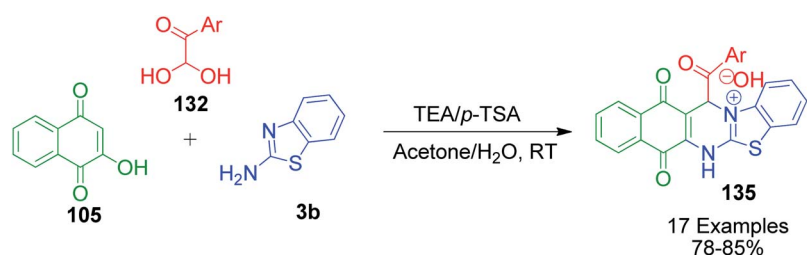
pyrimidine **119** derivatives through an efficient one-pot method. In this method, the reactions between 2-aminopyrimidine/2-aminopyridine **116** and **117**, aromatic aldehydes **4** and 3-methyl-1-phenyl-2-pyrazolin-5-one **115** were performed in the presence of 15 mol% phosphorus oxide under refluxing ethanol (Scheme 40).¹⁰⁸ 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**.¹⁰⁹ Three different reaction conditions were used to study the scope of the process, where 2-aminoazines **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

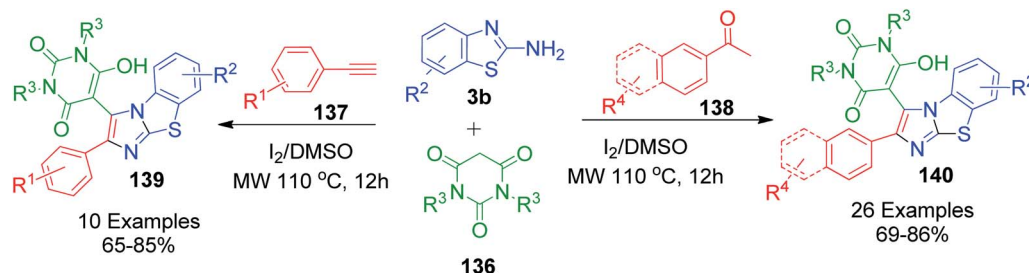
performed in the presence of TEA/AcOH (1 : 2) by N. Etivand *et al.*¹¹⁰ and EtOH/AcOH under microwave irradiation by J. Wang and coworkers (Scheme 41).¹¹¹

K. Meena *et al.* developed the catalyst-free synthesis of benzo[d]imidazo[2,1-b]thiazoles **131**, wherein 2-aminobenzothiazole derivatives **3a** and dimedone **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).¹¹²

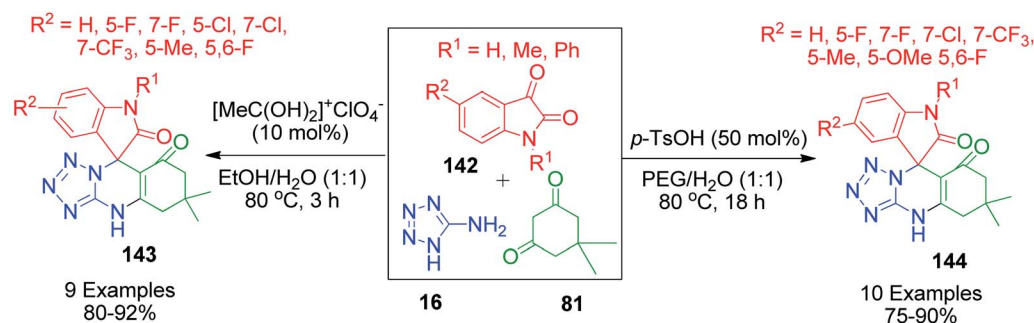
A lemon juice-mediated ecofriendly one-pot three-component approach for the synthesis of diverse pharmaceutically important tricyclic fused imidazoles **134** tethered with aryl and various cyclic 1,3-dicarbonyls was developed by A. Saha and coworkers. This metal-free strategy involved reactions between arylglyoxals **132** and *N*-alkyl-4-hydroxyquinolone/4-hydroxycoumarin **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).¹¹³



Scheme 44 Synthesis of novel benzo[g]thiazolo[2,3-b]quinazolin-4-ium hydroxide derivatives.



Scheme 45 Synthesis of 2-arylbenzo[d]imidazo[2,1-b]thiazoles **139** and **140** linked with a barbituric acid moiety.



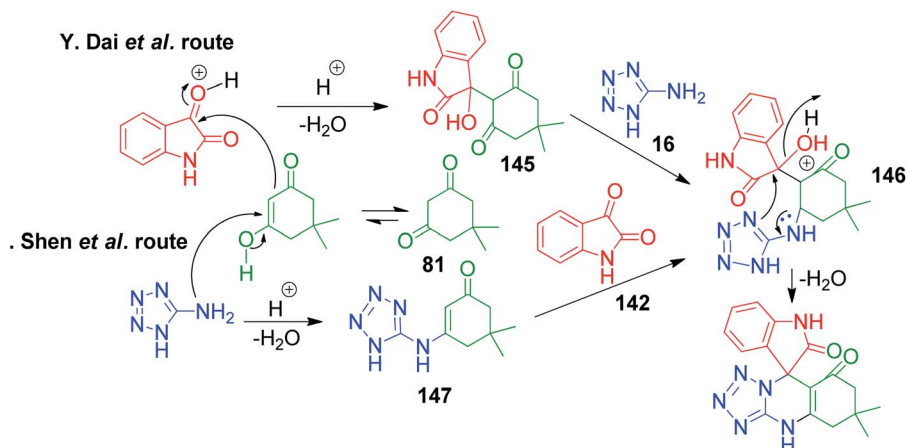
Scheme 46 Synthesis of spiro-imidazoquinazolinones **143** and **144** in the presence of acid catalysts.

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).¹¹⁴

Instead of using arylglyoxals directly, A. Jana *et al.* utilized aryl alkynes 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*]

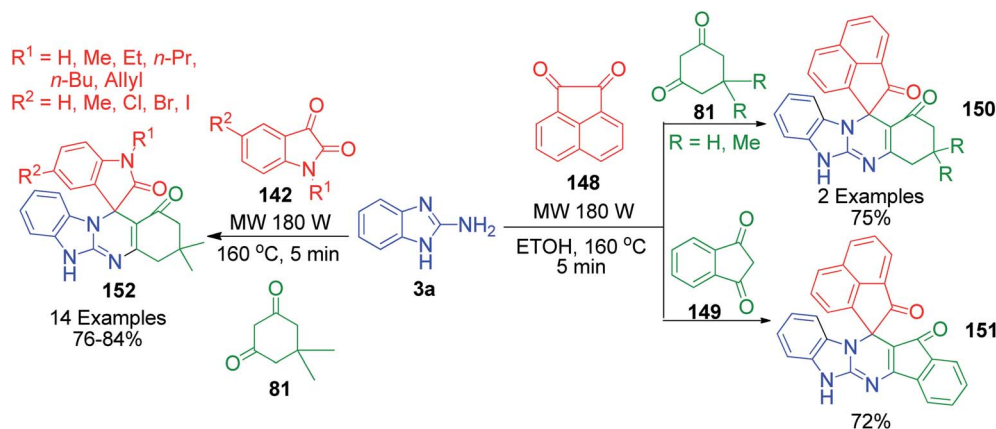
thiazoles linked with a barbituric acid moiety. These three-component reactions were performed between 2-aminobenzothiazole derivatives **3b**, barbituric acid derivatives **136** and aryl alkynes/aryl methyl ketones **137** and **138** at 110 °C under microwave heating. Mechanistically, aryl alkynes **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).¹¹⁵

When aldehydes are replaced by ketones such as isatin, acenaphthoquinone and related compounds in three-



Scheme 47 Mechanistic routes illustrating the generation of a common intermediate **146** through two different pathways for the synthesis of spiro-quinazolinones.





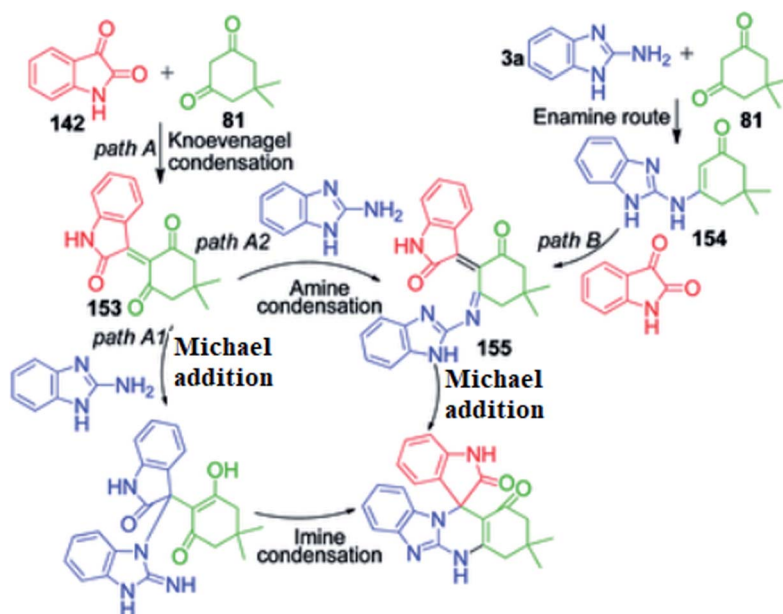
Scheme 48 Synthesis of spiro-benzimidazoquinazolinones under microwave irradiation.

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 ($[\text{MeC}(\text{OH})_2]^+\text{ClO}_4^-$) 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).

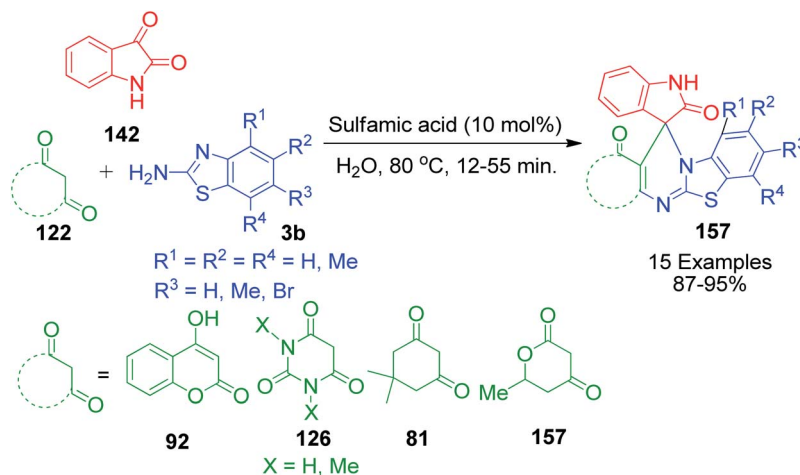
In the first step of the mechanistic route described by Y. Dai *et al.*, the condensation of isatin and dimedone was proposed to give intermediate **145**, which is then attacked by 5-amino-1*H*-tetrazole to provide intermediate **146**. This intermediate **147** in the study by M. Shen *et al.* was 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).

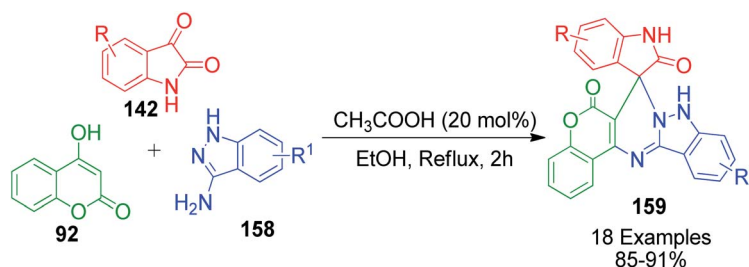
P. Maloo's group reported a straightforward novel multi-component route to access spiro-benzimidazoquinazolinones **150**, **151** and **152**.¹¹⁸ It involves a one-pot three-component reaction of acenaphthoquinone/isatin **148** and **142**, 1,3-diketone **81** and 2-aminobenzimidazole **3a** in ethanol 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



Scheme 49 Proposed mechanistic pathways for the synthesis of spiro-benzimidazoquinazolinones.



Scheme 50 Synthesis of structurally diverse spiroheterocycles with fused heterosystems.



Scheme 51 Synthesis of indazole-fused spiroheterocycles 159 catalyzed by acetic acid.

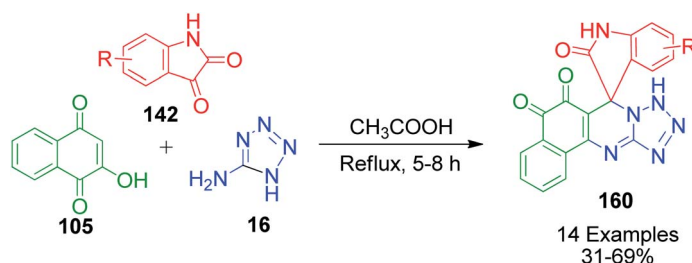
isatin generates intermediate **153**, which undergoes reaction with 2-aminobenzimidazole **3a** in two possible ways *via* the Knoevenagel-Michael-imine route (path A1) or Knoevenagel-imine-Michael route (path A2). In path B, enamine **154** is generated through dimedone **81** and 2-aminobenzimidazole, 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-aminobenzothiazole **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 1*H*-indazole-3-amine **158** instead of 2-aminobenzothiazole **3b** in a one-pot three-component condensation with 4-hydroxy-2*H*-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

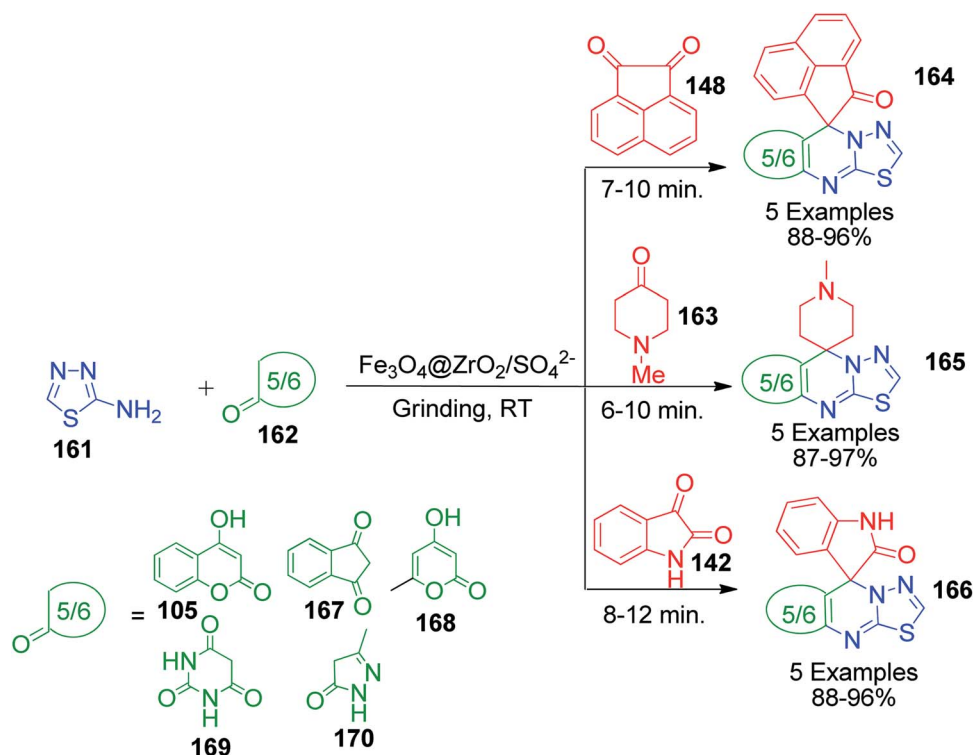
A series of novel spirooxindole-*O*-naphthoquinone-tetrazolo [1,5-*a*]pyrimidine hybrids **160** was synthesized and evaluated as potent antitumor agents by L. Wu and coworkers. The synthesis of these ternary hybrid molecules was carried out through the condensation reaction between 2-hydroxy-1,4-naphthoquinone **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



Scheme 52 Synthesis of spirooxindole-*O*-naphthoquinone-tetrazolo[1,5-*a*]pyrimidine.

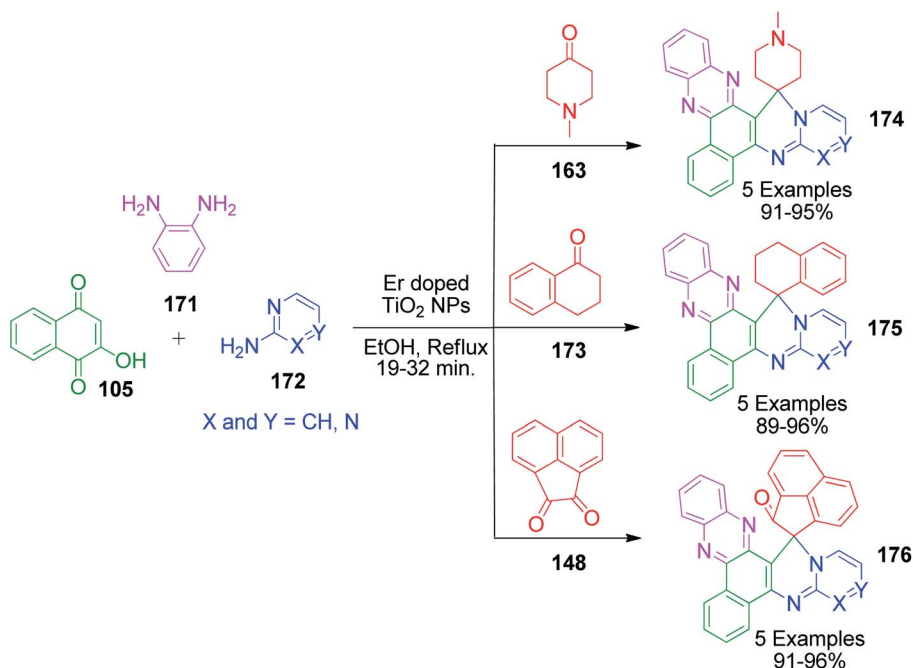




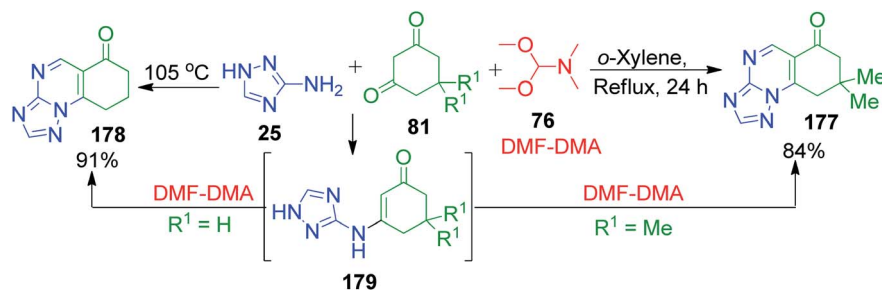
Scheme 53 Synthesis of spiroheterocycles spiroannulated with 1,3,4-thiadiazolo[3,2-*a*]pyrimidine.

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 ($\text{Fe}_3\text{O}_4@\text{ZrO}_2/\text{SO}_4^{2-}$) under solvent-free conditions with grinding at room temperature (Scheme 53).¹²²

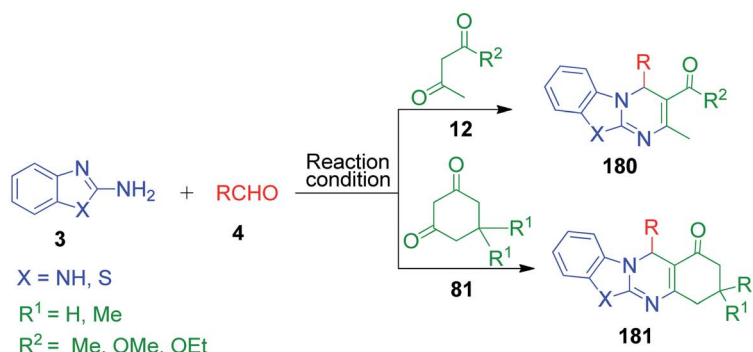
K. Verma *et al.* developed a domino protocol to construct spiroannulated pyrimidophenazines **174**, **175** and **176**. The synthesis of these hybrid molecules with advantageous heterocyclic substructures involves the four-component reaction of 2-hydroxynaphthalene-1,4-dione **105**, benzene-1,2-diamine **171**, cyclic ketones (**163**, **173** and **148**) and 2-aminoazines **172** in the presence of erbium-doped TiO_2 NPs as a recyclable and reusable



Scheme 54 Four-component synthesis of spiroannulated pyrimidophenazines.



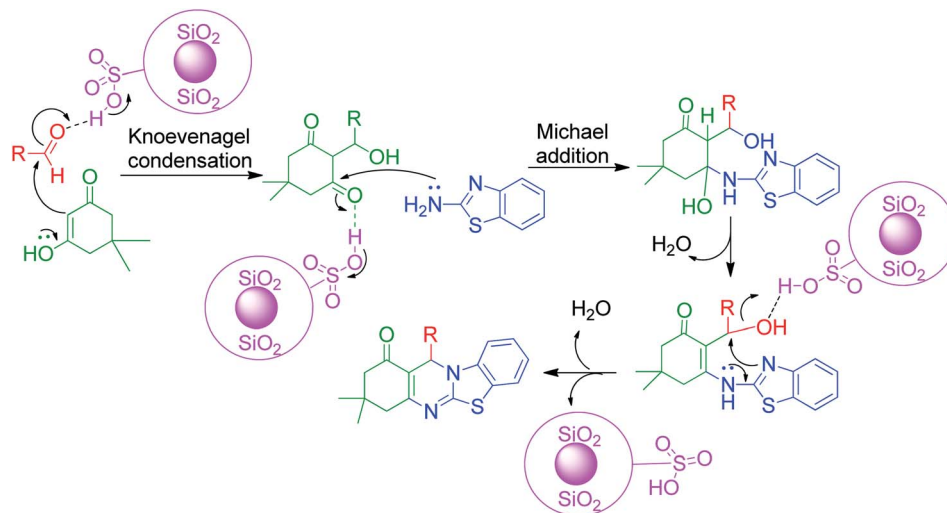
Scheme 55 Three-component synthesis of 7-unsubstituted 4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines 177 and 178.



X	Reaction conditions	Time	Yield (%)	No. of examples		Reference
				180	181	
S	TBAHS (30 mol%), Ethylene glycol, 120 °C	1–2 h	68– 83	8	2	126
S	FeF ₃ (10 mol%), 100 °C	0.5 h	70– 97	8	18	127
S	C/TiO ₂ -SO ₃ -SbCl ₂ (0.1 g), 90 °C	1–3 h	85– 93	13	5	128
S	Hydrotalcite (Mg-Al-CO ₃), 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-Fe ₃ O ₄ @SiO ₂ @SO ₃ , 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.

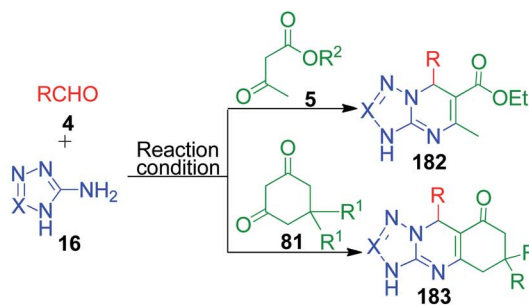




Scheme 57 Proposed reaction pathway to explain the synthesis of benzothiazolopyrimidines.

heterogeneous acid catalyst under refluxing ethanol (Scheme 54).¹²³ The doping of TiO₂ with erbium was found to enhance the catalytic efficiency of TiO₂, facilitating the reaction to provide the products with comparatively better yields.

Formaldehyde equivalents, dimethoxy *N,N*-dimethylmethanamine (DMF-DMA) **76**, provide less substituted fused quinoxalinone rings, as shown in the approach developed by C.-B. Zhang and coworkers.¹²⁴ In their reactions, cyclohexane-1,3-



X	Reaction conditions	Time (min)	Yield (%)	No. of examples		Reference
				182	183	
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	(γ-Fe ₂ O ₃ @Ph-PMO-NaHSO ₄) 100 °C	10–40	85–96	3	19	134

Scheme 58 Some reported methods for the synthesis of tetrazolo/triazolo fused pyrimidines.



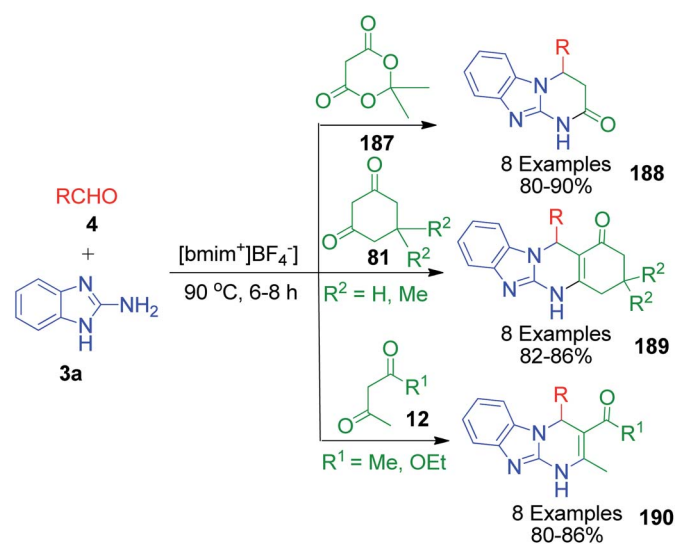
dione **81** and DMF-DMA **76** were mixed and heated at 60 °C. After the mixture was completely homogenized, 3-amino-1,2,4-triazole **25** was added and then the reaction temperature was increased to 105 °C. After a few minutes, the solidified mixture was cooled and diluted with propan-2-ol to obtain 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).¹²⁵

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-diketocompounds **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.¹²⁶ Other catalysts have also been used to explore this methodology such as FeF₃,¹²⁷ SbCl₂ grafted over sulfonic acid-functionalized carbon@titania composites (C/TiO₂-SO₃-SbCl₂),¹²⁸ Mg-Al-CO₃ hydrotalcite,⁸⁵ chitosan in 2% acetic acid,⁸⁶ nano-Fe₃O₄@-SiO₂@SO₃,⁴⁵ graphite oxide¹²⁹ (Scheme 56). The mechanism when the reaction is catalyzed using nano-Fe₃O₄@SiO₂@SO₃ as proposed by the author is shown in Scheme 57.

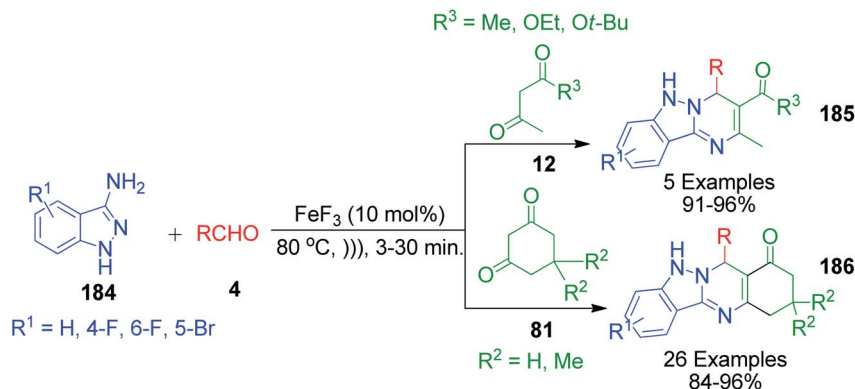
3-Amino-1,2,4-triazole/5-aminotetrazole **16** has also been utilized together with cyclic and non-cyclic β -ketocompounds for the synthesis of various tetrazolo/triazolo-fused pyrimidine moieties **182** and **183**. K. Kumari *et al.* demonstrated a three-component reaction, wherein a mixture containing 3-amino-1,2,4-triazole **17**, aromatic aldehyde **3**, dimedone/ethyl acetoacetate **83** and **4** was grounded using an agate mortar in the presence of [Bmim]BF₄.¹³⁰ 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.¹³¹ Similarly, other catalysts such as Nafion-H,¹³² PEG-400,¹³³ and NaHSO₄ immobilized on core/shell phenylene-bridged periodic mesoporous organosilica magnetic nanoparticles (γ -Fe₂O₃@Ph-PMO-NaHSO₄)¹³⁴ 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 1*H*-indazole-3-amines **184**, cyclic **81** and acyclic 1,3-dicarbonyl compounds **12** and various aldehydes **4** as starting components (Scheme 59).¹³⁵ 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.

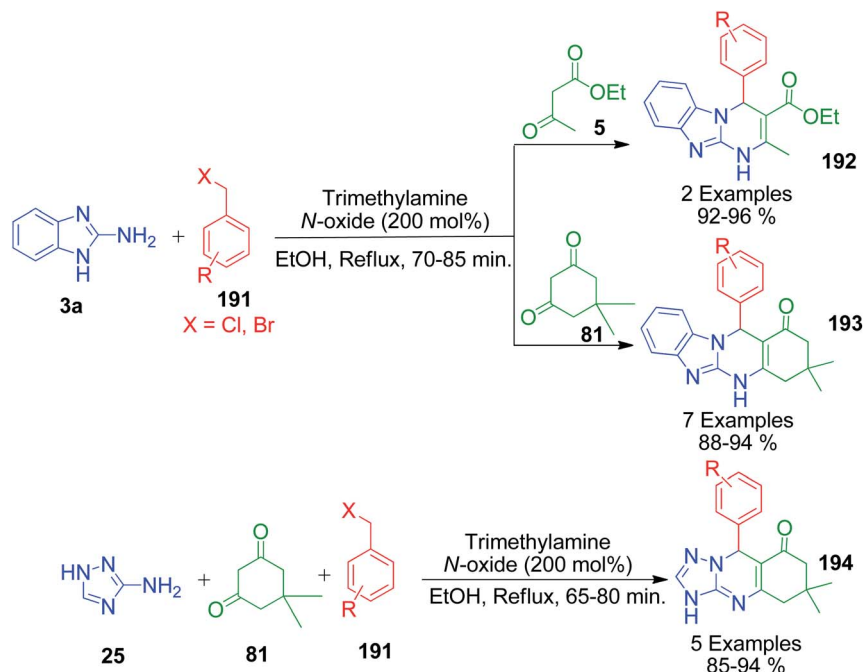


Scheme 60 Ionic liquid-mediated synthesis of various pyrimidine derivatives.



Scheme 59 Ultrasonic wave-assisted synthesis of tetrahydroindazolo[3,2-*b*]quinazoline.



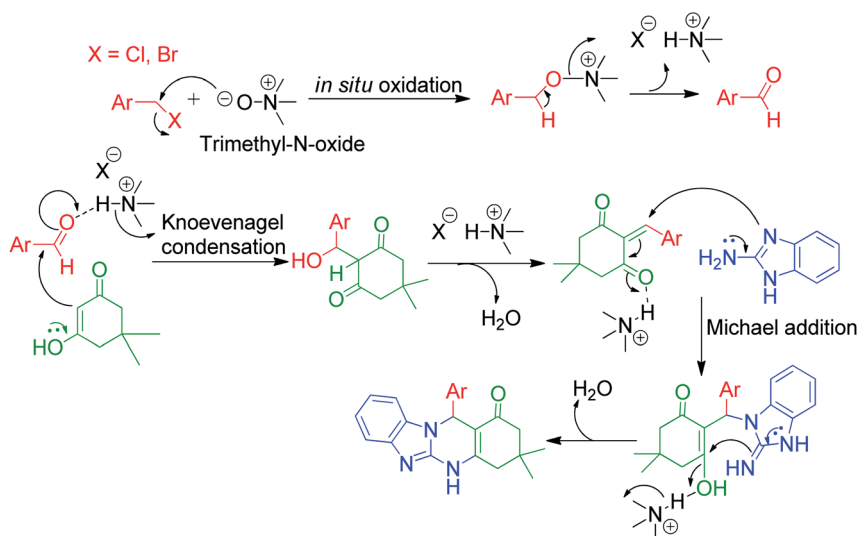


Scheme 61 An interesting protocol for the synthesis of triazolo/benzimidazolo quinazolinones.

A straightforward and green route to 4-aryl-3,4-dihydro-1*H*-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.¹³⁶ 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/benzimidazolo 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

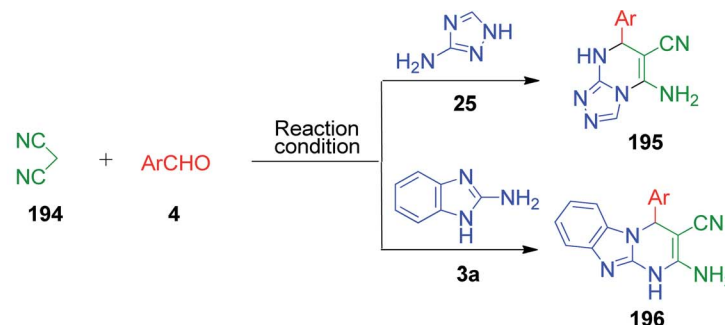


Scheme 62 Proposed mechanistic route to explain the synthesis of triazolo/benzimidazolo quinazolinones.

refluxing ethanol (Scheme 61).¹³⁷ 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).

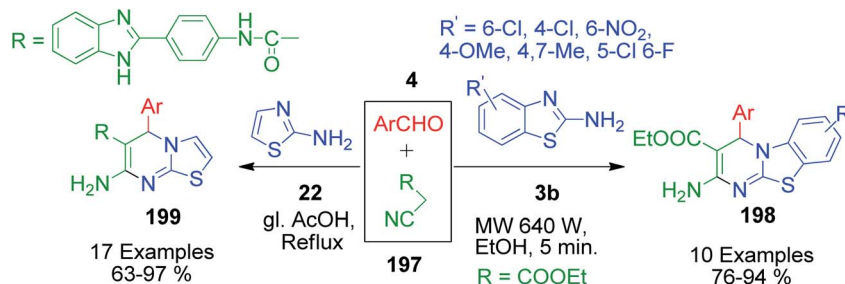
2.1.1.4 MCRs involving malonitrile and analogous compounds. Azaheterocycle condensed pyrimidine systems have also been synthesized using nitrile group-activated methylene



Reaction condition	Time (min)	Yield (%)	No. of example		Reference
			195	196	
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			
H ₃ BO ₃ (20 mol%), CTAB (15 mol%), H ₂ O, 60 °C	20	80–96	11	-	139
DBU (100 mol%), EtOH, Reflux	20	82–92	16	-	140
[H ₂ -DABCO][H ₂ PO ₄] ₂ , 100 °C	30–75	90–96	10	-	141
[H ₂ -DABCO][ClO ₄] ₂ , 100 °C	25–60				
γ -Fe ₂ O ₃ @SiO ₂ @ [Bis-APTES]Cl ₂ NPs, 90 °C	20–50	86–95	12	-	89
RHA-[pmim]HSO ₄ , 100 °C	2–5	88–93	-	10	80
PEG-400:H ₂ O (4:1), Reflux	6–8 h	72–86	-	7	142
Na ⁺ -MMT-[pmim]HSO ₄ , 100 °C		87–95	-	22	31
[H-pi]HSO ₄ (3.5 mol%), 100 °C		85–97	10	12	143

Scheme 63 Synthesis of multi-substituted [1,2,4]-triazolo-[4,3-a]pyrimidines.





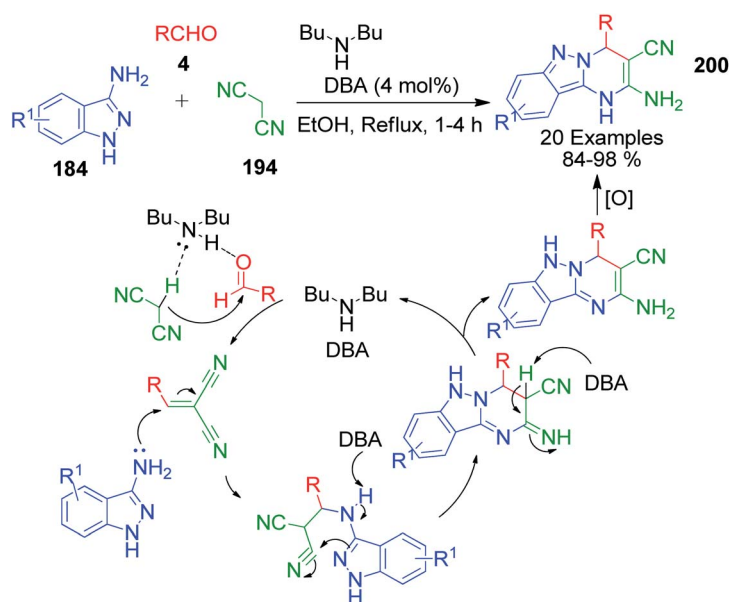
Scheme 64 Synthesis of thiazole/benzothiazole ring-fused pyrimidine derivatives.

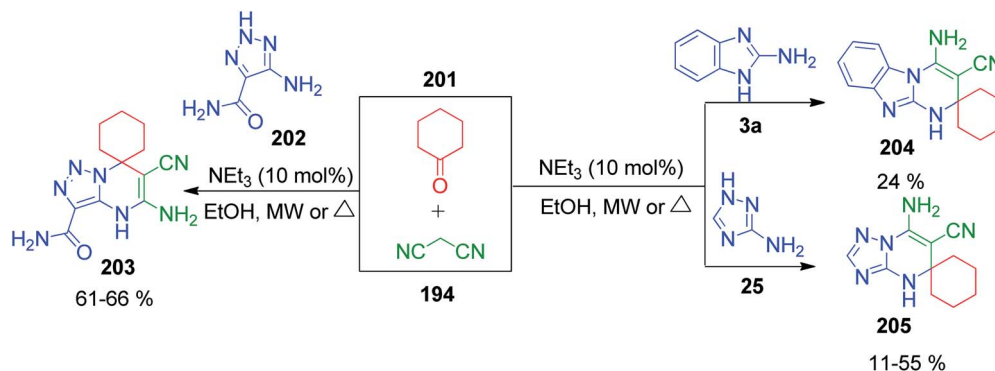
compounds such as malonitrile and alkyl cyanoacetate. K. Ablajan *et al.* described a method involving the synthesis of 5-amino-7-aryl-7,8-dihydro-[1,2,4] triazolo[4,3-*a*]-pyrimidine-6-carbonitrile derivatives **195** and **196** *via* the one-pot reaction of 3-amino-1,2,4-triazole **25**, malononitrile **194** and aryl aldehydes **4** in the presence of 20 mol% NaOH in ethanol under conventional heating or ultrasonic irradiation.¹³⁸ 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 (H_3BO_3) in aqueous micellar,¹³⁹ DBU,¹⁴⁰ $[\text{H}_2\text{-DABCO}][\text{H}_2\text{PO}_4]_2$ or $\text{DABCO}[\text{ClO}_4]_2$,¹⁴¹ $\gamma\text{-Fe}_2\text{O}_3@ \text{SiO}_2@ [\text{Bis-APTES}]\text{Cl}_2$ nanoparticles,⁸⁹ Brönsted acidic ionic liquid supported on rice husk ash ($\text{RHA-}[\text{pmim}]\text{HSO}_4$),⁸⁰ polyethylene glycol (PEG-400) in water,¹⁴² nanoporous sodium montmorillonite clay ($\text{Na}^+\text{-MMT}$)-modified 1-methyl-3-(trimethoxysilylpropyl)-imidazolium hydrogen sulfate ($\text{Na}^+\text{-MMT-}[\text{pmim}]\text{HSO}_4$),³¹ and 1,4-piperazinium hydrogen sulfate ($[\text{H-pi}]\text{HSO}_4$).¹⁴³ 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.

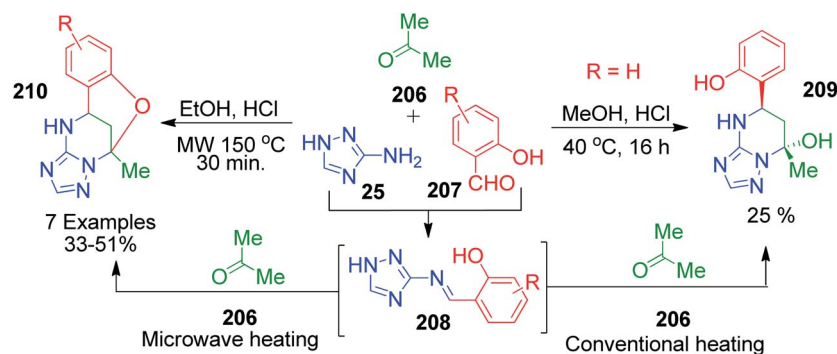
S. Nalawade and coworkers reported a method to achieve the regioselective synthesis of pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylate **198** by the reaction of ethylcyanoacetate with substituted benzaldehyde **4** and 2-aminobenzothiazol **3b** in ethanol under microwave irradiation operating at 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-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)-2-cyanoacetamide **199** was prepared by mixing ethyl cyanoacetate with 4-(1*H*-benzo[*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).¹⁴⁵

Novel tricyclic pyrimido[1,2-*b*]indazole-3-carbonitrile derivatives **200** containing both biologically active pyrimidine and

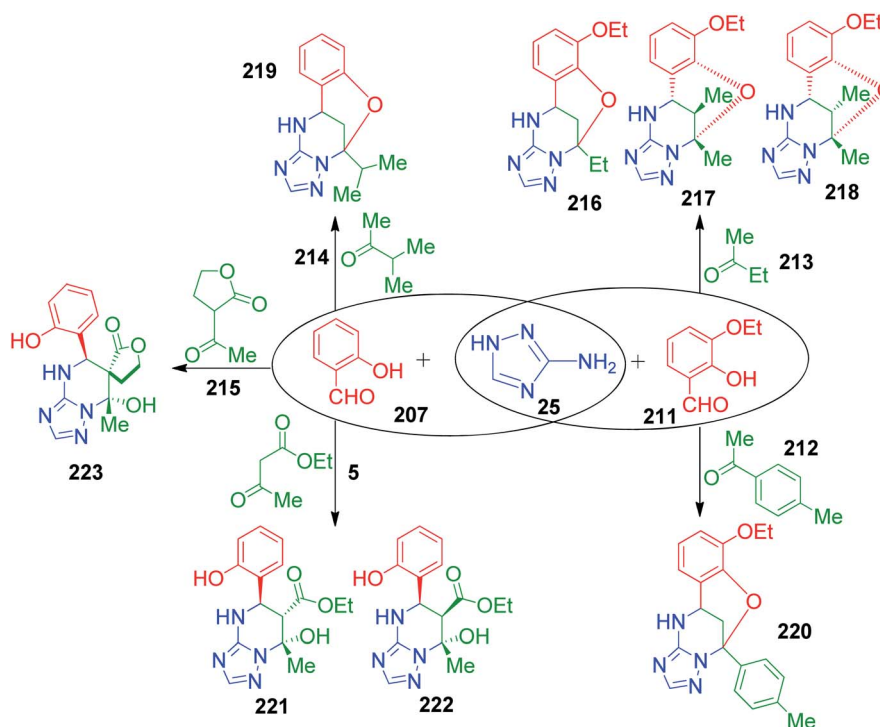
Scheme 65 Synthesis and proposed mechanism for tricyclic pyrimido[1,2-*b*]indazole-3-carbonitriles **200**.



Scheme 66 Synthesis of triazole and benzimidazole-fused spiro derivatives under microwave and conventional heating.

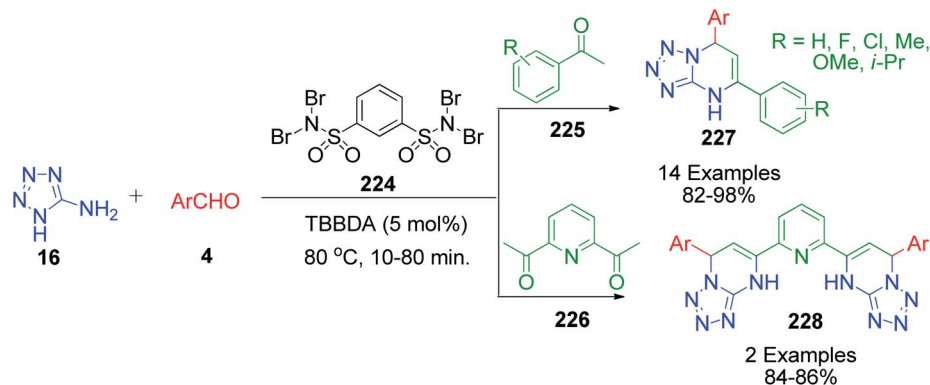


Scheme 67 Synthesis of two different products under microwave and conventional heating.

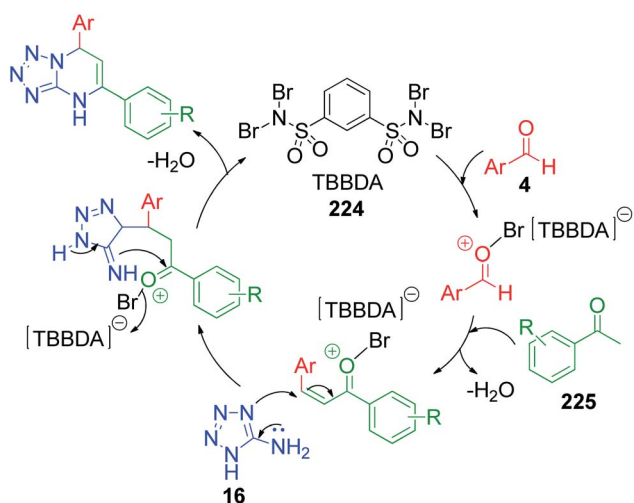


Scheme 68 Synthesis of various tetrahydropyrimidines depending upon the structure of acetones used.





Scheme 69 Solvent-free synthesis of dihydropyrimidines and bis-dihydropyrimidines.

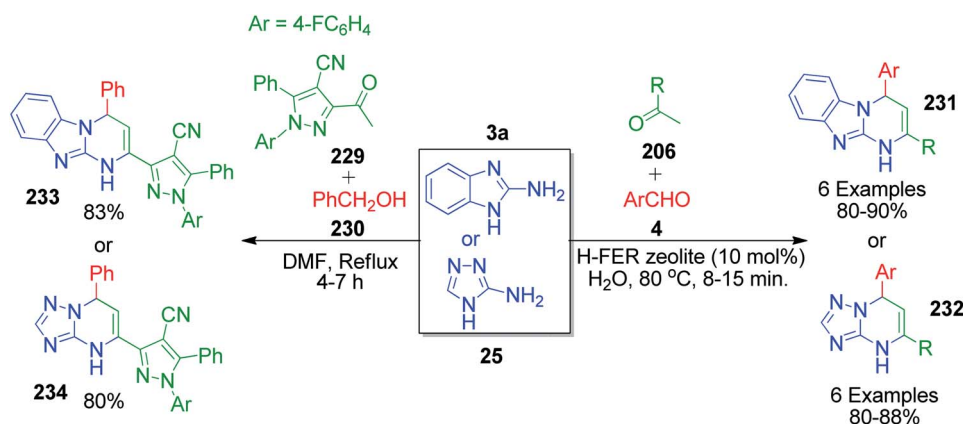


Scheme 70 Proposed mechanistic pathway to dihydropyrimidines.

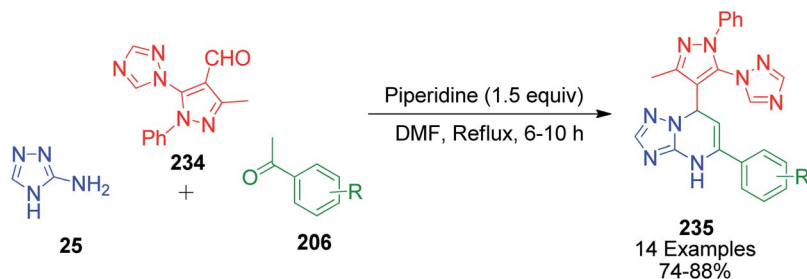
indazole templates were synthesized *via* the three-component reaction of 1H-indazol-3-amine **184**, aldehydes **4**, and malononitrile **194** catalyzed by the base di-*n*-butylamine (DBA) in ethanol.¹⁴⁶ This group-assisted-purification (GAP) chemistry process follows a proposed mechanism, as shown 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).¹⁴⁷

2.1.1.5 MCRs involving acetone and analogues compounds. The Biginelli-like three-component condensation following an unexpected alternative direction leading to a tetrahydropyrimidine 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).¹⁴⁸ 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 71 Synthesis of [1,2,4]triazolo[1,5-a]pyrimidines and pyrimido[1,2-a]benzimidazole derivatives.



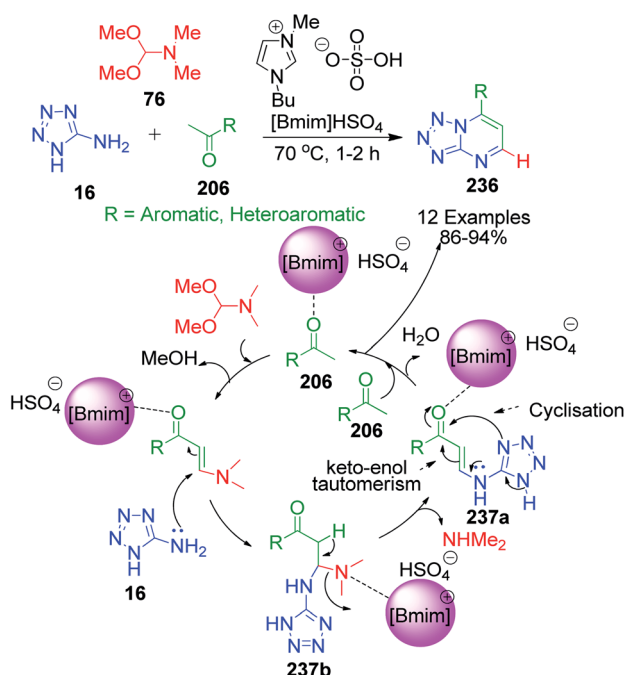
Scheme 72 Piperidine-catalyzed synthesis of new pyrazole-triazolopyrimidine hybrids.

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 **211** 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 spirypyrimidine **223** was observed with 71% yield when 3-acetyl-dihydrofuran-2(3*H*)-one **215** was used in the present Biginelli-like multicomponent reaction (Scheme 68).

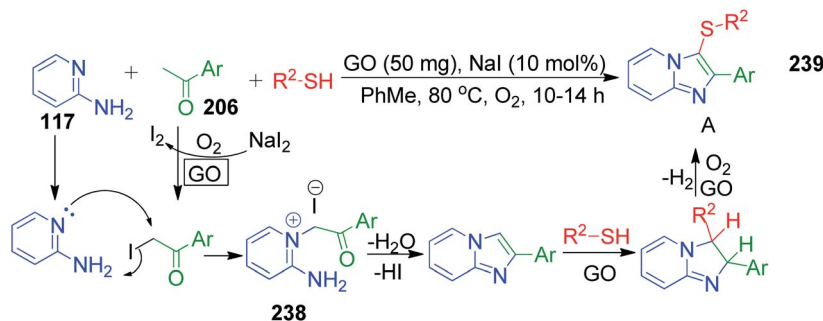
Methyl ketones work analogously to β -dicarbonyl compounds in the MCR but have less acidic protons compared to the latter due to the presence of only one electron-withdrawing keto group. R. Ghorbani-Vaghei *et al.* developed a series of tetrazole-fused pyrimidine derivatives utilizing acetophenone **225**, 5-aminotetrazole **16** and various aromatic aldehydes **4**.⁴² Condensation of these reactants at 80 °C under solvent-free conditions together with *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide (TBBDA) **224** as a catalyst afforded 5,7-diaryl-4,7-dihydro-tetrazolo[1,5-*a*]pyrimidines **227**. They also reported the synthesis of novel bis-dihydro-tetrazolo[1,5-*a*]pyrimidine **228** via the reaction of diacetylpyridine **226** with 2 equivalents of each aldehyde **4** and 5-aminotetrazole **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 acetophenone 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-ferrierite 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**.¹⁴⁹ A different methyl ketone-linked compound, 3-acetyl-1-(4-fluorophenyl)-5-phenyl-1*H*-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)-1*H*-pyrazole-4-carbonitrile/1-(4-fluorophenyl)-3-(5,8-dihydro-5-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-7-yl)-5-phenyl-1*H*-pyrazole-4-carbonitriles **233** and **234** (Scheme 71).¹⁵⁰

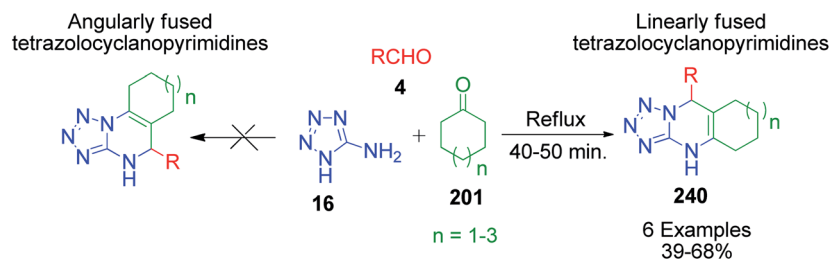


Scheme 73 Ionic liquid-mediated synthesis of fused tetrazolo[1,5-*a*]pyrimidines and proposed mechanistic pathway.





Scheme 74 Selective and tandem protocol to access 3-sulfenylimidazo[1,2-a]pyridines.

Scheme 75 Synthesis of tetrazolopyrimidines annulated to C₆–C₈ carbocycles.

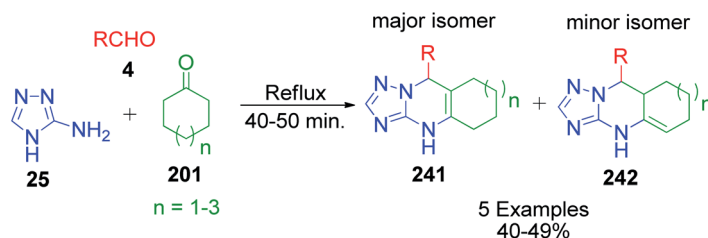
V. Pogaku *et al.* developed a one-pot three-component approach to synthesize novel pyrazole-linked triazolopyrimidines as a potent α -glucosidase inhibitor by performing a reaction using acetophenone derivatives **206**, 3-methyl-1-phenyl-5-(1*H*-1,2,4-triazol-1-yl)-1*H*-pyrazole-4-carbaldehyde **234** and 4*H*-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-Dimethylformamidedimethylacetal **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-amino-1H-tetrazole **16**, dimethylformamidedimethylacetal **76** and acetophenones **206** was carried out in the ionic liquid 1-butyl-3-methylimidazolium hydrogen sulfate [bmim]HSO₄ at 70 °C. The formation of tetrazolo[1,5-*a*]pyrimidine **236** was proposed to proceed through α,β -unsaturated ketone intermediate **237a** generated *in situ* from the ionic liquid-supported condensation of acetophenone **206** and *N,N*-dimethylformamidedimethylacetal **76**. This intermediate is then

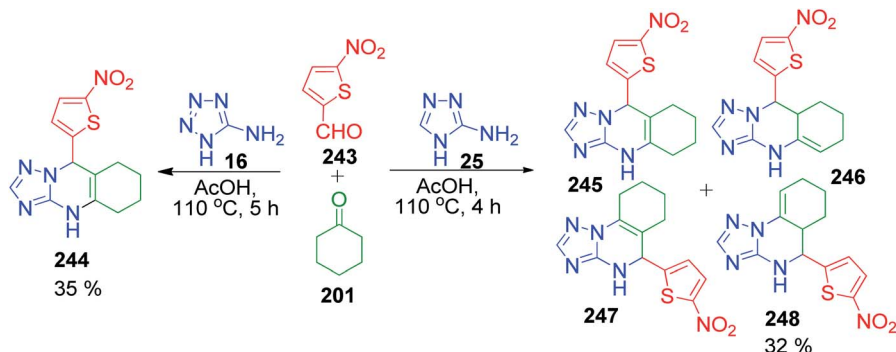
attacked by 5-amino-1H-tetrazole **16** followed by the subsequent loss of dimethyl amine to form another α,β -unsaturated ketone intermediate **237b**. The final step involves the keto–enol tautomerism of this intermediate, followed by cyclization *via* the elimination of a water molecule (Scheme 73).

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 *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).

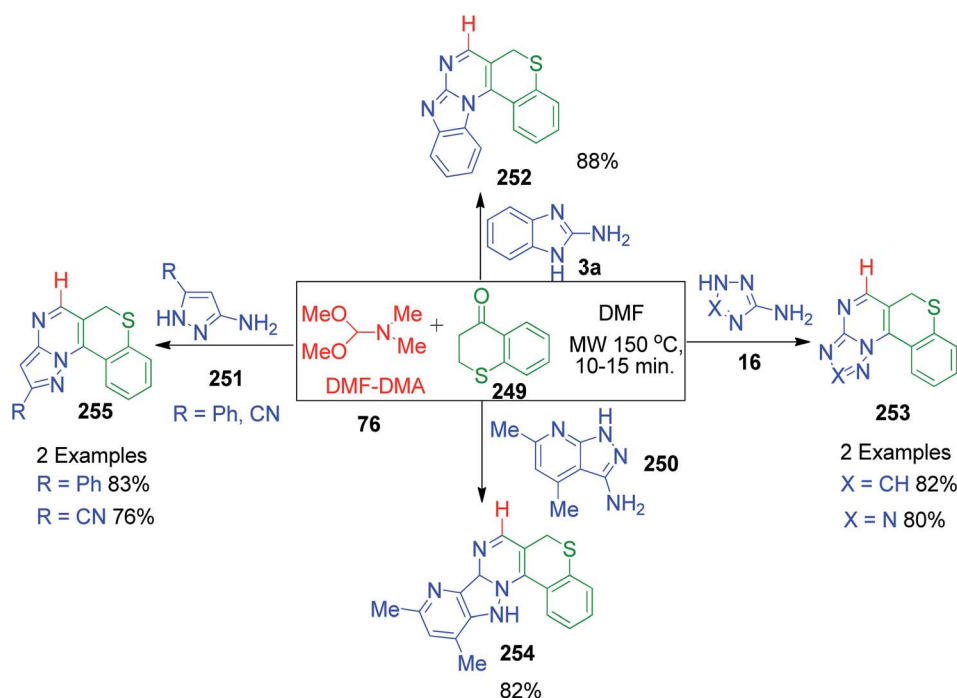
2.1.1.6 MCRs involving cyclohexanone and analogous compounds. A. A. Matveeva reported the synthesis of linearly structured azoloquinazolines with an admixture of isomers with angular ring fusion by the treatment of 3-amino-4*H*-1,2,4-triazole/5-amino-1*H*-tetrazole with α,β -unsaturated ketones of



Scheme 76 Synthesis of two isomers of linearly fused pyrimidine derivatives.



Scheme 77 Synthesis of linearly and angularly fused tetrazolo/triazoloquinazolines.



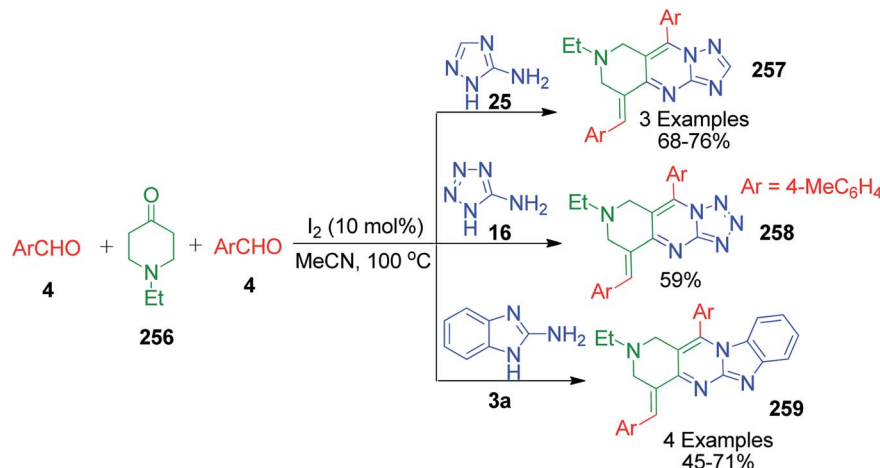
Scheme 78 Microwave-assisted synthesis of various azole-fused pyrimidines.

cyclohexanone series. The extension of this reaction to ylidenecyclohexanone analogues with a greater alicycle size (C_7 and C_8) 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 C_6 to C_8 carbocycles was studied. The reactions were carried out by refluxing a solventless equimolar mixture of 5-amino-1*H*-tetrazole **16**, aldehyde **4**, *viz.* furfural and benzaldehyde, and ketone **201**, *viz.* cyclohexanone, cycloheptanone, and cyclooctanone, for 40–50 min, resulting in the formation of cyclanotetrazolopyrimidines **240** in moderate yields (Scheme 75).¹⁵⁵ The regioselectivity 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.

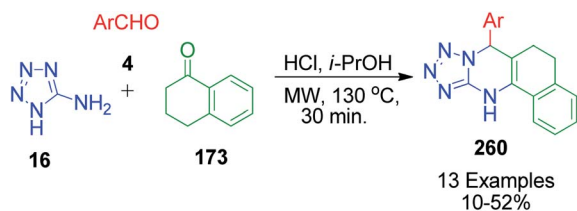
Next, the same researcher described the synthesis of two isomers of linearly fused pyrimidine derivatives with a C_6 – C_8 cycloalkene ring fused at the C^5 – C^6 bond, differing by the position of the double bond in the cycloalkene ring.¹⁵⁶ In this method, a more nucleophilic aminoazole, 4*H*-1,2,4-triazol-5-amine **25**, was heated with equimolar amounts of benzaldehyde/furfural **4** and cycloalkanone **201** (C_6 – C_8) under refluxing conditions (Scheme 76). Phenyl(furyl)-substituted linearly fused cycloalkatriazolopyrimidines **241** and **242** containing a common double bond to the cycloalkene and tetrahydropyrimidine rings were obtained as the major isomers together with a minor isomer having a C^4 – C^5 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-





Scheme 79 Iodine-catalyzed synthesis of various azole fused pyrimidines.



Scheme 80 Synthesis of novel tetrazolo-fused pyrimidines under microwave heating.

aminotetrazole/3-amino-4*H*-1,2,4-triazole **16** and **25** with 5-nitrothiophene-2-carbaldehyde **243** and cyclohexanone **201** in acetic acid at 110 °C. The obtained product, 9-(5-nitrothiophen-2-yl)-4,5,6,7,8,9-hexahydrotetrazolo[5,1-*b*]-quinazoline **244** was found to be linearly fused and consistent with previous reports. An analogous reaction with 3-amino-4*H*-1,2,4-triazole afforded a mixture of linearly and angularly fused isomeric hexahydro-triazoloquinazolines **245**, **246**, **247** and **248** (Scheme 77).¹⁵⁷

E. M. H. Abbas *et al.* developed an approach where dimethylformamide-dimethylacetal **76** (DMF-DMA) was utilized as an alternative to formaldehyde in the MCR synthesis of novel poly-heterocyclic ring systems **252**, **253**, **254** and **255**. Various azole-fused pyrimidine systems **16**, **3a**, **250** and **251** were obtained by the three-component reactions between 1-benzothiopyran-4-ones **249**, various aminoazoles and DMF-DMA **76** performed in refluxing DMF under controlled microwave heating (Scheme 78).¹⁵⁸

The same research group also reported a direct and efficient approach for the synthesis of pyrido[4,3-*d*]triazolo[1',5'-*a*]pyrimidines **257**, pyrido[4,3-*d*]tetrazolo[1',5'-*a*]pyrimidine **258** and pyrido[4,3-4',5']pyrimido[1',2'-*a*]benzimidazoles **259**. Condensation of 1-ethyl-4-piperidone **256** and two equivalents of appropriate aromatic aldehyde **4** with 3-amino[1,2,4]triazole/5-aminotetrazole **25** and **16** in the presence of iodine under refluxing acetonitrile afforded the corresponding triazolo/tetrazolopyrimidines **257** and **258**. Reaction with 2-amino-benzimidazole **3a** under the same conditions afforded the

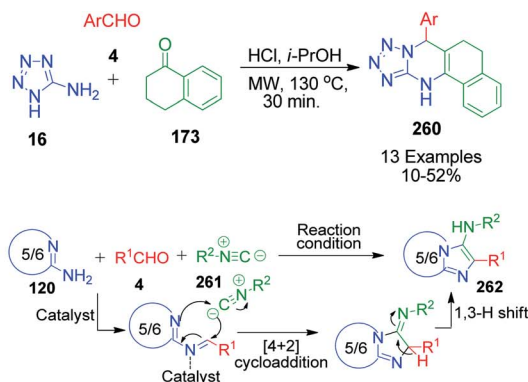
corresponding 1,2,3,4-tetrahydro-pyrido[4,3-*d*]benzoimidazolo[1,2-*a*]pyrimidines **259** (Scheme 80). When the reaction was carried out with 2 equivalents of 4-methyl benzaldehyde as the aldehydic component together with 2-aminobenzimidazole **3a** and 1-ethyl-4-piperidone, it yielded a mixture of an intermediate and the final product. The intermediate was then transformed into the final pyrimidine derivative *via in situ* oxidation (Scheme 79).¹⁵⁹

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 **260**. A reaction mixture containing α -tetralone **173**, 1*H*-tetrazol-5-amine **16**, and aromatic aldehyde **4** in isopropanol was heated under microwave irradiation at 130 °C using hydrochloric acid as a catalyst. The corresponding 7-aryl-5,6,7,12-tetrahydrobenzo[*h*]tetrazolo[5,1-*b*]quinazolines **260** were obtained after 30 min in 10–52% yield (Scheme 81).¹⁶⁰

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 **4**, 2-aminoazine/azoles **120** and isonitrile **261** 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

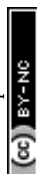
behaves as a vinylidene carbenoid, to give the intermediate. A subsequent prototropic shift generates the final fused 3-aminoimidazoles. Earlier published reviews illustrate multicomponent reactions based on the GBB reaction leading to the

synthesis of fused imidazole derivatives and their importance in the drug discovery program.^{161,162} In this review, we cover the recently developed GBB methods that have not been covered before. S. Keshipour and coworkers¹⁶³ used a *p*-TSOH/ZnCl₂



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%), ClCH 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.



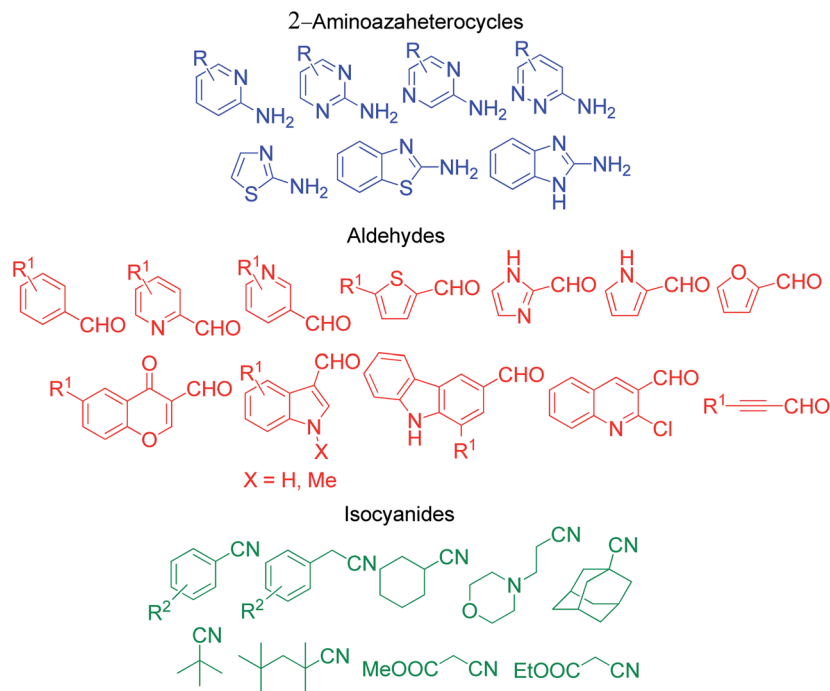
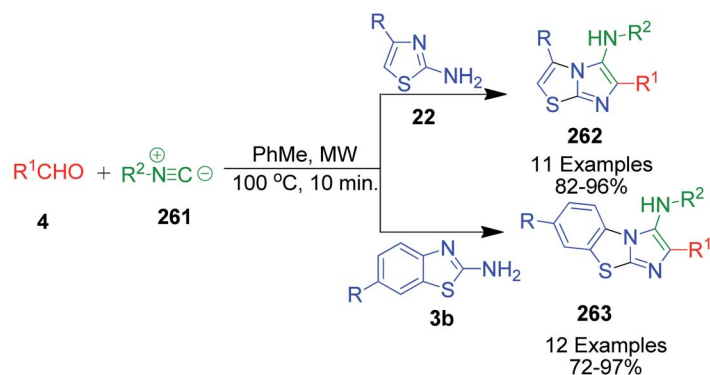
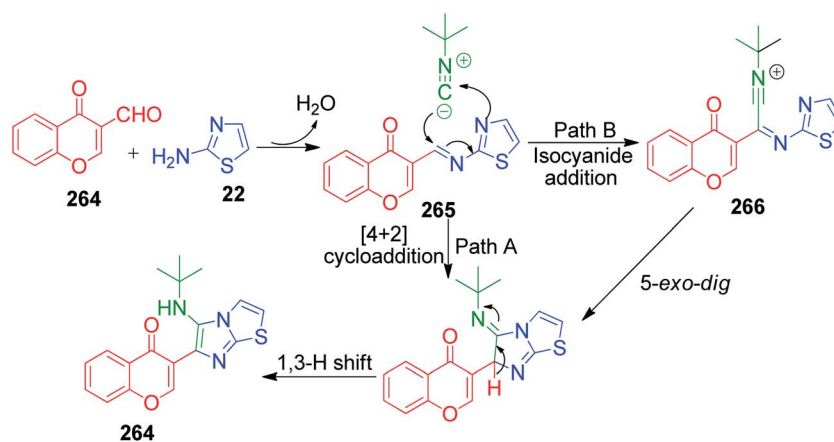


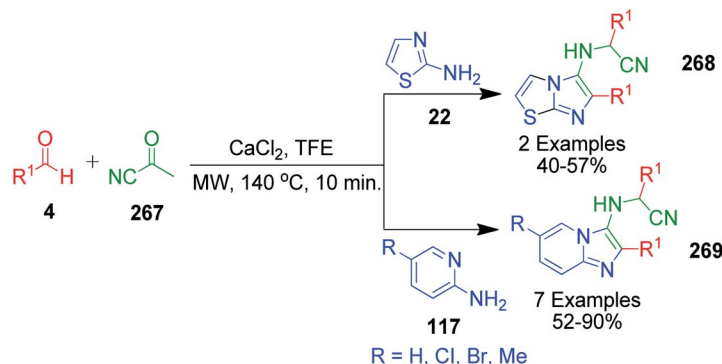
Fig. 6 Various derivatives of aminoazaheterocycles, aldehydes and isocyanides used in the GBB reaction.



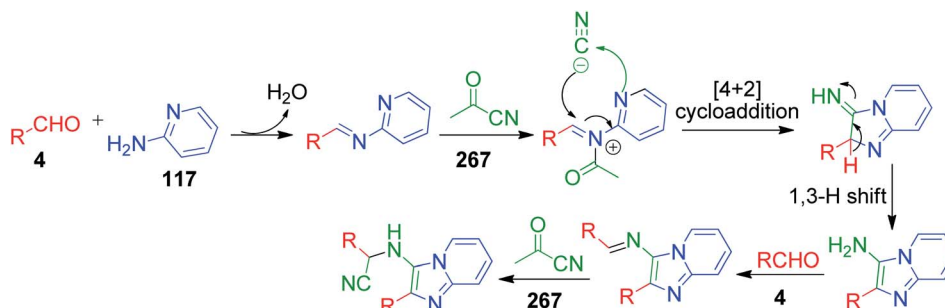
Scheme 82 Catalyst-free microwave-assisted GBB reaction.



Scheme 83 Reaction mechanism to explain the synthesis of GBB product.



Scheme 84 Microwave-assisted GBB reaction to synthesize substituted imidazoles.

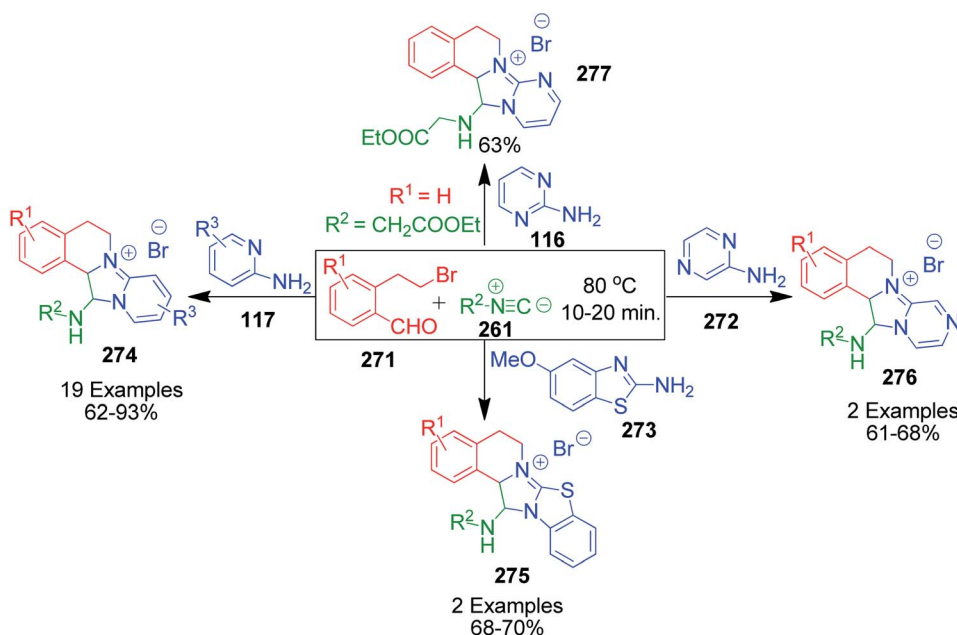


Scheme 85 Proposed mechanism involving the GBB reaction followed by Strecker reaction.

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 ,¹⁶⁴ NH_4Cl ,¹⁶⁵ urea-based/choline chloride system,¹⁶⁶ HCl /dioxane¹⁶⁷ glacial acetic acid,¹⁶⁸ β -cyclodextrin- SO_3H ,¹⁶⁹ $\text{Yb}(\text{OTf})_3$,^{171,172} InCl_3 ,¹⁷³ $\text{P}_2\text{O}_5/\text{SiO}_2$,¹⁷⁴ calix[n]arenes- SO_3H ,¹⁷⁵ $\text{Cu}(\text{OTf})_2/$

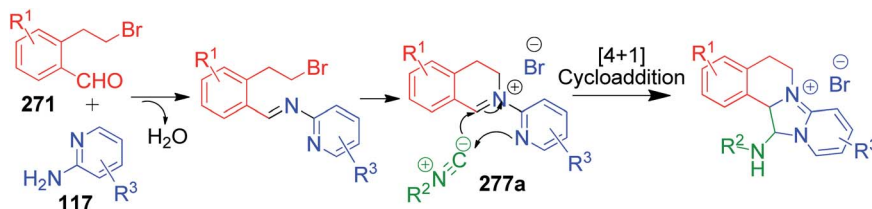
$\text{CuOTf} \cdot \text{C}_6\text{H}_6$,¹⁷⁶ electrostatically enhanced sulfuric acid (EESA),¹⁷⁷ visible light (24 W CFL),¹⁷⁸ and ZrCl_4 .¹⁷⁹ A brief summary regarding the reaction conditions, time, yields, *etc.* is shown in Scheme 81 (Fig. 6).

A series of twenty-three novel unsymmetrical bis-heterocycles having either imidazo[2,1-*b*]thiazole **262** or benzo

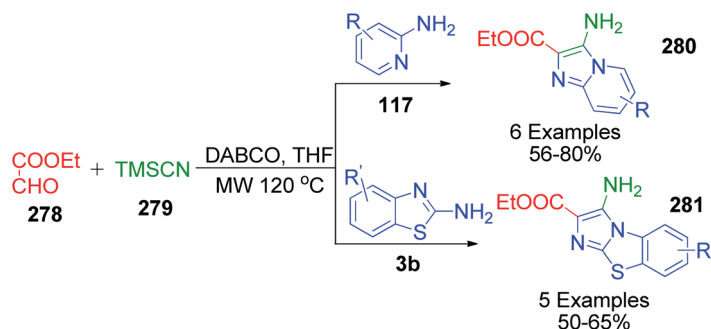


Scheme 86 Catalyst- and solvent-free synthesis of pyridoimidazo-DHIQ salts.

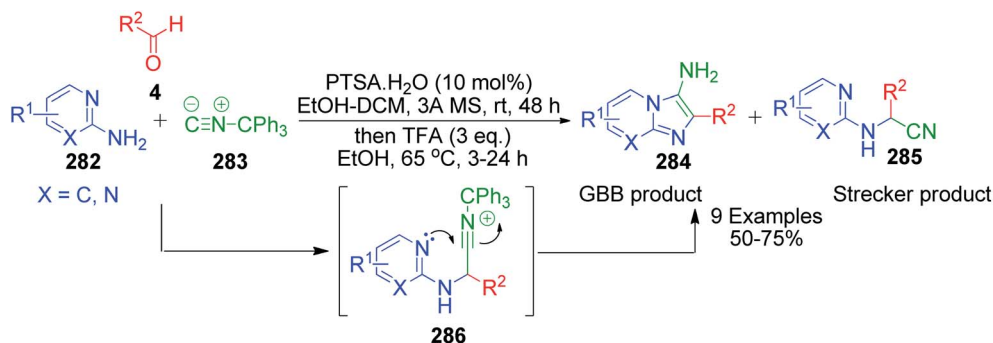




Scheme 87 Proposed mechanism involving a reactive cyclic iminium-induced GBB double annulation cascade route.



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



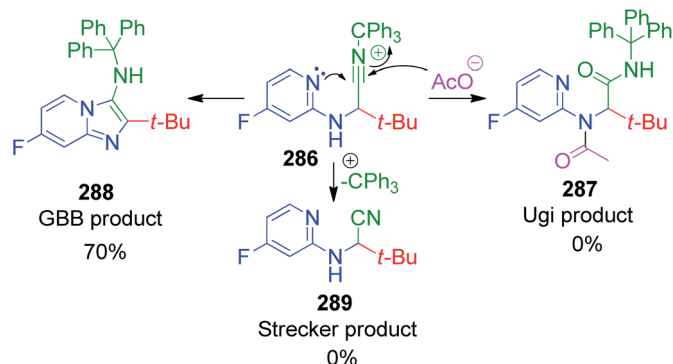
Scheme 89 Synthesis of imidazo[1,2-a]pyridin-3-amines through GBB 3-CR condensation/deprotection protocol.

[d]imidazo[2,1-b]thiazole **263** 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).¹⁸⁰ 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 **22** with aldehyde **264** to form an imine intermediate **265**. 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 **264**. In non-concerted pathway B, the nucleophilic addition of isocyanide to imine takes place to form nitrilium ion **266**, which undergoes sequentially a 5-*exo*-dig cyclization and

a prototropic shift to generate the target product **264** (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 **268** and **269** *via* the reaction of 2-aminothiazole/2-aminopyridine **22** and **117**, two equivalents of each aldehyde **4** and acetyl cyanide **267** in the presence of calcium chloride at 140 °C (Scheme 84).¹⁸¹ This methodology utilizes acetyl cyanide as a non-classical isocyanide replacement for TMSCN in a microwave-assisted GBB reaction followed by Strecker reaction under catalyst-free conditions (Scheme 85).

A. Sagar *et al.* developed an interesting one-pot GBB double annulation cascade process to synthesize diverse dihydroisoquinoline (DHIQ) salts **274**, **275**, **276** and **277**. In this catalyst- and solvent-free protocol, a reaction mixture containing various heteroaromatic amines **116**, **117**, **272** and **273**, 2-(2-bromoethyl)benzaldehyde derivatives **271** and isocyanides **261**

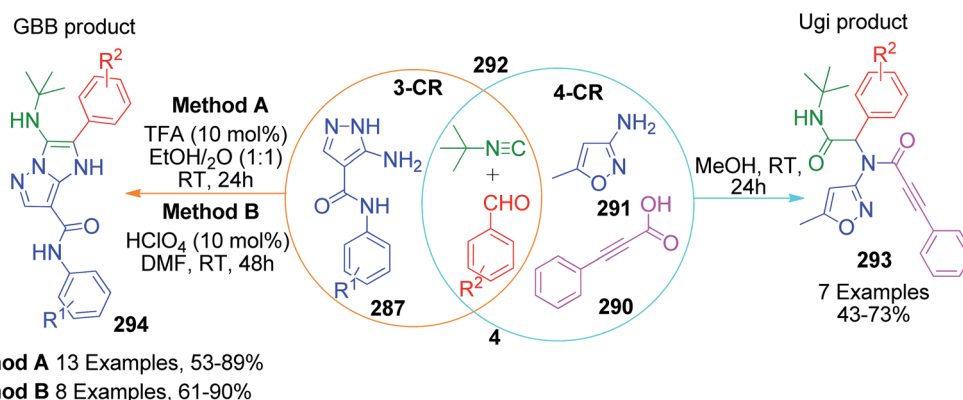


Scheme 90 Fate of nitrilium ion intermediate in the Ugi, Strecker and GBB reactions.

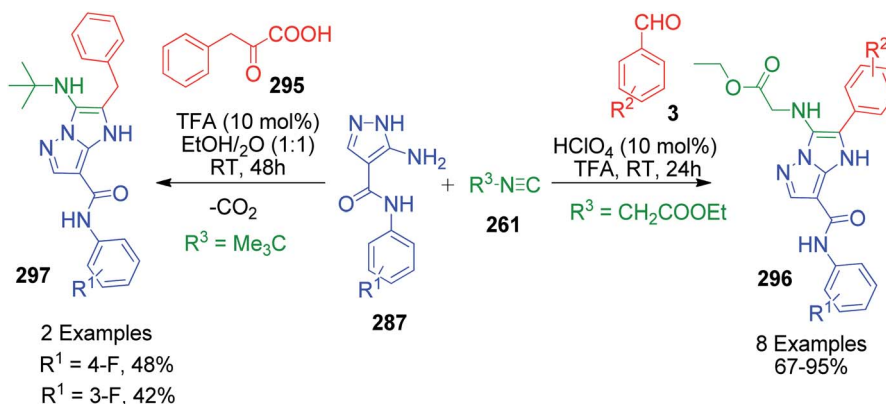
was heated at 80 °C for 10–20 min, leading to the construction of two privileged heterocyclic rings (Scheme 86).¹⁸² Mechanistically, the formation of pyridoimidazo-DHIQ salts **274–277** starts with the reactive cyclic iminium ion **277a** generated *in situ* from heteroaromatic amines and 2-(2-bromoethyl)benzaldehyde 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).¹⁸³ 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**.

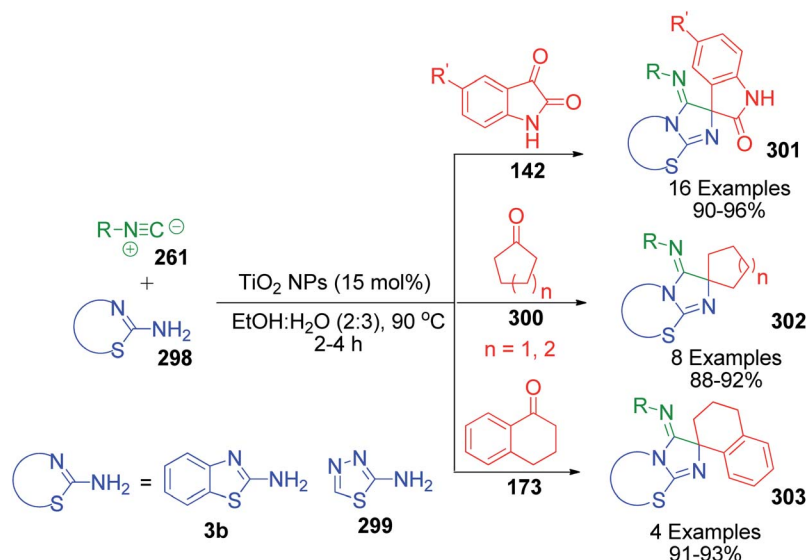
R. C. Cioc *et al.* reported a similar reaction, which describes the application of trityl isocyanide, as new isonitrile equivalent in a combinatorial approach for the first time. The Strecker reaction of 6-chloro-2-aminopyridine **282** with trityl isocyanide **283** and aldehyde **4** under the reaction conditions exclusively provided α -amino nitrile over the imidazo[1,2-*a*]pyridine **285** (Scheme 89).¹⁸⁴ 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



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



Scheme 92 GBB reaction with 5-amino-*N*-aryl-1H-pyrazole-4-carboxamide under two different conditions.

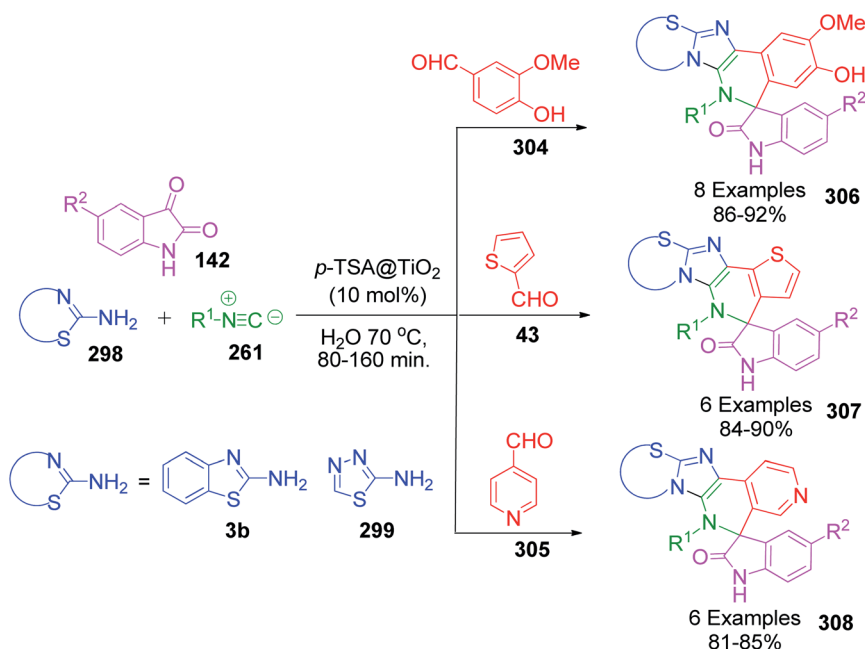


Scheme 93 Synthesis of structurally diverse spiroheterocycles.

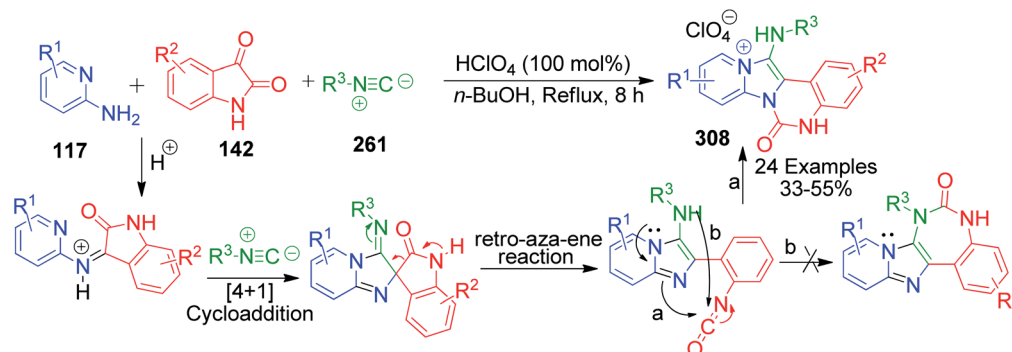
intramolecular trapping by the pyridine nitrogen rather than fragmentation. Significant fragmentation of the nitrilium ion (GBB product/Strecker product ratio = 5 : 1) was also observed for the electron-deficient 5-fluoro-2-aminopyridine. The detriylation of the GBB products was observed to be facile 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

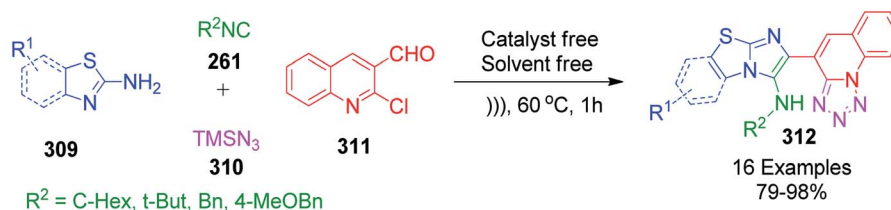
on the NMR analysis, the selective formation of the GBB product clearly indicated the complete predominance of this pathway as no evidence of the Strecker and Ugi products was found. As expected, the addition of an external nucleophile (acetate) did not compete with the intramolecular trapping of the 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 Brønsted acid (possibly through hydrogen bonding rather than protonation) completely suppressed the nitrilium ion fragmentation towards the Strecker product 289 (Scheme 90).



Scheme 94 Synthesis of spirooxindoles via GBB and Pictet-Spengler reaction.



Scheme 95 Synthesis of tetracyclic-fused imidazo[1,2-*a*]pyridines via sequential GBB, *retro*-aza-ene and intramolecular nucleophilic reaction pathways.



Scheme 96 Ultrasound-assisted synthesis of imidazo[2,1-*b*]thiazoles and benzo[*d*]imidazo[2,1-*b*]thiazoles.

The well-known aminoazoles, 3-amino-5-methylisoxazole 291 and 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamides 287, were studied by M. V. Murlykina *et al.* as amine components in the Ugi and GBB multicomponent reactions (Scheme 91).¹⁸⁵ Particularly, 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamide 287 reacted as 1,3-binucleophile with aromatic aldehydes 4 and alkylisocyanides 292 with the formation of 3-(alkylamino)-*N*,2-diaryl-1*H*-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-phenylpropionamides 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-amino-1,3,4-thiadiazole 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).¹⁸⁶

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-amino-1,3,4-

thiadiazole 3b/299, isocyanides 261, isatins 142 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).¹⁸⁷

B. Yang *et al.* developed a novel one-pot three-component protocol for biologically and pharmaceutically important tetracyclic-fused imidazo[1,2-*a*]pyridines 308.¹⁸⁸ 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 benzodiazepinone-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. Á. 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 312.¹⁸⁹ This solvent- and catalyst-free approach utilizes 2-aminothiazoles/2-aminobenzothiazoles 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 antiamebic activities against various Gram-positive and Gram-negative bacteria.

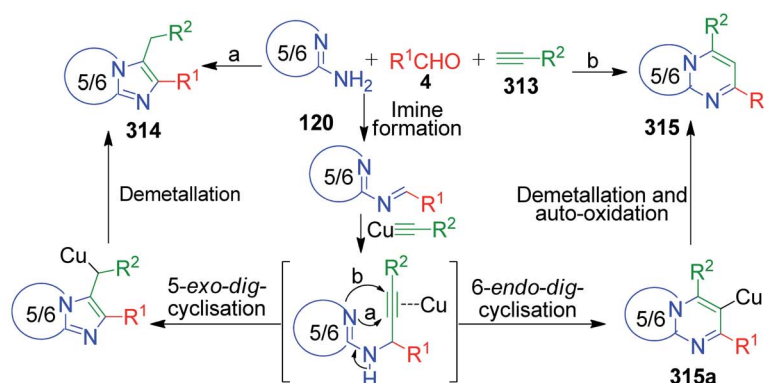
2.1.1.8 MCRs involving alkynes and analogous compounds. Organic compounds containing acetylene bonds adjacent to



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 CuCl and Cu(OTf)₂.¹⁹⁰ 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 CuSO₄/TsOH-catalyzed three-component reaction using 2-aminopyridines, aldehydes and alkynes through 5-*exo*-dig cycloisomerization.¹⁹¹ S. K. Guchhait *et al.* explored the catalytic efficiency of a mixed Cu(I)–Cu(II) system by partial reduction of in situ-generated CuSO₄



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	CuI (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.

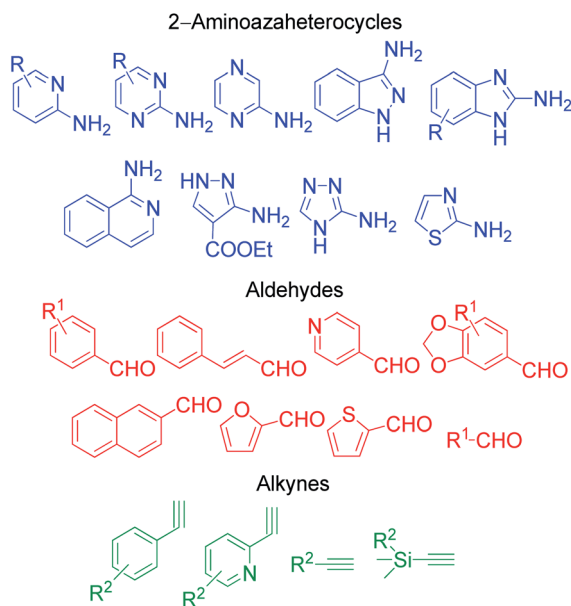


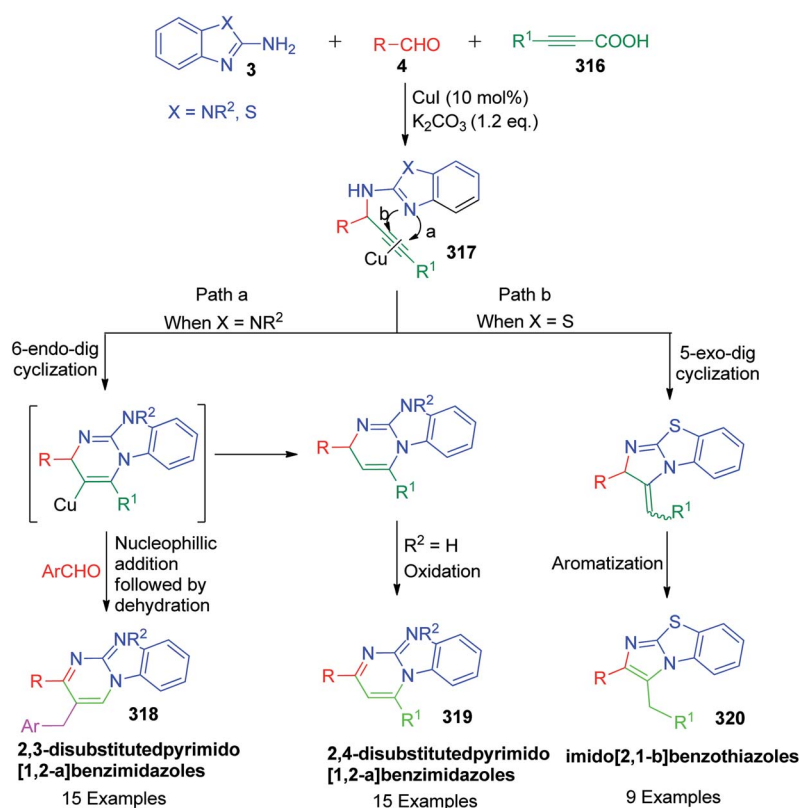
Fig. 7 Various 5/6 membered 2-aminoazaheteroaromatic compounds, aldehydes and alkynes used in the Cu-catalyzed 5-exo-dig/6-endo-dig-cyclisation process.

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 cycloisomerization and prototropic shift (Scheme 97, path a).¹⁹²

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-*endo*-dig cyclization reaction. Herein, the coupling between 2-aminobenzimidazole 120, aldehydes 4, and alkynes 313 was carried out, leading to the formation of propargylamine intermediate 315a, which regioselectively undergoes 6-*endo*-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-*endo*-dig cyclization was published by J. Palaniraja *et al.*, wherein the A³ coupling reaction between 1*H*-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-*endo*-dig cyclization (Scheme 97, path b).¹⁹⁴ 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 alkynedicarboxylic acids 316.¹⁹⁵ The CuI and K₂CO₃-catalyzed MCR synthesis of pyrimido[1,2-*a*]benzimidazoles and imidazo[2,1-*b*]benzothiazoles proceeds through a 6-*endo*-dig and 5-*exo*-dig cyclization, respectively (Scheme 98).

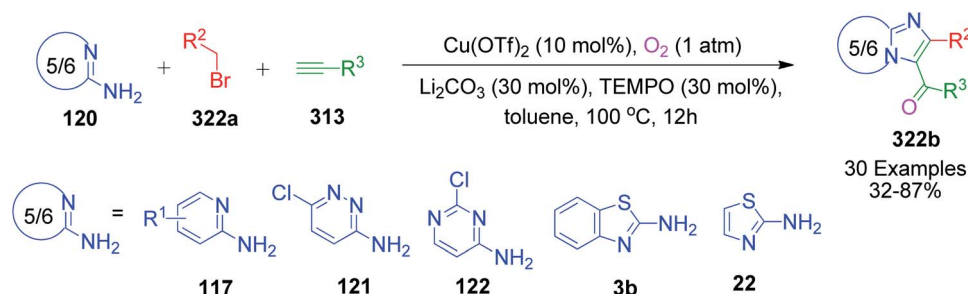


Scheme 98 Synthesis of pyrimido [1,2-*a*]benzimidazoles and imidazo [2,1-*b*]benzothiazoles *via* decarboxylic MCRs.





Scheme 99 Magnetic nanocatalyst-catalyzed synthesis of imidazo[1,2-a]pyridine derivatives via two different routes.



Scheme 100 Synthesis of imidazo-fused heterocycles through an oxidative cascade reaction.

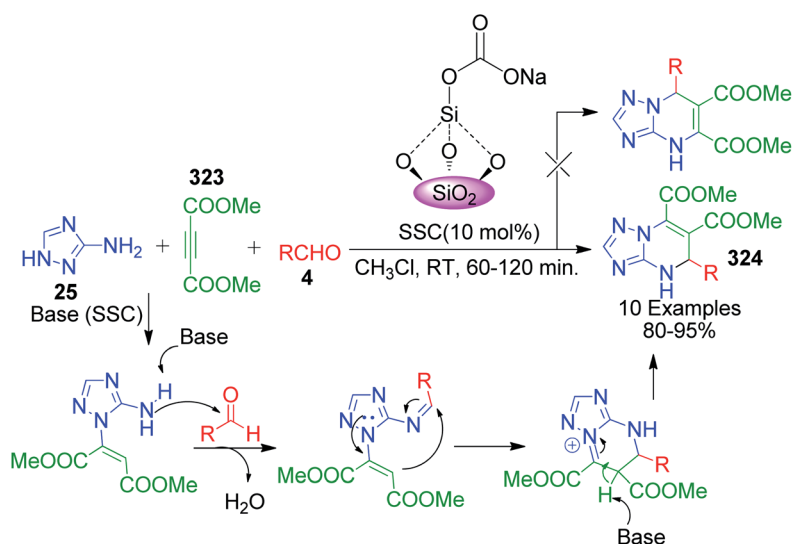
W. Sun *et al.* reported a one-pot multicomponent protocol utilizing magnetic $\text{Cu}^0\text{@HAP@}\gamma\text{-Fe}_2\text{O}_3$ hybrid to catalyze the synthesis of imidazo[1,2-a]pyridine derivatives **322** from 2-aminopyridine derivatives **117**, aldehydes **4**/glyoxylic acids **321**, and alkynes/alkynyl carboxylic acid **317**.¹⁹⁶ 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 $\text{Cu}(\text{OTf})_2$ and

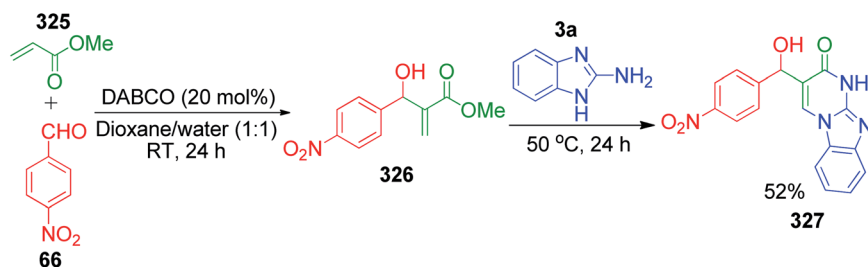
Li_2CO_3 -catalyzed reaction was conducted using terminal alkyne **313**, 2-amino N-heterocycle **120**, benzyl/allylic bromide **322a** and TEMPO (as an oxidant) in toluene under an oxygenated environment at 100 °C (Scheme 100). After 10 h, the target products, densely functionalized imidazo-fused heterocycles **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

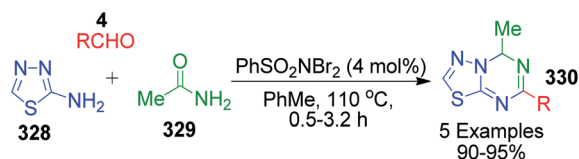
2.1.1.9 MCRs involving miscellaneous compounds. Li's group discovered DABCO as a promoter for the reaction between 4-



Scheme 101 Regioselective synthesis of fused imidazo[1,2-a]pyrimidines using a solid base catalyst.



Scheme 102 Sequential three-component synthesis of benzimidazo[1,2-*a*]pyrimidinone based on Baylis–Hillman reaction.



Scheme 103 Synthesis of thiadiazolotriazine derivatives using benzene sulphonamide dibromide as a catalyst.

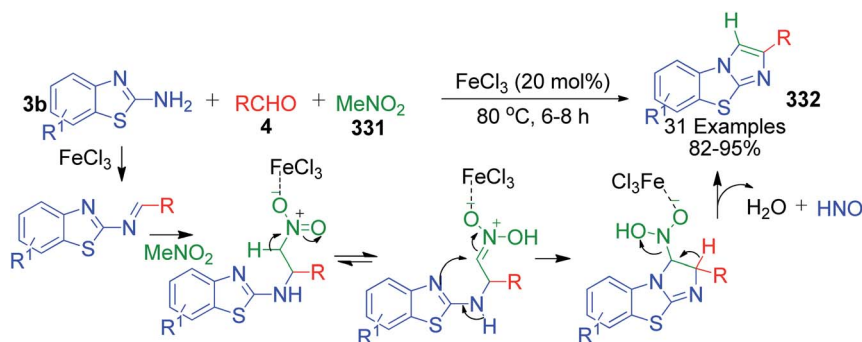
nitrobenzaldehyde **68** and methyl acrylate **325** and subsequent addition of 2-aminobenzimidazole **3a**.¹⁹⁹ In this sequential three-component reaction, 1,4-dioxane/H₂O (1 : 1), as a reaction medium, and three equivalents of methyl acrylate **325** were used for smooth access to Baylis–Hillman alcohol **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

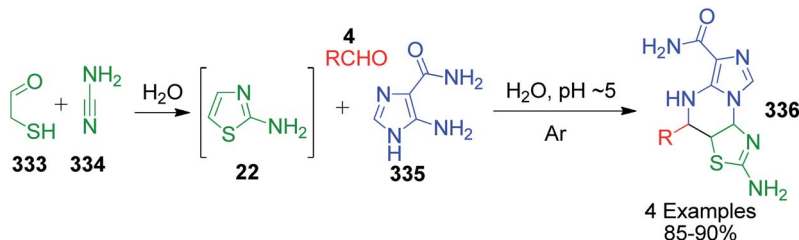
catalyst benzene sulphonamide dibromide was synthesized and employed in the one-pot condensation of 2-amino thiadiazol **328**, aromatic aldehydes **4** and acetamide **329** in toluene under reflux conditions, which afforded thiadiazole-fused triazine derivatives **330** in excellent yields (Scheme 103).²⁰⁰

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.²⁰¹ 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.²⁰² The interesting feature of this approach involves the *in situ* generation of 2-aminothiazole **22** from β -mercapto-acetaldehyde **333** and cyanamide **334** in water at neutral pH, which then undergoes a three-component reaction

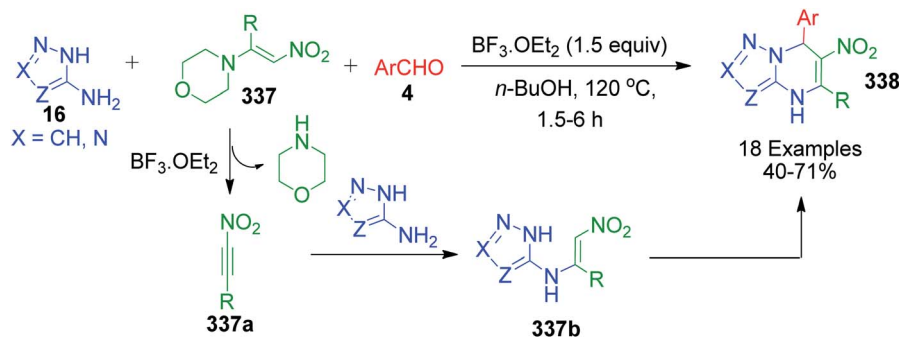


Scheme 104 FeCl₃-catalyzed solvent-free synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole derivatives.



Scheme 105 Synthesis of thiazole-fused pyrimidines involving the *in situ* generation of 2-aminothiazole.



Scheme 106 Synthesis of 4,7-dihydro-5-*R*-7-aryl-6-nitroazolo[1,5-*a*]pyrimidines.

with 4-amino-imidazole 5-carboxamide **335** and various aldehydes **4** in water at pH around 5.0 under an argon atmosphere (Scheme 105).

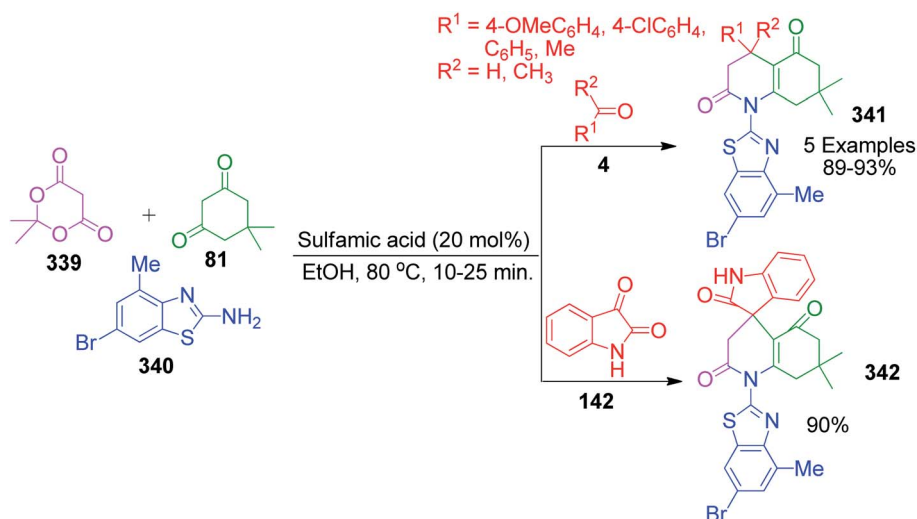
D. N. Lyapustin *et al.* employed morpholino-nitroalkenes **337** in a reaction with aminoazoles **16** and aromatic aldehydes **4** to report the multicomponent synthesis of 4,7-dihydro-5-*R*-7-aryl-6-nitroazolo[1,5-*a*]pyrimidines **338**. The reaction was performed with 1.5 equivalents of boron trifluoride etherate in butanol at 120 °C for 1.5–6 h.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-aminoazaaromaticheterocycles as 1,1-binucleophiles are based on the participation of the exocyclic NH₂-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.

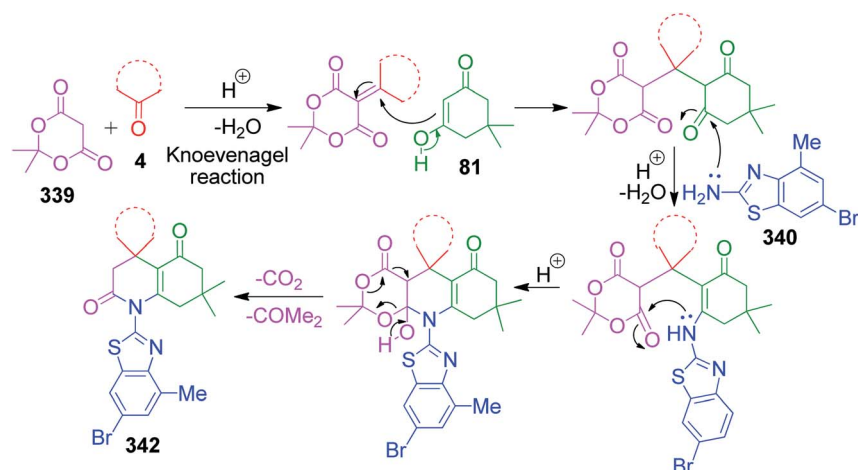
2.1.2.1 MCRs involving β -dicarbonyl compounds. Dimedone, Meldrum's acid, 1,3-indanedione, and barbituric acid and its *N,N*-dialkyl derivatives are the frequently used β -dicarbonyl compounds in MCRs as they possess acidic hydrogens between two strong electron withdrawing group. M. Kumar's group conducted 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 benzothiazolylquinoline-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).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 -dicarbonyls. The intermediate formed after the addition of 2-aminobenzothiazole **340** to the



Scheme 107 One-pot four-component synthesis of benzothiazolylquinoline-2,5-diones and their spiro analogues.



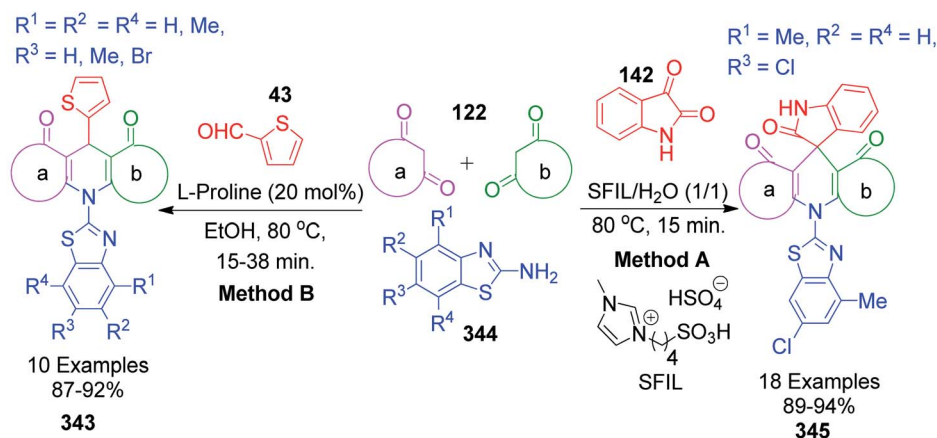


Scheme 108 Proposed reaction mechanism to benzothiazolylquinoline-2,5-diones and their spiro analogues.

dimedone ring with the removal of a water molecule undergoes intramolecular attack by the exocyclic amino group of benzothiazole 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).

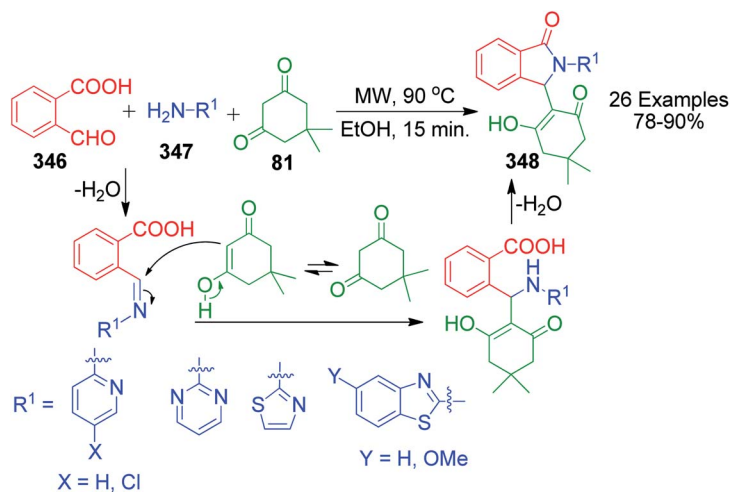
On a similar basis, they described a diversity oriented synthetic protocol to access unsymmetrically annulated 1,4-



Method	Ring a	Ring b	Reference
A			205
B			206

Scheme 109 Synthesis of unsymmetrically annulated 1,4-dihydropyridine spiro- and non-spiroheterocycles tethered with benzothiazole derivatives.

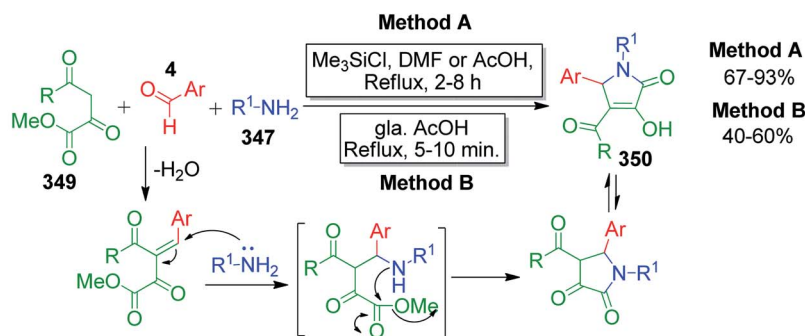




Scheme 110 Microwave-assisted catalyst-free synthesis of substituted isoindolinones.

dihydropyridine spiroheterocycles **345** via the four-component domino reaction of 2-aminobenzothiazoles **344**, isatin **143** and two different cyclic β -diketones **123** 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).²⁰⁵ 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	R	R ¹	Reference
A	 X = H, 2-Cl, 4-Cl X = O, S		208
B	 X = O, S		209

Scheme 111 Two different methods to synthesize polysubstituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones through a three-component condensation reaction.

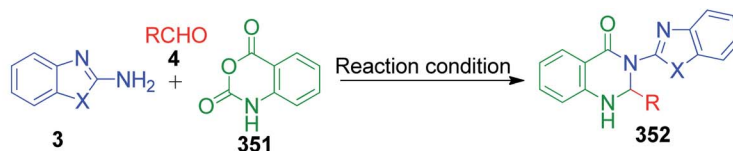
and reaction time. Easy separation of the ionic liquid after completion of the reaction led to its reuse for at least five cycles without any appreciable loss in activity. After two years, the same group demonstrated a modified version of this approach, where a heteroaromatic aldehyde replaces isatin 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.²⁰⁶ For the construction of these fused heterosystems, they utilized a variety of cyclic β -dicarbonyl compounds **122** except Meldrum'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**.²⁰⁷

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**.

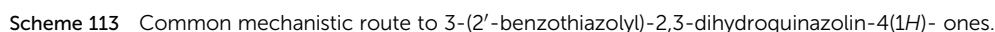
Pyruvic acid and its derivatives also function as active methylene compounds in the reaction, where AAH acts as a 1,1-binucleophile, and the article concerning this was published by S. V. Ryabukhin and coworkers, which revealed the parallel synthesis of a series of 3-hydroxy-1,5-dihydro-2H-pyrrol-2-one 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(H ₂ PO ₄) ₃ (16 mol%), 100 °C	13–20 min	79–86	6	210
S, NH	H ₃ PO ₄ -Al ₂ O ₃ , 120 °C	8–16 min	80–93	13	211
	Cellulose-SO ₃ H (4 mol%), 100 °C	3–20 min	85–96	12	212
S	Zr(HSO ₄) ₄ (20 mol%), 80 °C	30–60 min	80–92	11	213
S, NH	Fe ₃ O ₄ @SiO ₂ -imid-PMA ⁿ H ₂ O:EtOH (1:3(v/v)), Reflux	1.5–4 h	87–95	8	214
	Fe ₃ O ₄ @SiO ₂ -imid-PMA ⁿ 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.

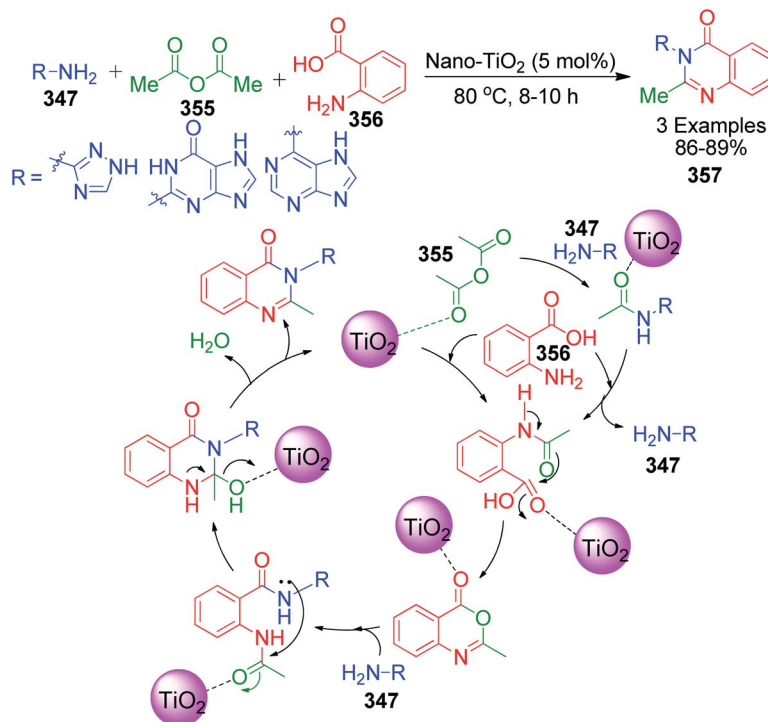




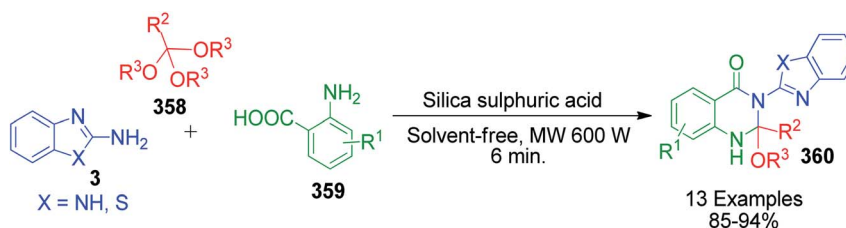
2.1.2.2 MCRs involving organic anhydrides. Organic anhydrides such as isatoic anhydride and acetic anhydride were also explored in this category of reactions by several research groups,

H. R. Shaterian *et al.* described a one-pot three-component cyclocondensation reaction between isatoic anhydride **351**, 2-aminobenzothiazole **3** and aldehydes **4**, leading to the formation of quinazolinone derivatives **352**. The reaction, which was catalyzed by a heterogeneous catalyst, $[\text{Al}(\text{H}_2\text{PO}_4)_3]$, 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.²¹⁰ 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 acid²¹¹ and cellulose-supported sulfonic acid²¹² 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





Scheme 115 Nano-TiO₂-catalysed synthesis of tetrazolopyrimidine and proposed reaction pathway.



Scheme 116 Microwave-assisted synthesis of quinazolinones tethered with benzimidazole/benzothiazole.

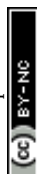
activity. An analogous method was reported by L. Wu, where condensation of the starting materials was effected using $\text{Zr}(\text{HSO}_4)_4$ as an acid promoter under solvent-free conditions.²¹³ M. Esmailpour *et al.* developed an efficient $\text{Fe}_3\text{-O}_4\text{@SiO}_2\text{-imid-PMA}^n$ 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.²¹⁴ A brief comparison of the reported methods in terms of reaction time and yields is shown in Scheme 112.

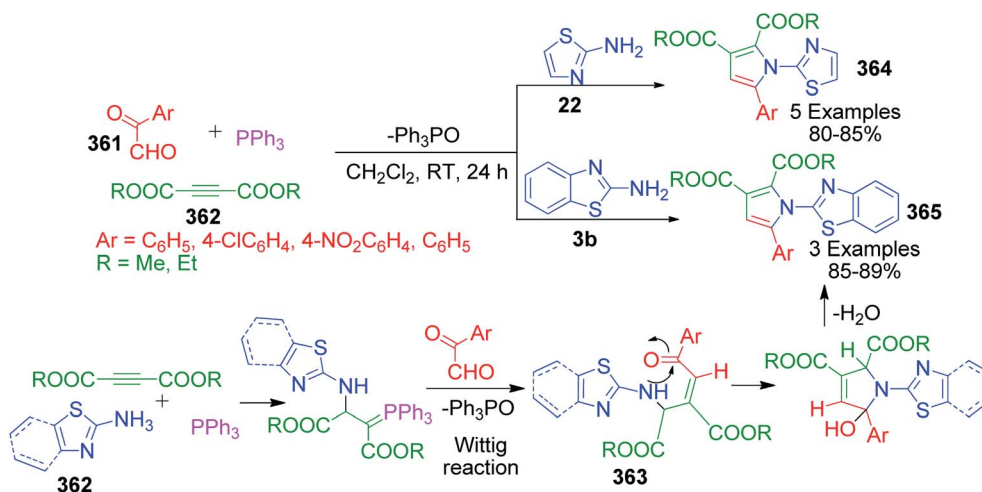
According to the authors, these methods follow a common mechanistic pathway, in which an acid-base interaction between catalyst and isatoic anhydride **351** is suggested as the initial step to generate reactive intermediate **352a**, which undergoes nucleophilic attack on the carbonyl carbon by AAH **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).

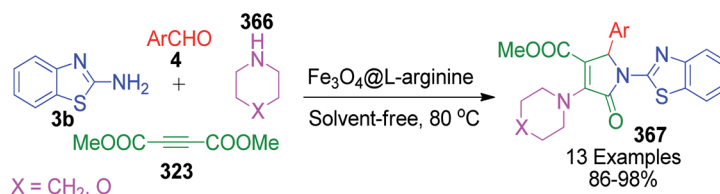
In contrast to the acid-catalyzed reactions discussed above, a catalyst-free approach for the synthesis of these heterocyclic compounds was developed by J. M. Khurana and S. Kumar. The strategy involved heating a mixture containing the starting materials in water-ethanol 1 : 1 (v/v) system at 80 °C for 30 min.²¹⁵ The corresponding products, 2,3-dihydro quinazolin-4(1*H*)-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. Khalafi-Nezhad *et al.* through a different method, which employed acetic anhydride **355**, anthranilic acid **356** and





Scheme 117 One-pot synthesis of polysubstituted pyrrole derivatives and proposed mechanistic route.



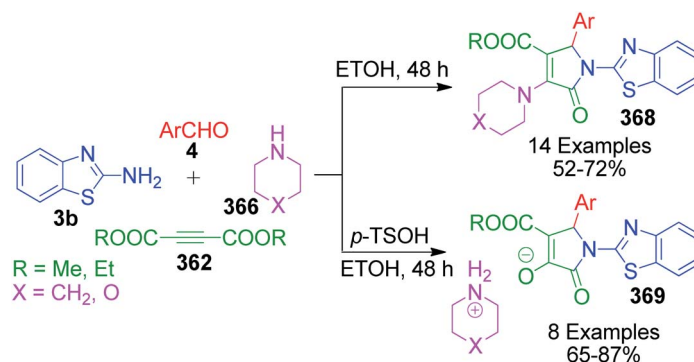
Scheme 118 Synthesis of pyrrolidinones via four-component reactions.

various AAH 347. The use of anthranilic acid plays a crucial role in this three-component reaction as it possess 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.

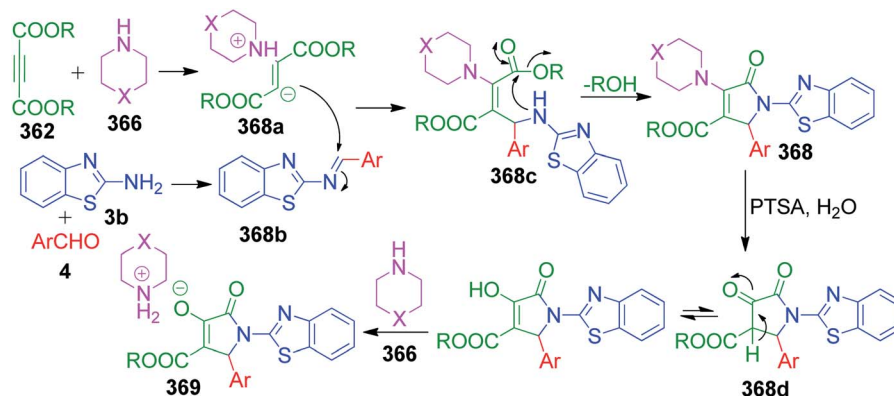
S. Koroji *et al.* developed a microwave-assisted silica sulfuric acid-catalyzed one-pot synthesis of novel 3-(benzo[d]thiazol-2-

yl)-2-alkyl or 3-(2-benzimidazolyl)-2-alkyl quinazolin-4(3*H*)-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 a 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-



Scheme 119 Synthesis of pyrrolidinones via four-component reactions.



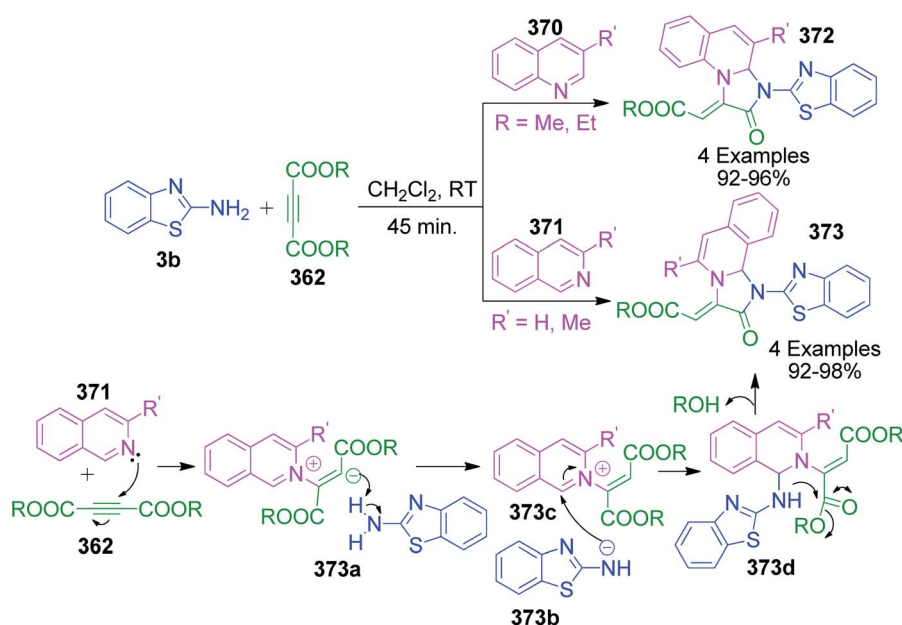
Scheme 120 Proposed mechanism for the formation of pyrrolidinones.

promoted three-component reaction between dialkylacetylenedicarboxylates **362**, arylglyoxals **361** and 2-aminothiazole/2-aminobenzothiazole **22/3b**.²¹⁸ 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 arylglyoxal in a Wittig manner to afford intermediate **363**. The final pyrroles **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.²¹⁹ When a solvent-free mixture containing 2-aminobenzothiazole **3b**, dimethyl

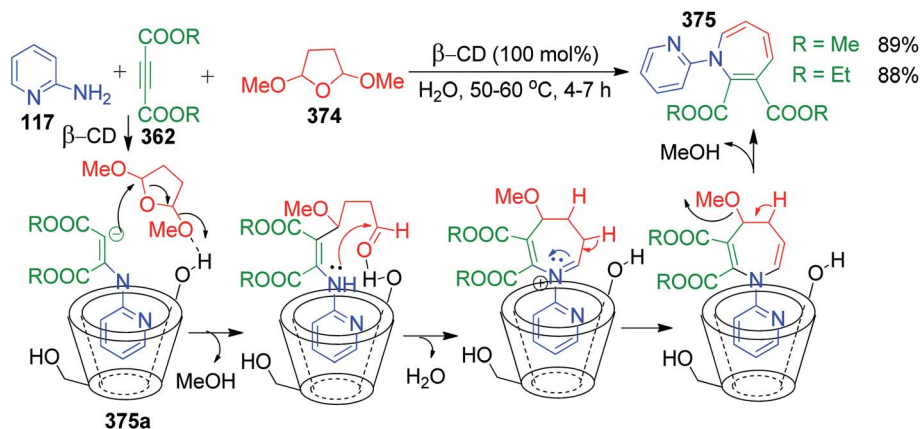
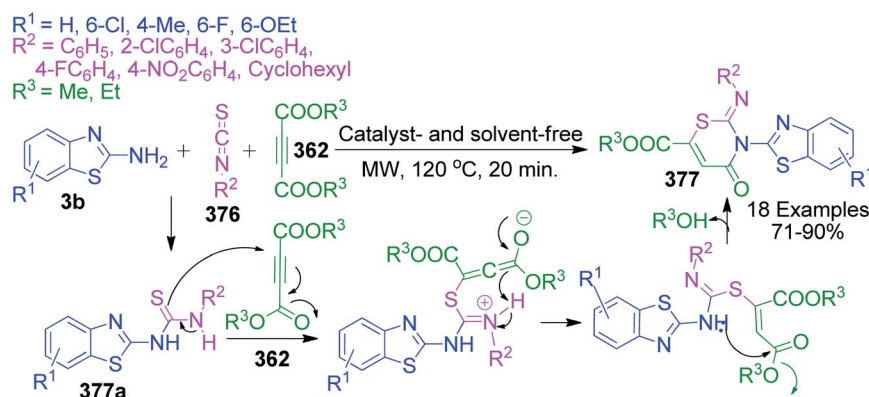
acetylenedicarboxylate **323**, aromatic aldehyde **4** and piperidine/morpholine **366** was heated in the presence of $\text{Fe}_3\text{O}_4/\text{L-arginine}$ nanoparticles at 80 °C, 2-pyrrolidinones **367** were obtained in excellent yields (Scheme 118). As a magnetic nanocatalyst, $\text{Fe}_3\text{O}_4/\text{L-arginine}$ 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**.²²⁰ 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 121 Synthesis of novel functionalized dihydroimidazo[2,1-a]isoquinolines and dihydroimidazo[2,1-a] quinolines.



Scheme 122 Construction of substituted azepine ring promoted by β -CD.

Scheme 123 Catalyst- and solvent-free synthesis of (Z)-alkyl 3-(benzo[d]thiazol-2-yl)-4-oxo-2-(cyclohexyl/arylimino)-3,4-dihydro-2H-1,3-thiazine-6-carboxylates under microwave irradiation.

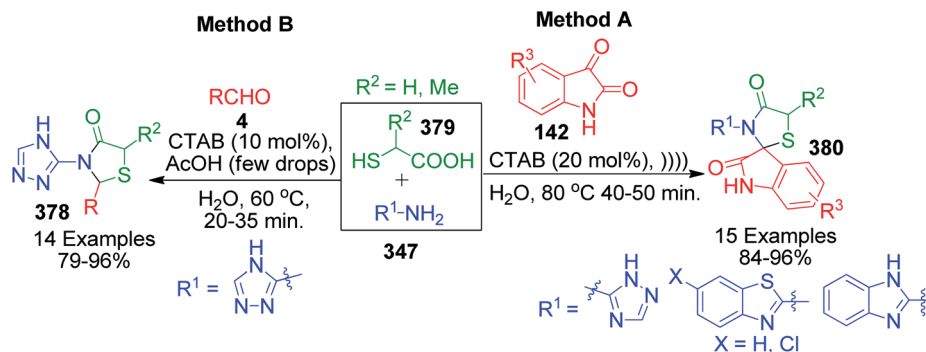
reaction is further conducted with the remaining reactants toward the target compounds at moderate temperature. The reaction was stirred for two days to get both products in satisfactory yields. Moreover, the acid catalyst PTSA was required for the synthesis of morpholinium/piperidinium 2-pyrrolidinon-3-olates, 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 **366** and DAAD **362** and imine intermediate **368b** from aldehyde **4** and 2-aminobenzothiazole **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 pyrrolidinedione **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).

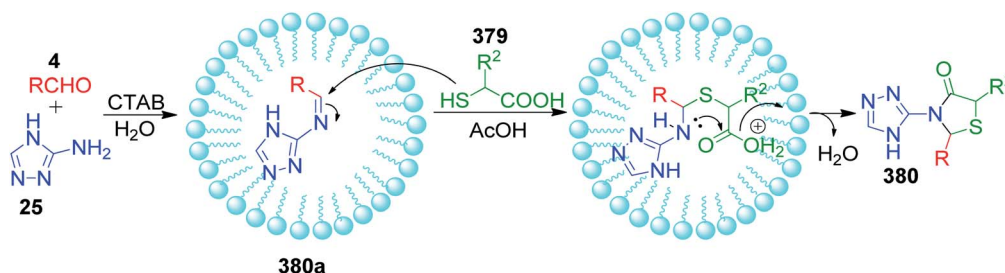
A closely related reaction based on the use of the 1,3-dipolar intermediate, which allows the construction of a fused imidazole ring, was reported by S. Arab-Salmanabadi and coworkers. Their approach gave a way to access a series of novel functionalized quinolones and isoquinoline-fused dihydroimidazoles **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.²²¹ 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-





Scheme 124 Ultrasonic wave-assisted synthesis of spiro[indole-3,2C'-thiazolidinone]-2,4-diones.



Scheme 125 Proposed mechanism for the formation of triazole-linked thiazolidinones.

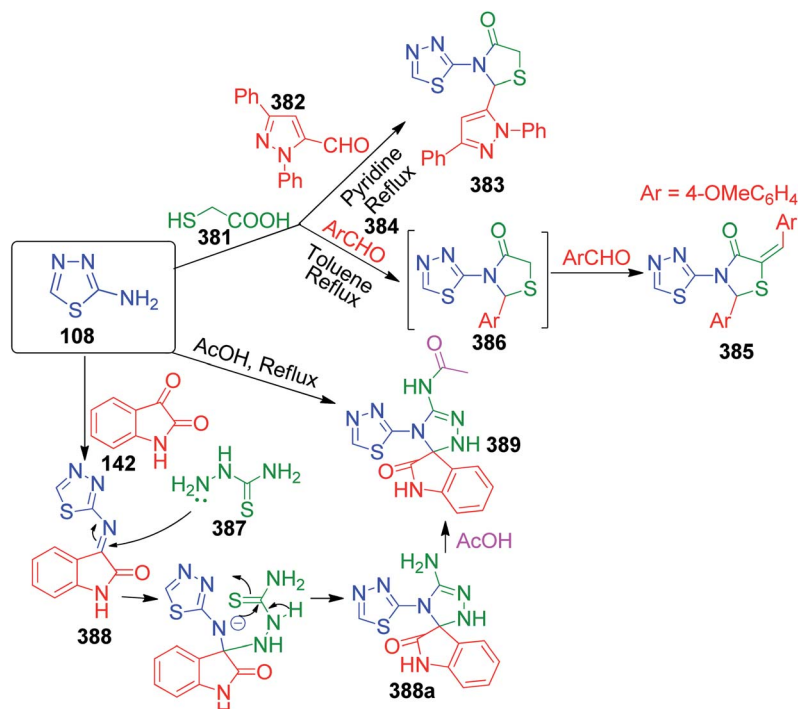
aminopyridine **117** and 2,5-dimethoxytetrahydrofuran **374** were mixed in neutral water.²²² Various cyclodextrins such as α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, 2-hydroxy propyl β -cyclodextrin and methyl- β -cyclodextrin were examined for their efficiency as promoters. However, the corresponding 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 a methanol molecule, affording the desired substituted azepine ring.

Next, P. Wadhwa's group developed a catalyst- and solvent-free approach for the diversity-oriented synthesis of thiazole linked thiazin derivatives **377** from the three-component reaction of 2-aminobenzothiazoles **3b**, various isothiocyanates **376** and DAAD **362** irradiated under microwave heating at 120 °C for 30 min.²²³ Conversely, when the same combination of reactants was heated in the conventional way, the products were formed

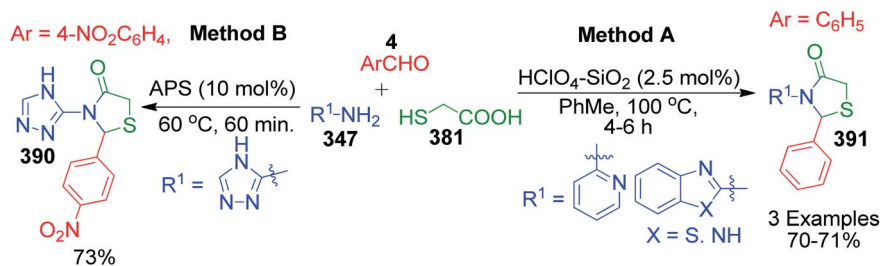
after 10 h with low yields. With microwave heating, the quality of their approach was enhanced greatly both in terms of reaction time and product yield. The wide scope of this protocol was highlighted by the use of various substituted derivatives of 2-aminobenzothiazole **3b** and isothiocyanates **376**. The reaction progress as suggested by the authors starts with the formation of *N,N'*-substituted thiourea intermediate **377a** by nucleophilic attack of 2-aminobenzothiazoles **3b** on the electrophilic carbon center of isothiocyanate **376**, which further attacks the C–C triple bond of dialkylacetylenedicarboxylates **362** through the soft sulfur terminal, followed by intramolecular cyclisation with 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.²²⁴ 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





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

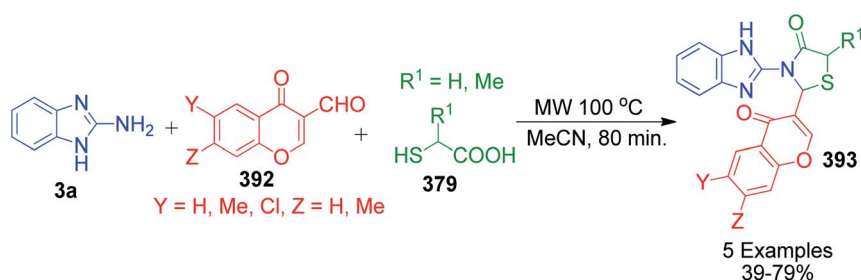


Scheme 127 Two different methods to synthesize thiazolidinone ring system.

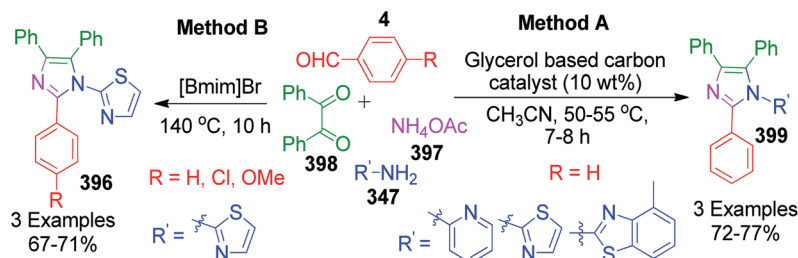
378. In this methodology, isatin was replaced with aromatic aldehydes **4** and the reaction was conducted in aqueous medium employing acetic acid as the organocatalyst. The starting materials, different aldehydes, 3-amino-1,2,4-triazole and α -mercaptocarboxylic acids were heated in a conventional way and the temperature was maintained at 60 °C for 20–35 min (Scheme 124, Method B).²²⁵ 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 **380a** in aqueous micellar medium from heterocyclic amine **25** and carbonyl compounds **4** (aldehydes



Scheme 128 Microwave-assisted synthesis of chromone-based thiazolidinones.

Scheme 129 Synthesis of thiazolidine ring-linked indeno[1,2-*b*]quinoxaline.

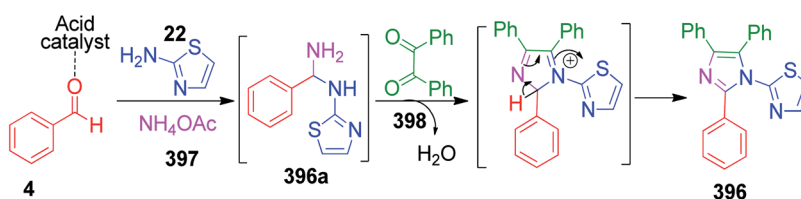
Scheme 130 Four-component synthesis of tetra-substituted imidazoles under different conditions.

and isatin), which experience *in situ* nucleophilic attack from the sulfur atom of α -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 *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-1*H*-pyrazole-5-carbaldehyde 382 and mercaptoacetic acid 381 in pyridine at reflux for 19 h.²²⁶ Conversely, when *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 385 *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 389 was assumed to proceed *via* ketimine intermediate 388 obtained from the condensation of 2-amino-1,3,4-thiadiazole 108 with isatin 142. This ketimine

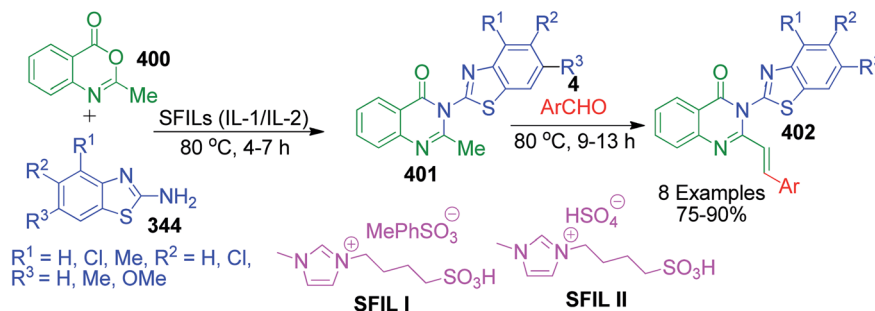
intermediate 388 is then attacked by thiosemicarbazide 387 and subsequent cyclocondensation affords intermediate 388a, the acetylation of which gives the final product (Scheme 126).

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).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 $\text{HClO}_4\text{-SiO}_2 > \text{TfOH-SiO}_2 \gg \text{H}_2\text{SO}_4\text{-SiO}_2 > p\text{-TsOH-SiO}_2 > \text{MsOH-SiO}_2 \sim \text{HBF}_4\text{-SiO}_2 > \text{TFA-SiO}_2 \sim \text{HOAc-SiO}_2$. Further, they designed and performed some reactions to make a clear distinction between the superiority of two heterogeneous catalyst systems, $\text{HClO}_4\text{-SiO}_2$ 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-aminobenzothiazole, while benzaldehyde 4 and mercaptoacetic acid 381 were common to both. With $\text{HClO}_4\text{-SiO}_2$, 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

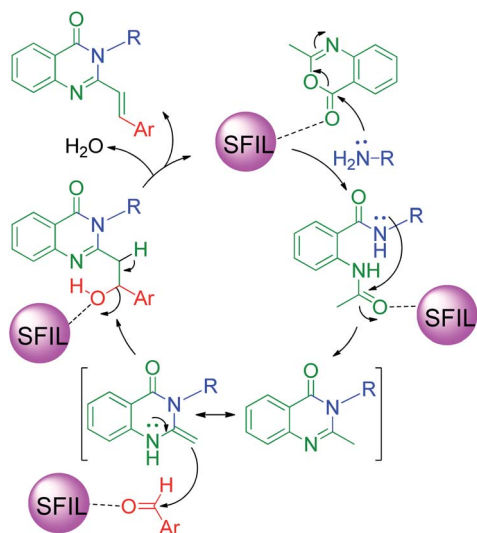


Scheme 131 Proposed mechanistic route to tetra-substituted imidazoles.





Scheme 132 Synthesis of 3-benzothiazolyl-2-styrylquinazolin-4(3H)-ones through sequential one-pot three-component reaction.



Scheme 133 Plausible mechanism for the formation of quinazolinones.

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).²²⁸

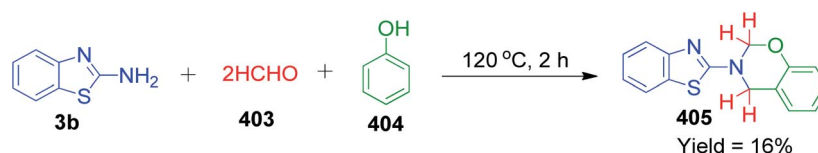
Next, the synthesis of chromone-based thiazolidinone ring **393** was reported in the article published by N. M. Drosos *et al.*, wherein a mixture containing mercaptoacetic acid **379** and its 2-methyl derivative with various 3-formylchromones **392** and 2-aminobenzimidazole **3a** was irradiated with microwaves at 100 °C. The corresponding products were obtained after 80 min in moderate to good yields (Scheme 128).²²⁹ 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*]quinoxalinone, α -mercaptocarboxylic acid **381** and 2-amino-benzothiazole **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*]quinoxaline **395** 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.

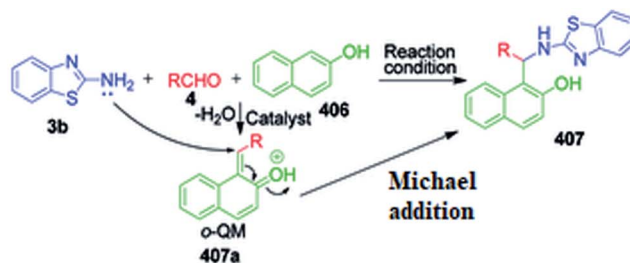
2.1.2.5 MCRs involving miscellaneous substrates. In this section, we describe MCRs based on reagents that cannot be categorized in a particular section. The first example includes the synthesis of substituted imidazole derivatives **399** by K. Ramesh *et al.* through easily available starting materials, benzaldehyde **4**, ammonium acetate **397**, 2-aminobenzothiazole/2-aminobenzothiazole/2-aminopyridine **347** 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).²³¹ 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-aminobenzothiazole **22**, aromatic aldehyde **4**, ammonium acetate **397** and benzil **398** at 140 °C (Scheme 130, Method B).²³²

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



Scheme 134 Solvent-free synthesis of benzothiazole-tethered benzoxazine ring.





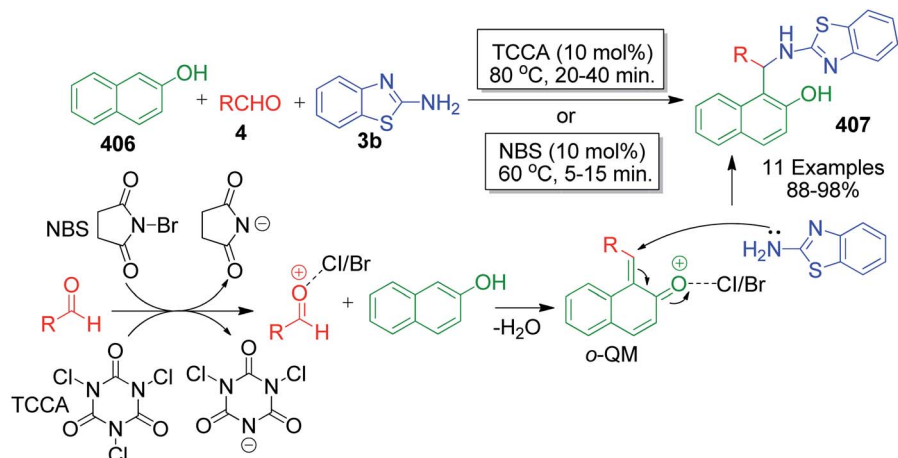
Reaction condition	Time	Yield (%)	No. of examples	Reference
SDS (20 mol%), H ₂ O, 100 °C	1–3 h	71–93	16	235
NaHSO ₄ .H ₂ O (10 mol%), 100 °C	4–30 min	52–95	26	236
H ₂ O/HPA (3 mol%), 45 °C	1–2 h	62–92	15	237
(RHA)-[pmim]HSO ₄ 100 °C	3–5 min	87–94	16	238
Hydrotalcite or KOH/MgO, 70 °C	2–3.5 h	72–93	11	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
NH ₃ (CH ₂) ₅ NH ₃ BiCl ₅ (0.1 mol%), 100 °C	7–50 min	79–99	7	242
Fe ₃ O ₄ @SiO ₂ -Propyl-Pip-SO ₃ H.HSO ₄ , 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		
Fe ₃ O ₄ @SiO ₂ @(CH ₂) ₃ -Urea-SO ₃ H/HCl, 90–95 °C	15–50 min	70–96	16	245
Fe ₃ O ₄ @SiO ₂ -ZrCl ₂ -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.

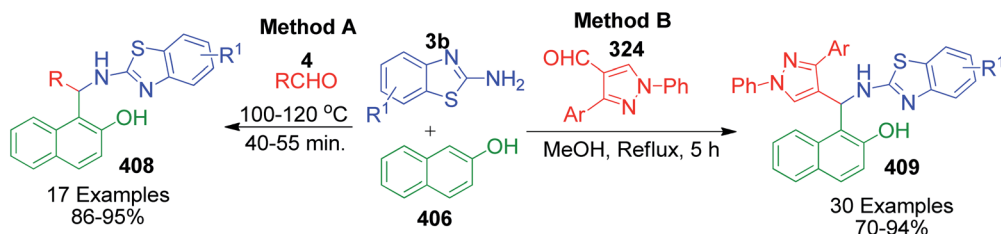
of aldehyde 4. The desired product is obtained from this diamine intermediate 396a, which is condensed with 1,2-diketone 398 with the removal of two molecules of water followed by rearrangement.

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

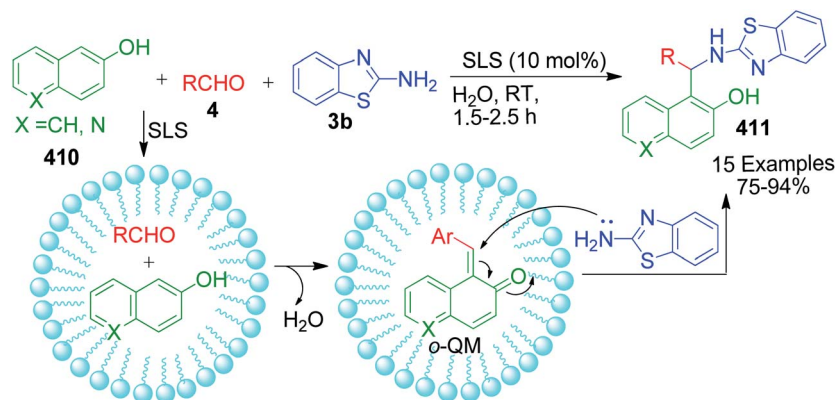




Scheme 136 TCCA and NBS-catalyzed synthesis of 1-(benzothiazolylamino)methyl-2-naphthols.



Scheme 137 Synthesis of 2-aminobenzothiazolomethylnaphthols under catalyst-free conditions.



Scheme 138 Sodium lauryl sulphate-promoted synthesis of 2-aminobenzothiazolomethyl naphthols.

recycling abilities. Initially, 2-methyl-3,1-benzoxazin-4-one **400** and 2-aminobenzothiazoles **344** were combined with the help of SO_3H -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).²³³ 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.

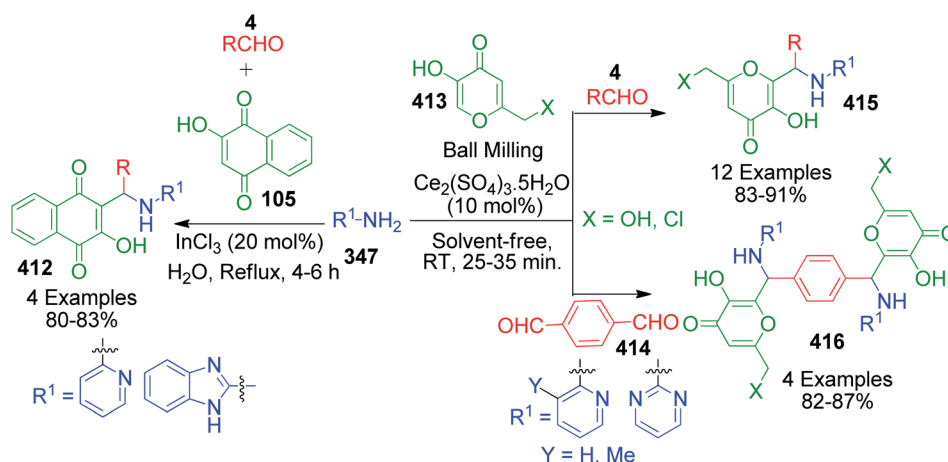
The simplest aldehyde, formaldehyde **403**, was used in a three-component reaction with 2-aminobenzothiazole **3b** and phenol **404** to construct benzothiazole tethered benzoxazine ring **405** by F. Shan and coworkers. The mixture containing the reactants was heated under solvent-free conditions at 120 °C for 2 h to afford the desired product in 16% yield (Scheme 134).²³⁴ The same reaction when carried out with 2-aminothiazole was found to be unsuccessful.

2.2. Aromatic α -aminoazaheterocycles as mononucleophiles

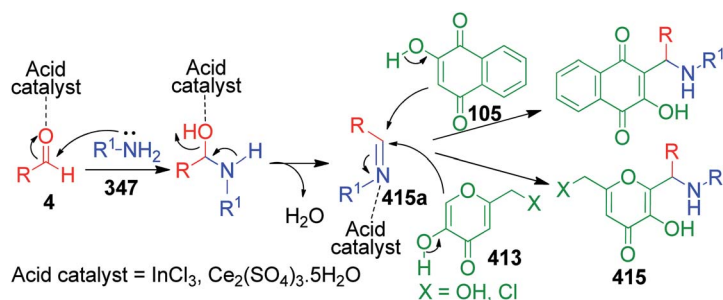
2.2.1 MCRs involving β -naphthol and analogous substrate (synthesis of Betti's base). The preparation of Betti's base and its derivatives is an important area in synthetic chemistry because it involves the formation of C–C and C–N bonds under mild experimental conditions. A significant number of approaches 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 **406**, 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.²³⁵ Since then, a number of reactions have been carried out for the synthesis of 1-(benzothiazolylamino)methyl-2-naphthol derivatives **407** based

on the same platform with the help of catalysts/promoters such as $\text{NaHSO}_4 \cdot \text{H}_2\text{O}$,²³⁶ heteropolyacid (HPA) as a heterogenous catalyst,²³⁷ rice husk ash (RHA)-supported 1-methyl-3-(trimethoxysilylpropyl)-imidazolium hydrogen sulfate ($\text{RHA}[\text{pmim}]\text{HSO}_4$) as an acidic ionic liquid,²³⁸ KOH-loaded MgO/hydrotalcite as a basic catalyst,²³⁹ oxalic acid as an organo-catalyst,²⁴⁰ MPIL B,²⁴¹ $\text{NH}_3(\text{CH}_2)_5\text{NH}_3\text{BiCl}_5$,²⁴² $\text{Fe}_3\text{O}_4@\text{SiO}_2$ -Propyl-Pip- $\text{SO}_3\text{H} \cdot \text{HSO}_4$,²⁴³ γ -aminobutyric acid and isinglass a collagen peptide,²⁴⁴ $\text{Fe}_3\text{O}_4@\text{SiO}_2@(\text{CH}_2)_3\text{-urea-SO}_3\text{H}/\text{HCl}$,²⁴⁵ $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-ZrCl}_2\text{-MNPs}$,²⁴⁶ and (rMGO)-Au NPs²⁴⁷ (Scheme 135). The reaction mechanism for the formation of Betti's base proceeds through 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.

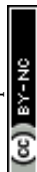
Besides these catalytic systems, some interesting and unique feature-embedded catalysts have also been reported to function as reaction promoters. Trichloroisocyanuric acid (TCCA)²⁴⁸ and N-bromosuccinimide (NBS)²⁴⁹ were successfully used to catalyze the three-component synthesis of 1-(benzothiazolylamino)methyl-2-naphthol derivatives **407**. TCCA and NBS undergo *in situ* release of electrophilic species, Cl^+ and Br^+ ions, respectively, which make the condensation between 2-naphthol **406**

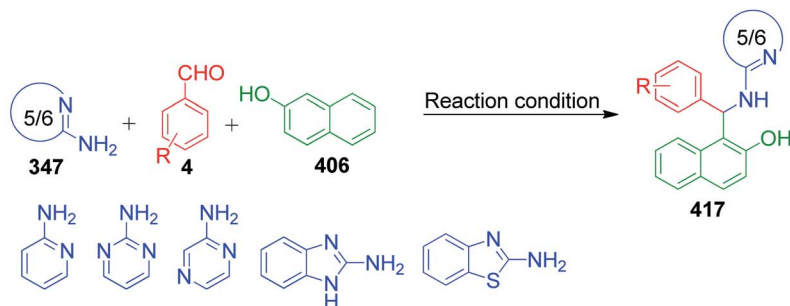


Scheme 139 Synthesis of Betti's base framework under two different reaction conditions.



Scheme 140 Proposed acid-catalyzed reaction pathway to Betti's base.





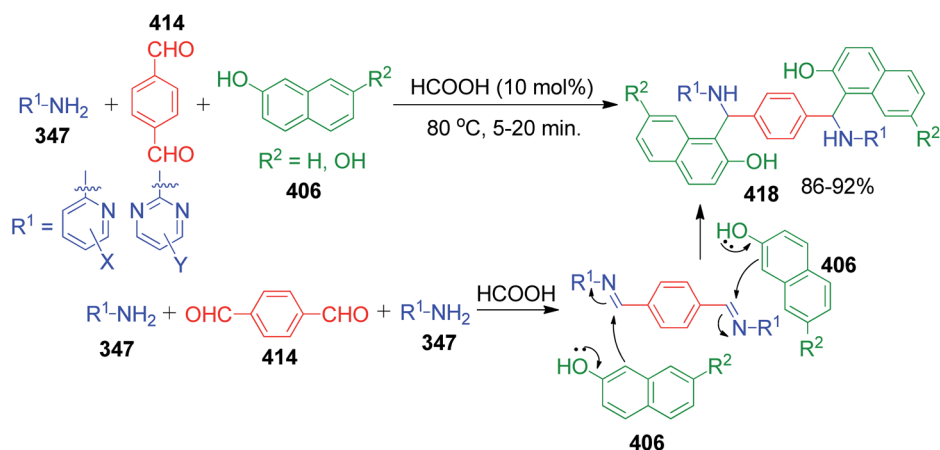
Reaction conditions	Time	Yield (%)	No. of examples	Reference
Fe ₃ O ₄ @MCM-48-SO ₃ H, RT	1–3 min	91–98	10	256
Catalyst-free, solvent-free, 125 °C,	1–6 min	87–94	11	257
Montmorillonite K-10 (10 mol%), EtOH, RT	8–10 h	81–93	20	258

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

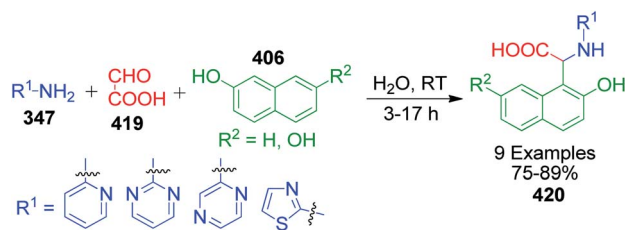
and aldehydes **4** easier by increasing the electrophilicity of the carbonyl carbon of the aldehyde (Scheme 136).

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).²⁵⁰ 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.²⁵¹ In addition, B. Nagaraju *et al.* also reported a simple and catalyst-free approach, wherein 2-aminobenzothiazoles, 2-naphthol **406**



Scheme 142 Formic acid-catalyzed synthesis of novel bis-Betti's bases under solvent-free conditions.



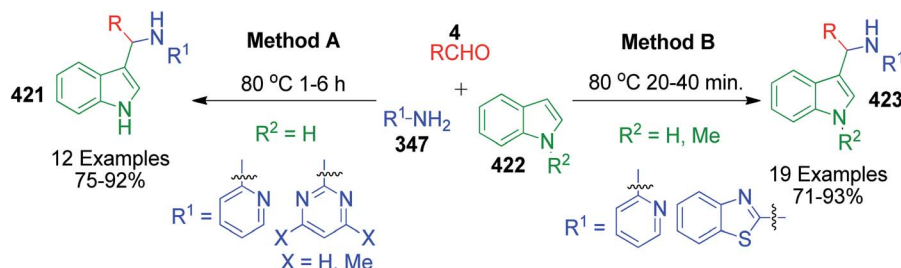
Scheme 143 Catalyst-free synthesis of Betti's base, α -naphthylglycines.

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 μ M.²⁵²

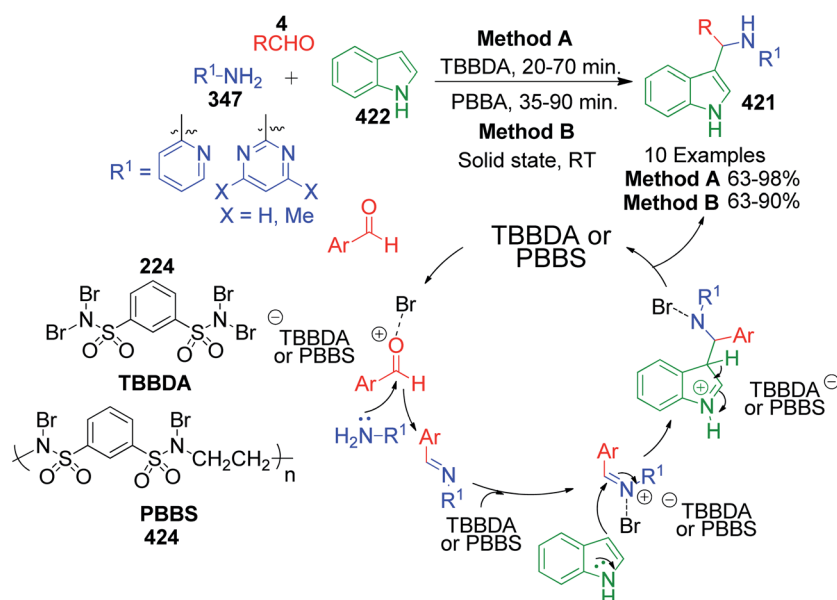
Analogous to 2-naphthol **406**, 6-hydroxyquinoline **410** also works as a key component, acting as a carbon nucleophile, in Betti's base synthesis. P. K. Sahu *et al.* depicted a clear picture of

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.²⁵³ 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.

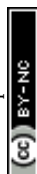
M. Dabiri's group utilized 2-hydroxynaphthalene-1,4-dione **105** as a replacement for 2-naphthol **406** in the same reaction to establish a simple route to some novel Betti's bases. In this approach, 2-aminobenzimidazole **3a** and 2-aminopyridine **117** were used as amino components and the three-component

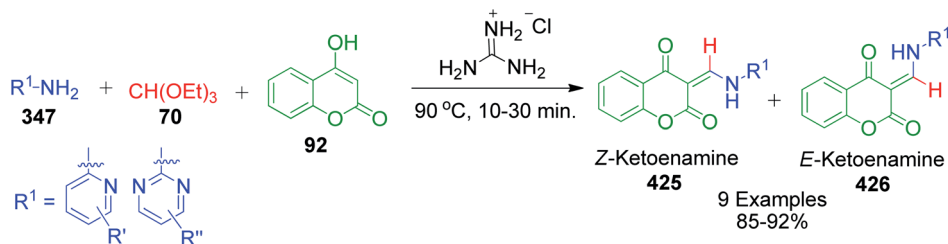


Scheme 144 Synthesis of α -aminoindoles under catalyst- and solvent-free conditions.

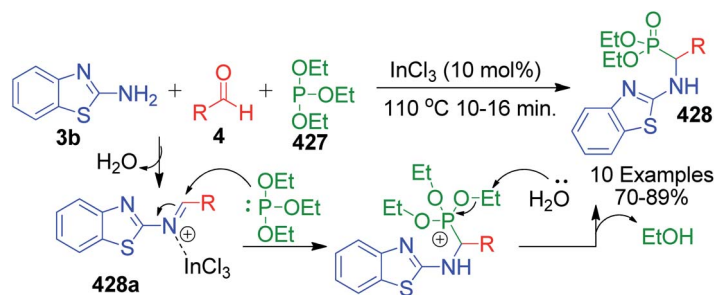
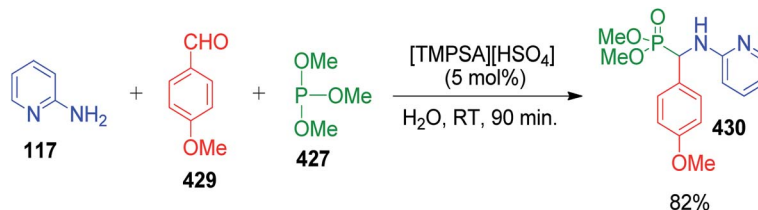


Scheme 145 Synthesis of α -aminoindoles under solid-state conditions.





Scheme 146 Synthesis of novel (Z/E)-3-[(heteroaryl(amino)methylidene)chromane-2,4-dione derivatives.

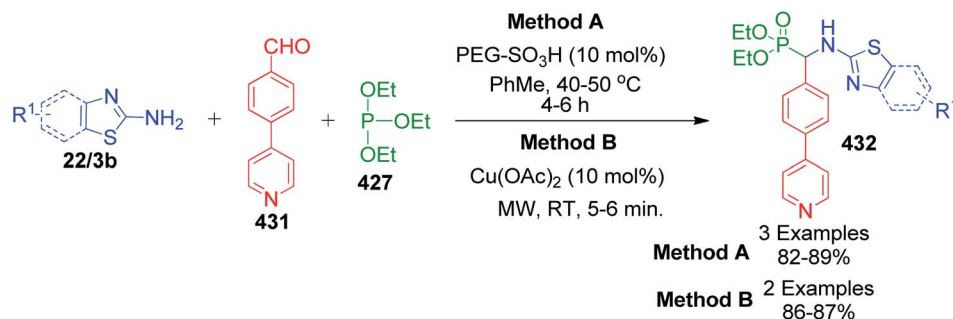
Scheme 147 Synthesis of α -aminophosphonates 428 catalyzed by InCl_3 .Scheme 148 Ionic liquid-mediated synthesis of α -aminophosphonate 430.

reaction was catalyzed by InCl_3 .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 InCl_3 (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 hetero-aromatic amines **347** were ground at room temperature together with a catalytic amount of cerium(III) sulphate.²⁵⁵ Utilization of terephthalaldehyde **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-benzenedialdehyde (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. Golshekan 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 Fe_3O_4 nanoparticles coated by MCM-48 mesoporous silica as a thin layer and the functional groups of sulfonic acid ($\text{Fe}_3\text{O}_4@\text{MCM-48-NaHSO}_4$) 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





Scheme 149 Methods developed by C. B. Reddy and coworkers to synthesize α -aminophosphonates.

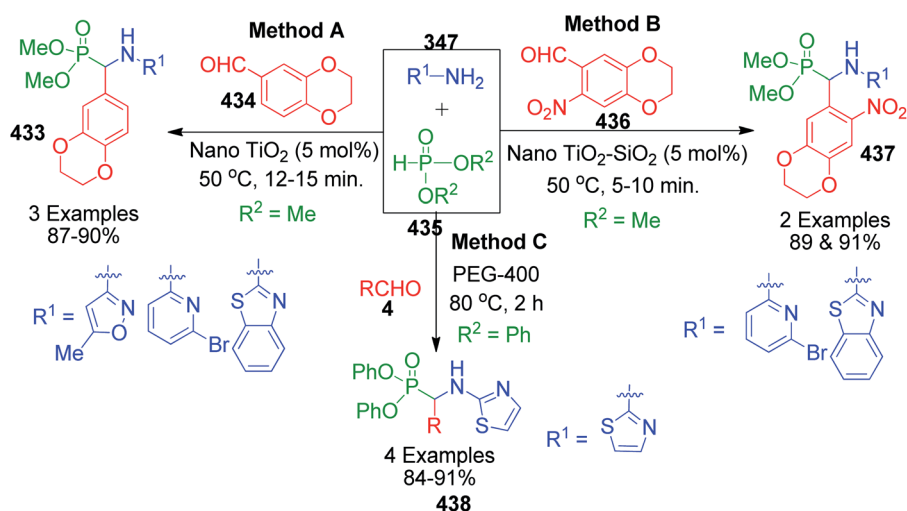
aminonaphthol (Betti's base) through a similar strategy, in which the same starting materials were heated at 125 °C under catalyst- and solvent-free conditions.²⁵⁷ In addition, S. Jayashree and K. Shivashankar also performed the same reaction in the presence of montmorillonite K-10 using ethanol as the solvent at room temperature.²⁵⁸ 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 terephthalaldehyde **414** and two molecules of each heteroaryl amines **347** and naphthols **406** in the presence of 10 mol% formic acid under solvent-free conditions at 80 °C (Scheme 142).²⁵⁹

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 heteroaryl amines **347** (2-aminopyrimidine, 2-aminopyrazine, 2-aminopyridine and 2-aminothiazole), glyoxalic acid **419** and naphthols **406** in water was allowed to interact either at room temperature or under reflux conditions (Scheme 143).²⁶⁰ A direct consequence of using

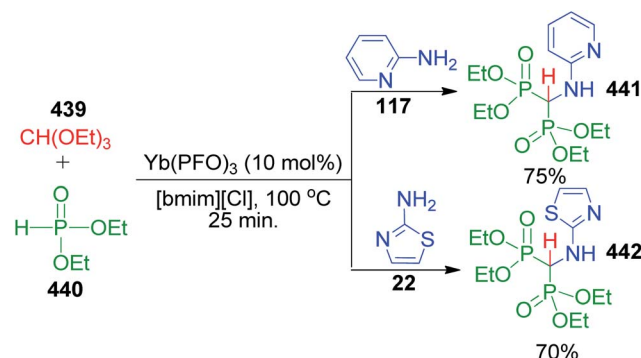
glyoxalic acid led to the formation of amino acid-type framework **420**. After this method was screened at two temperatures, it was found that the reaction performed at room temperature, which took slightly longer time in some cases, has the advantages of simplicity of the procedure, clean and easy 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 **406** with glyoxalic acid **419**, 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 **420** 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 **421** was achieved through the one-pot coupling reactions of indole **422**, aromatic



Scheme 150 Different methods involving dialkylphosphite to synthesize α -aminophosphonates.





Scheme 151 Ionic liquid-mediated ytterbium perfluorooctanoate-catalyzed synthesis of aminomethylene bisphosphonates.

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.²⁶¹ In 2012, S. Ke *et al.* synthesized some more novel α -aminoindoles **423** by conducting the same catalyst- and solvent-free reaction with 2-aminopyridine/2-aminobenzothiazole, indole and its *N*-methyl derivatives and various aldehydes **4** (Scheme 144, Method B).²⁶² 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*-ethyl-benzene-1,3-disulfonamide) (PBBS) **424** or *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide (TBBDA) **224** under solid-state conditions at room temperature.²⁶³ 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 α -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 attacked by indole, followed by rearrangement to produce the final structure (Scheme 145).

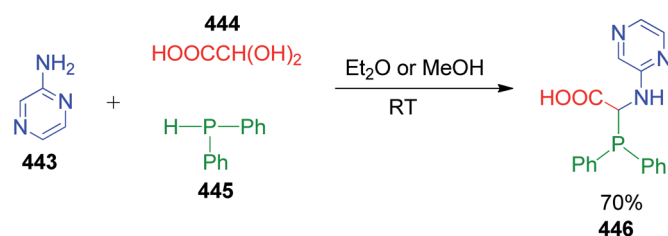
Recently, A. Olyaei *et al.* developed an efficient and straightforward approach utilizing triethyl orthoformate **70**

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)methylidene]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).²⁶⁴ 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 CDCl₃ and DMSO-*d*₆ at room temperature. Furthermore, the synthesized compounds involve intramolecular hydrogen bonds.

2.2.2 MCRs involving trialkylphosphite 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 α -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 α -aminophosphonate synthesis **428** based on the one-pot condensation reaction among 2-aminobenzothiazole **3b**, aldehydes **4**, and triethylphosphite **427** in the presence of InCl₃ as a catalyst.²⁶⁵ 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 InCl₃ 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 α -amino phosphonates **428** and EtOH (Scheme 147).

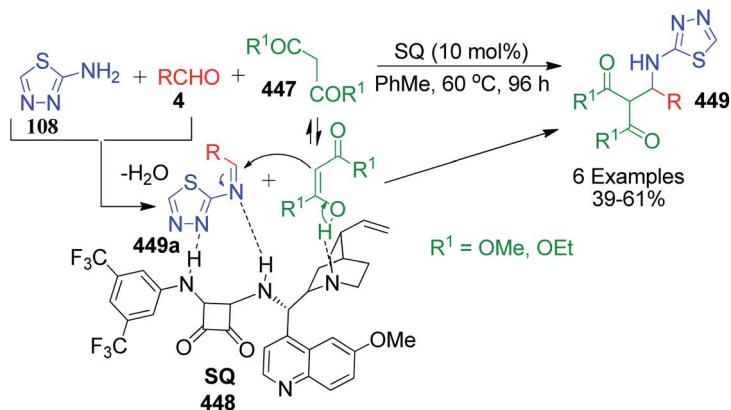
In an analogous method, the acidic ionic liquid-mediated reaction among 2-aminopyridine **117**, 4-methoxybenzaldehyde **429** and trimethylphosphite **427** was investigated by D. Fang and coworkers, which afforded the corresponding α -amino phosphonate **430** in 82% yield (Scheme 148). The ionic liquid ([TMPSA][HSO₄]), which catalyzed the reaction, was found to be recyclable and reusable for at least six times without significant decrease in its catalytic activity.²⁶⁶

In 2012, C. B. Reddy and coworkers explored the same reaction *via* a PEG–SO₃H-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**.²⁶⁷ 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·H₂O) as a catalyst (Scheme 149, Method B).²⁶⁸



Scheme 152 Catalyst-free synthesis of α -diphenylphosphino-*N*-(pyrazin-2-yl)glycine.





Scheme 153 Synthesis of chiral β -amino acid derivatives via Mannich-type reaction.

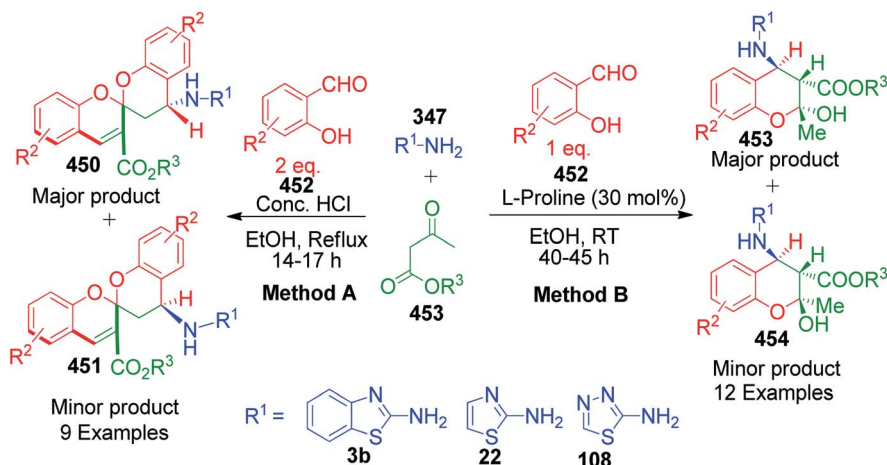
Following the success of the above-mentioned strategies, the same research reported a nano-titanium dioxide-catalyzed one-pot solvent-free Kabachnik–Fields reaction, wherein trialkylphosphite is replaced by dialkylphosphite. The three-component reaction was conducted using 2,3-dihydrobenzo[*b*] [1,4]dioxine-6-carbaldehyde **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).²⁶⁹ Recently, they synthesised 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).²⁷⁰ In addition, C. Sampath *et al.* also utilized dialkylphosphite **435** to develop a polyethylene glycol (PEG-400)-mediated green protocol, in which diphenyl phosphite **435**, 2-aminobenzothiazole **3b** and aromatic/heteroaromatic aldehydes **4** on mixing at 80 °C yielded α -aminophosphonates **438** in good to excellent yields (Scheme 150, Method C).²⁷¹

Next, the application of triethylorthoformate as an aldehydic component in the Kabachnik–Fields reaction was 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-aminobenzothiazole **22**) and triethylorthoformate **439** and two equivalents of diethyl phosphite **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).²⁷²

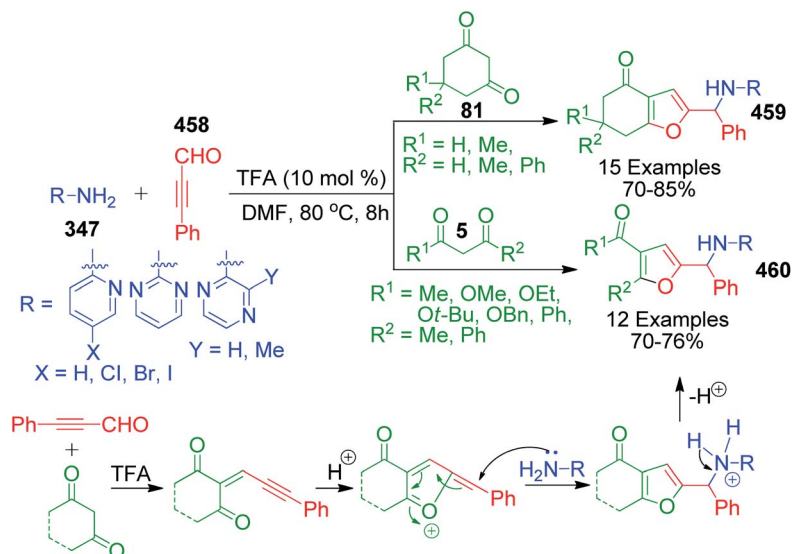
Recently, O. S. Soficheva *et al.* developed an interesting catalyst-free approach based on the three-component condensation of diphenylphosphine **445**, glyoxylic acid hydrate **444**, and 2-aminopyrazine **443**. The corresponding α -diphenylphosphino-*N*-(pyrazin-2-yl)glycine **446** was achieved in 70% yield when the starting materials were stirred in either methanol or diethyl ether at room temperature (Scheme 152).²⁷³

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



Scheme 154 Synthesis of hetaryl-amino-substituted 2,2'-spirobischromanecarboxylates and chromanecarboxylates.





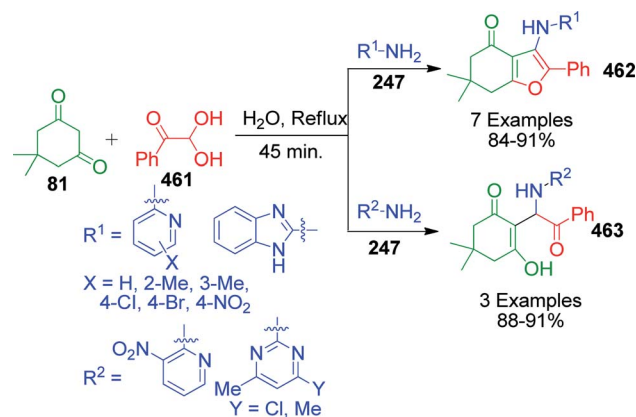
Scheme 155 Synthesis of unusual furan derivatives via TFA-catalyzed three-component domino reactions.

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.²⁷⁴ 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.

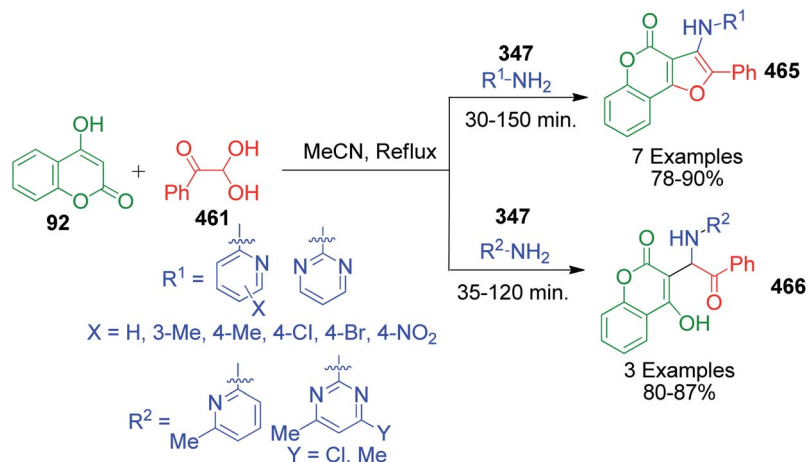
Another protocol utilizing an active methylene compound for the synthesis of hetaryl-amino-substituted 2,2'-spirobischromanecarboxylates **450** and **451** through a pseudo-four-component process under classical Biginelli reaction conditions was developed by J. Světlík and coworkers.²⁷⁵ This multi-component 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-hetaryl-amino-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).²⁷⁶

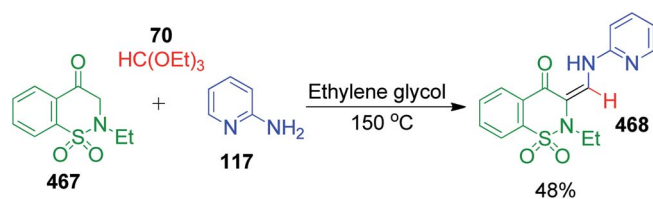
Next, P. Guo *et al.* developed a three-component domino reaction utilizing 1,3-dicarbonyl compounds **5** and **81** as the active methylene compounds, six-membered heteroaromatic amines **347** (pyrazin-2-amine **455**, pyrimidin-2-amine **456**, and pyridin-2-amine **457**) and phenylpropionaldehyde **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).²⁷⁷ The mechanistic insight was gained by performing a controlled experiment, wherein the condensed product, formed by 3-phenylpropionaldehyde **458** and 1,3-cyclohexanedione **81**, was allowed to react with pyrazin-2-amine **455** under the optimized reaction conditions, thereby obtaining the corresponding



Scheme 156 Three-component synthesis of furans and open ring structures depending on the type of heteroaryl amine.



Scheme 157 Extension of the work by A. Olyaei *et al.* with 4-hydroxycoumarine.



Scheme 158 Synthesis of an azomethine-type compound via a one-pot three-component reaction.

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 five-membered oxygen-containing species, which upon conjugate addition of the heterocyclic amine generates the desired furan derivatives **459** and **460**.

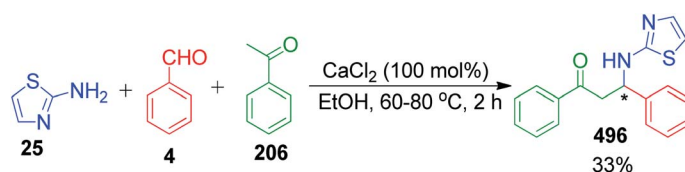
By utilizing phenylglyoxal monohydrate **461**, R. Khoeiniha *et al.* demonstrated the efficient and eco-friendly synthesis of novel 4-keto-4,5,6,7-tetrahydrobenzofurans **462** and **463**. This catalyst-free one-pot three-component condensation protocol involves the reaction among 2-aminopyridine **117** 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).²⁷⁸ 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 heteroaryl amines such as 6-methylpyridine, 2-amino-4-chloro-6-methylpyrimidine and 2-amino-4,6-dimethylpyrimidine, heteroaryl amino alkylation of coumarin occurs, which does not undergo closing of the ring to form furan derivatives **465** and **466** (Scheme 157).²⁷⁹

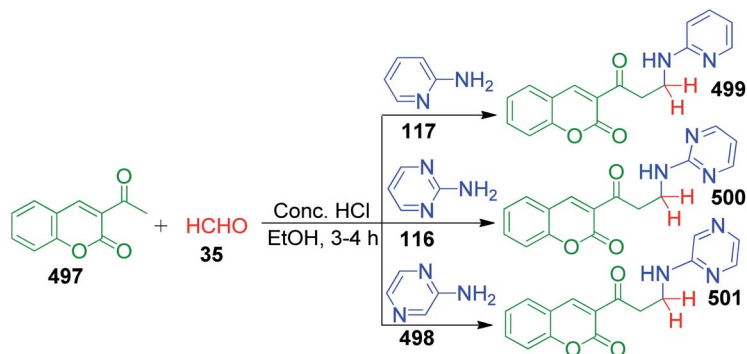
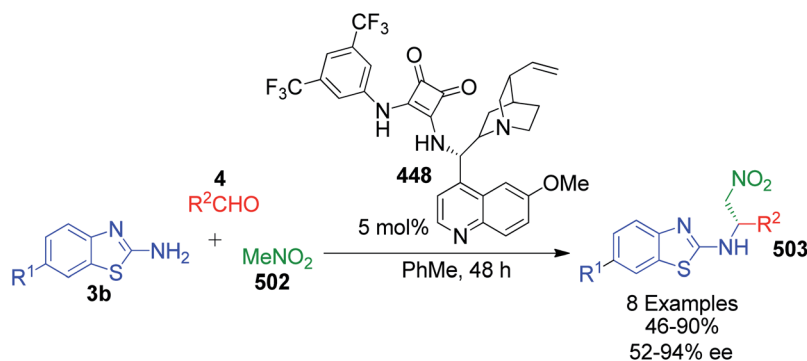
Sulfonamide-bearing compound **467** containing a nucleophilic carbon centre adjacent to one carbonyl group as a variant of the β -dicarbonyl compound in terms of its reaction profile was combined with 2-aminopyridine **117** and ethyl orthoformate **70** by O. Yu. Korshunov *et al.* to synthesize an 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).²⁸⁰ 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



Scheme 159 Synthesis of 2-aminoketone having a chiral center via a Mannich reaction.



Scheme 160 Synthesis of 2-aminoketones utilizing 3-acetylcoumarine as an alternative to β -dicarbonyl.

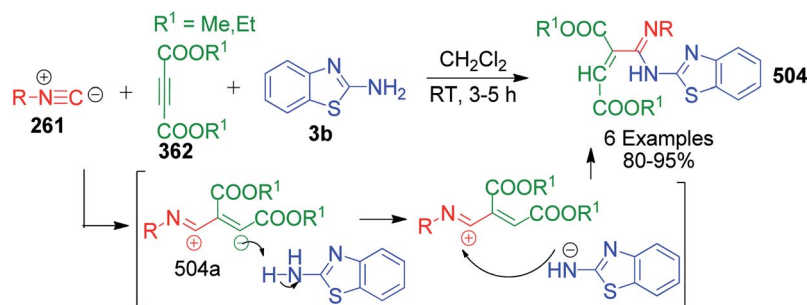
Scheme 161 One-pot three-component enantioselective aza-Henry reaction.

β -aminoketone **496** based on a calcium chloride-catalyzed one-pot three-component reaction *via* the Mannich reaction pathway.²⁸¹ 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 CaCl_2 (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.

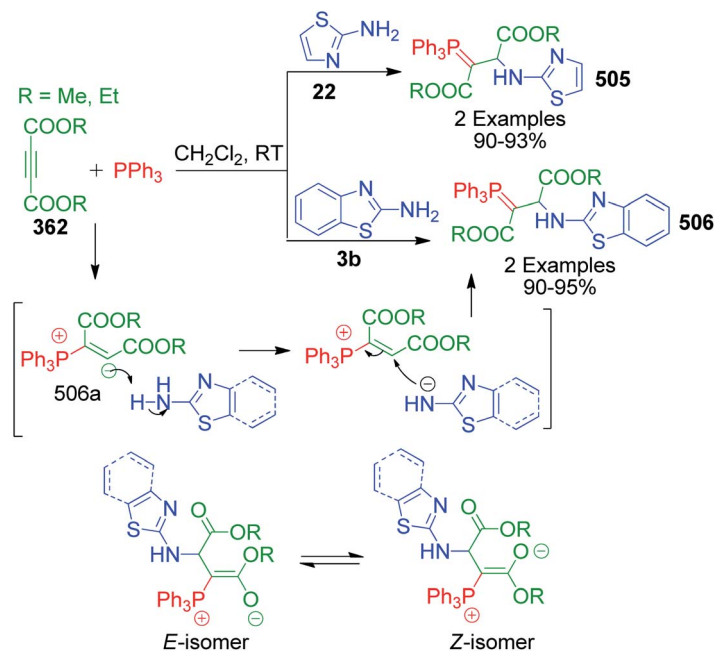
Next, R. B. Patil and S. D. Sawant reported the facile and interesting Mannich reaction-based synthesis of β -amino ketones **499**, **500** and **501** using 3-acetyloumarin **497** (an important class of bioactive molecules) as an alternative to β -dicarbonyl. The reaction was performed with an ethanolic

solution containing 3-acetylcoumarin, six-membered hetero-aromatic 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).²⁸² 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.

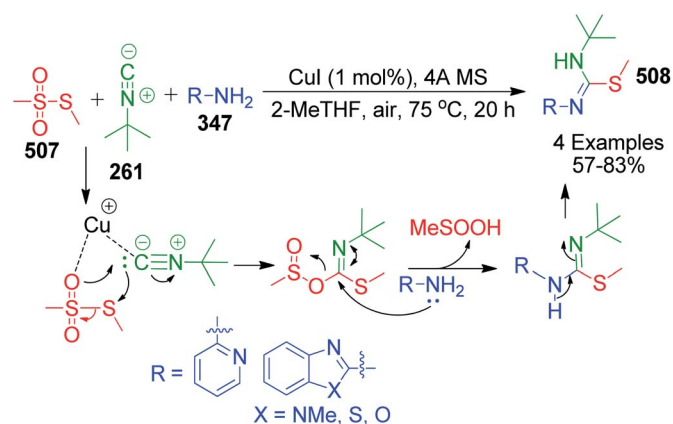
Furthermore, nitromethane as a reacting component in this category of reactions was introduced by H.-X. He and coworkers in a method wherein the cinchona-based squaramide **448**-catalyzed one-pot three-component enantioselective aza-Henry reaction was performed with 2-aminobenzothiazoles **3b**, aldehydes **4**, and nitromethane **502** in toluene at moderate temperature (Scheme 161).²⁸³ The corresponding β -nitro amines



Scheme 162 Catalyst-free synthesis of functionalized azadienes under mild reaction conditions.



Scheme 163 Synthesis of phosphorus ylides under mild reaction conditions.

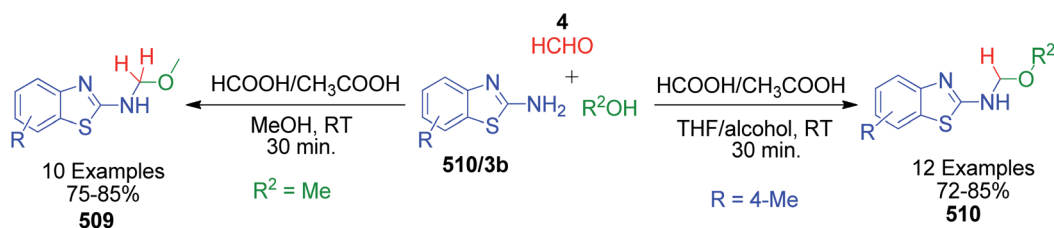


Scheme 164 CuI-promoted three-component synthesis of isothiourea.

503 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-aminobenzothiazoles 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 α -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-aminobenzothiazole **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-aminobenzothiazole **3b** (NH-acidic compound), and the

Scheme 165 Acid-catalyzed synthesis of *N,O*-acetal derivatives of 2-aminobenzothiazoles.

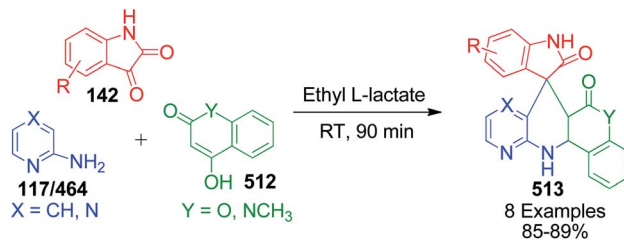
Review

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-Abbassinejad and coworkers performed reactions between triphenylphosphine, dialkylacetylene dicarboxylate **362** and 2-aminobenzothiazole **22**/2-aminobenzothiazole **3b** under mild conditions to afford phosphorus ylides.²⁸⁵ 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. Mampuy 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.²⁸⁶ 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 alcohols, solvent and reactant and offers a smooth way for the transformation.²⁸⁷ 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



Scheme 167 Catalyst-free synthesis of spirooxindole derivatives under mild conditions.

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-aminoazines (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.²⁸⁸ 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).

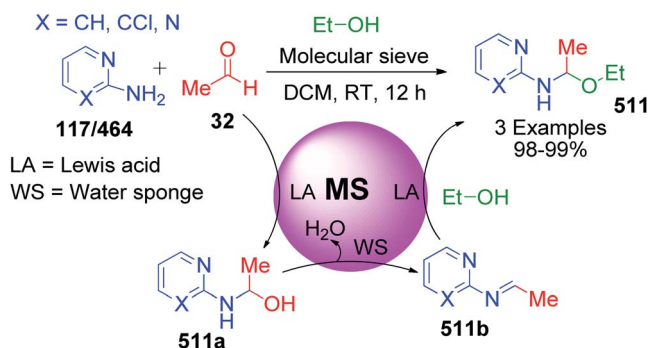
The synthesis of spirooxindole derivatives *via* a catalyst-free three-component domino protocol was developed recently by N. Kausar and coworkers.²⁸⁹ This green strategy involves the reaction between 2-aminopyridine/2-aminopyrazine **117** and **464**, isatin **142**, and 1,3-dicarbonyl compounds **512** 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 α -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.

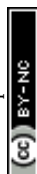


Scheme 166 Molecular sieve synthesis of *N,O*-acetal derivatives of some 2-aminoazines.



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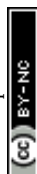
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