Recent applications of aminouracil in multicomponent reactions

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Abstract

6-Aminouracil and its derivatives are versatile heterocyclic compounds and are frequently employed to synthesize a wide array of fused uracils annulated with other heterocyclic rings which can serve to address biological and pharmacological targets. Multicomponent reactions (MCRs) are important in the synthesis of natural products and pharmaceuticals by forming heterocyclic molecular frameworks with generally high atom-economy in a single reaction step. This review embraces various modern synthetic strategies, summarizing recent research developments providing fused 6-aminouracil derivatives and to highlight the progress based on MCRs between 2015 and 2020.
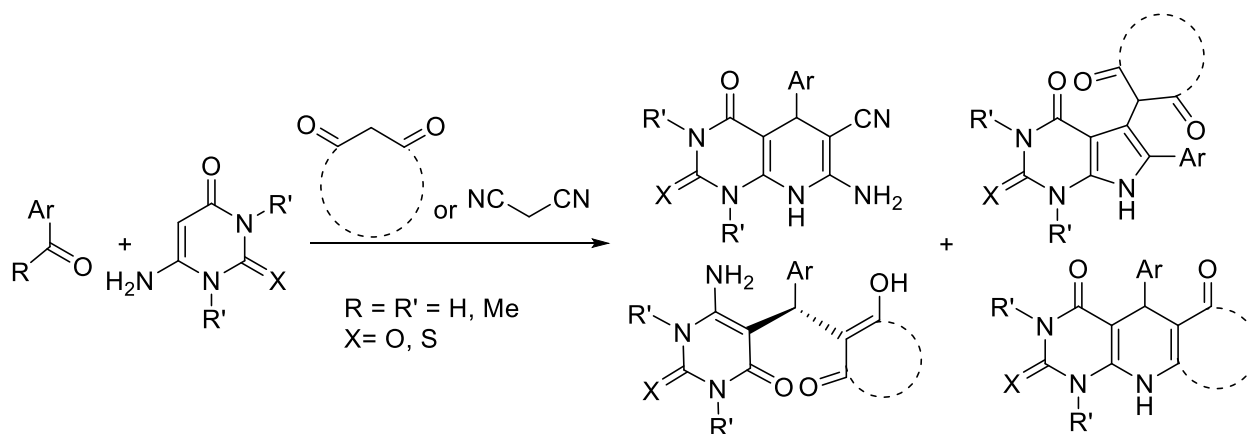
Keywords: 6-Aminouracil, synthesis, multicomponent reaction

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1. Introduction

Extensive use of heterocyclic compounds, especially in various industries dealing with drugs, foods, healthcare, dyes, polymers, etc., is increasing.[1-10] Furthermore, these materials are the main constituents of organic synthetic materials and of natural products.[11-13]

One of the primary starting materials and as a privileged scaffold, 6-aminouracil is a widespread subunit in various complex molecules, and their derivatives remain of great interest in organic chemistry. Since this molecule can act as both nucleophile and electrophile, it is of interest to many chemists. At position 3, the most significant nucleophilic activity is observed. This compound can be easily used to prepare fused annulated compounds with other materials and polycyclic compounds with biological targets such as pyrido-, pyrrolo- and pyrimido-pyrimidines.[14-16] These derivatives have presented a remarkably broad spectrum of pharmacological and biological activities , such as antimicrobial[17-19] and anticancer,[20-22] and they are employed as anticoagulant,[22,23] antifungal,[24-26] antiviral,[27-29] antitumor,[30,31] antioxidant,[32,33] anti-inflammatory agents,[34,35] HIV protease inhibitors,[36-38] antiallergics,[39] and tyrosine kinase inhibitors.[40]
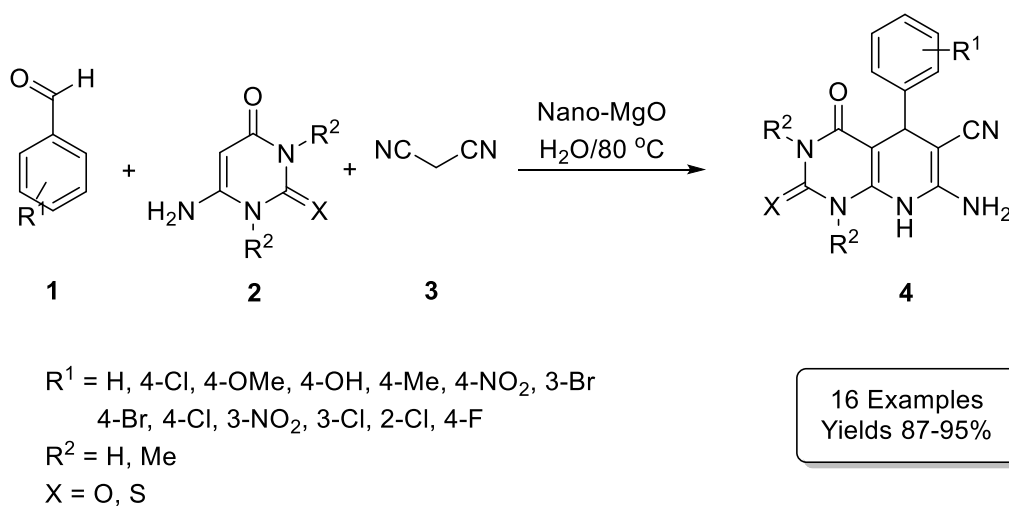
To prepare new heterocyclic molecules, in particular compounds with pharmaceutical and biological activities, chemists always try to prepare such compounds using the least amount of energy and in the shortest time. In recent years, one-pot multicomponent reactions (MCRs) have made it possible to achieve this goal by simultaneously combining several substances, accompanied by the breaking and formation of several bonds. For a rapid and green methodology in modern organic synthesis to prepare molecular diversity and complexity from simple and readily available substrates, organic and medicinal chemists can use one-pot (MCR) processes as powerful and productive synthetic tools. This method proved to be of considerable utility to researchers to obtain desired complex heterocyclic frameworks by condensation of more than two reactants in a single operational step.[41-48]

Herein, in continuation of studies towards the synthesis of heterocyclic scaffolds via multicomponent reactions,[49-52] and because the 6-aminouracil is frequently used as a starting material in synthesizing these compounds. This review is devoted to recent applications of 6-aminouracil and its derivatives in synthesizing diverse heterocyclic compounds based on MCRs from 2015 to 2020.

2. Synthesis of Pyrido-pyrimidine Compounds

A green and sustainable approach for the preparation of a series of pyrido[2,3-*d*]pyrimidine derivatives via three-component reaction of 6-aminouracil derivatives (**2**), with malononitrile (**3**) and various aromatic aldehydes (**1**) in the presence of a novel nanocrystalline MgO with high efficiency was reported by Mokhtary *et*

al. in water as a green solvent at 80 °C (Scheme 1).[53] In materials science, MgO is an exciting and popular material for researchers and has been the subject of extensive theoretical and experimental studies in surface science. The optical properties and its impressive optical architecture can be made in various molds such as nanosheets and nanoparticles.[54] This makes MgO nanoparticles attractive catalysts due to their large surface area. Today, nanocatalysts are considered to form a bridge between homogeneous and heterogeneous catalysts.


R¹ = H, 4-Cl, 4-OMe, 4-OH, 4-Me, 4-NO₂, 3-Br
   4-Br, 4-Cl, 3-NO₂, 3-Cl, 2-Cl, 4-F
R² = H, Me
X = O, S

16 Examples
Yields 87-95%

Scheme 1. Efficient one-pot synthesis of pyrido[2,3-*d*]pyrimidines catalyzed by nanocrystalline MgO.[53]

In a follow-up investigation in 2015, the Mohammadi Ziarani group found a green procedure for the three-component synthesis of pyrido[2,3-*d*]pyrimidine derivatives in water.[55] For this purpose, the single-pot, three-component condensation reaction of 6-aminouracil (**2**), various aromatic aldehydes (**1**), and malononitrile (**3**) in the presence of sulfonic acid functionalized SBA-15 (SBA-Pr-SO₃H) as a highly active nanoporous heterogeneous acid catalyst proceed rapidly in solvent-free at 60 °C in good to excellent yields (Scheme 2). They studied the biological activities of desired products found, and some of them shown antimicrobial activities against some fungi and Gram-positive and -negative bacteria.

One of the exciting candidates for solid supports in catalytic reactions is SBA-15 (*Santa Barbara Amorphous-15*), a mesoporous nanocatalyst. This nanocatalyst has high thermal stability, high surface area, fine pore size distributions, well ordered hexagonal arrays of cylindrical channels, thick silica walls, large pore size, and the appreciable number of silanol groups at the surface of its channels. To improve its physical and chemical properties, this efficient and practical support can be improved. In acid-catalyzed reactions, the acidification of SBA-15 can increase its acidic properties as an efficient, heterogeneous, and reusable catalyst.[57]

Upadhyay *et al.* demonstrated a convenient and economical new approach for electosynthesizing biologically important pyrido[2,3-*d*]pyrimidine derivatives via a one-pot three-component reaction. A wide variety of aromatic aldehydes (**1**) and dimedone (**5**) or malononitrile (**3**) and 6-aminouracil derivatives (**2**) undergo this reaction to afford these heterocycles' high yields (Scheme 3).[57] In this reaction, sodium bromide is used as a supporting electrolyte in an undivided cell with a constant current and ethanol as a solvent. In electrochemistry, the electron acts as the sole reagent, so it does not require acid, nor base, nor catalyst, nor an electrogenerated base (EGB) to conduct good efficiency reactions. The literature mentioned the advantages of the electrosynthesis method as being mild reaction conditions, decreased energy requirements,

atom economy, and reduction byproducts, and can be used in a wide range of oxidation and reduction reactions.
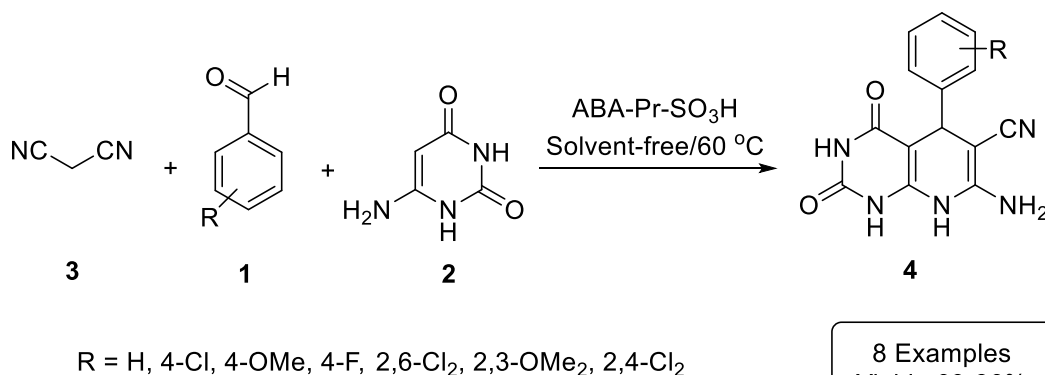
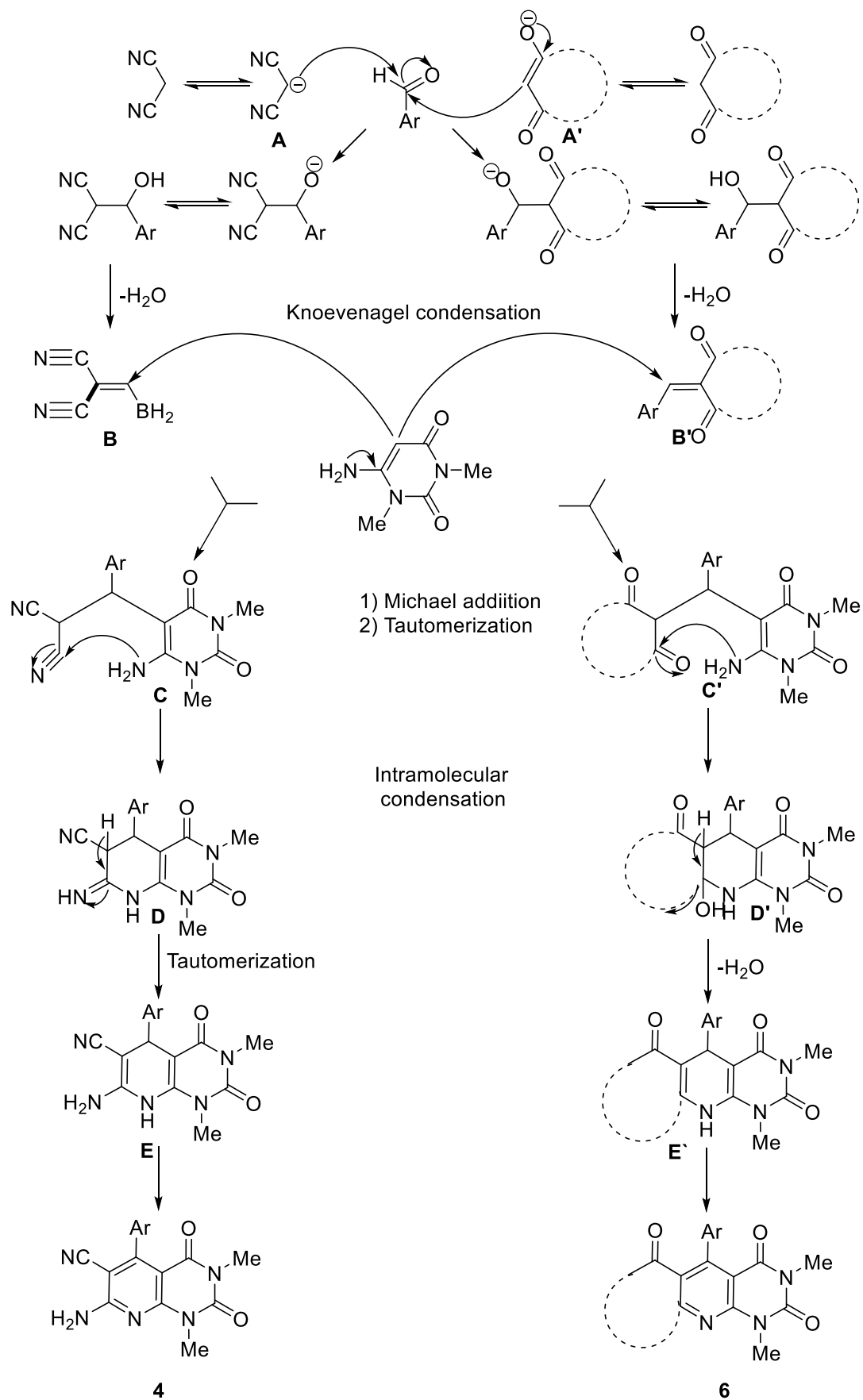**Scheme 2.** One-pot synthesis of pyrido[2,3-*d*]pyrimidine derivatives using sulfonic acid functionalized SBA-15.[55]
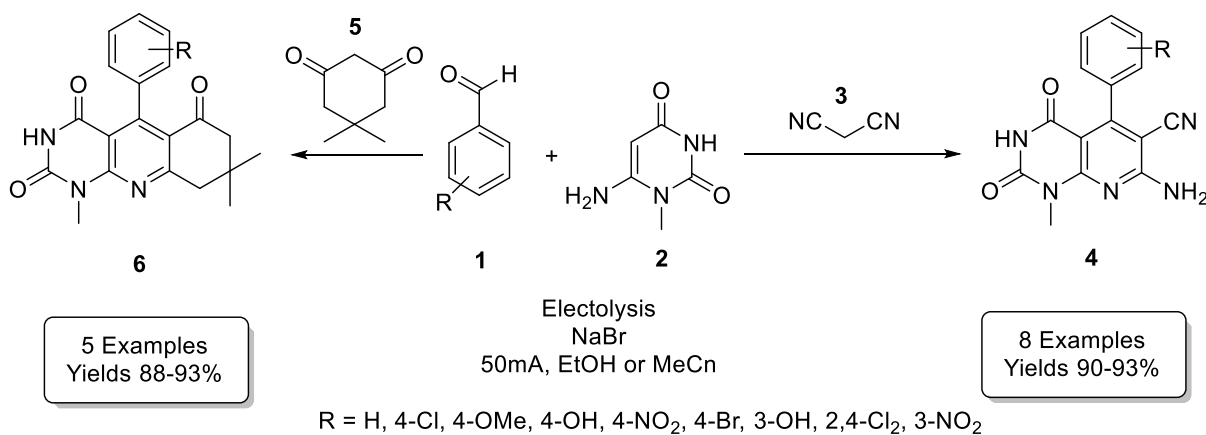

Scheme 3. One-pot three-component synthesis of fused pyridines via electrochemical approach.[57]

The authors suggested that a plausible reaction mechanism included the following steps (Scheme 4). The solvents or catalysts help to activate the electrophile by the acidic moiety or the nucleophiles by the basic moiety and play an important role in forming anion methylene actives malononitrile (**3**), the dehydration, and tautomerization process. The Knoevenagel condensation between aldehyde (**1**) and prepared anion of methylene actives or malononitrile (**3**) followed by eliminating water to afford intermediate (B or B'). Subsequent Michael-type addition of 6-aminouracil derivative (**2**) to intermediate (B or B') gives the intermediate C or C'. Cyclization of intermediate followed by dehydration affords the corresponding intermediate (E or E`). This intermediate undergoes oxidation to give final product (**4**) or (**6**).

Scheme 4. Proposed mechanism for the synthesis of fused pyridine derivatives.

In 2016,[58] using a one-pot Knoevenagel-Michael addition pathway, the group of Hashmi has developed the synthesis of pyrido[2,3-*d*]pyrimidine derivatives (**8**). In this method, the reaction of substituted aromatic aldehydes (**1**), cyanoacetamide (**7**) and 6-aminouracil (**2**) in *N,N*-dimethylformamide (DMF) in the presence of 4-dimethyl aminopyridine (DMAP) as organo-catalyst under ultrasonic irradiation has been used to prepare the final product (Scheme 5). It is interesting to note that the reaction proceeded in good to excellent yields (81-93%) with no significant variation in the yield of the product among the substrates tested. Nowadays, sono-promoted transformations are recognized as a powerful and green method; therefore, they are widely used to increase the reaction rates and product efficiency of organic compounds. Usually, ultrasonic-assisted organic synthesis (UAOS) accelerates the reaction time, reduces the induction period, and enhances the efficiency of catalysts, which has prominent effects on the chemical reaction.


R = H, 4-Me, 2-OMe, 3,4-OMe, 3-OH, 4-OH, 4-Cl
4-OMe, 4-Br, 2-Cl, 3-NO$_2$, 2-NO$_2$,4-NO$_2$

13 Examples
Yields 81-93%
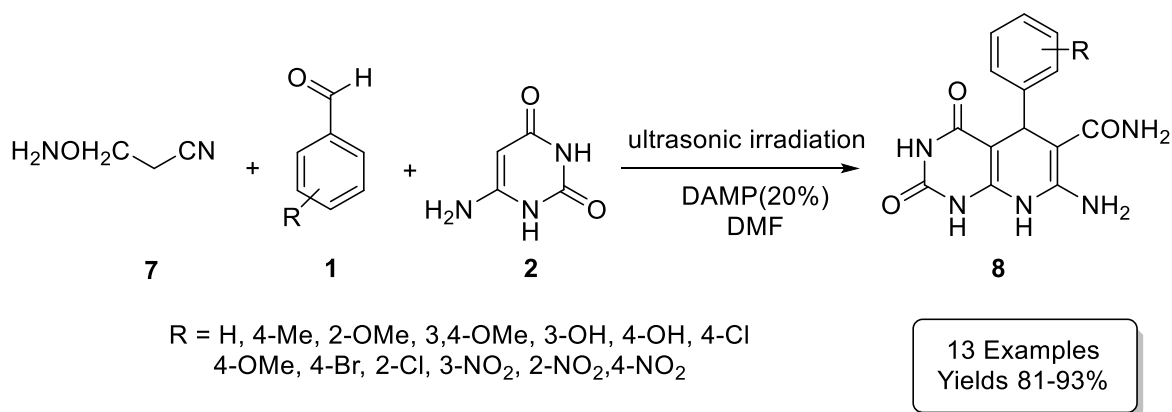
Scheme5. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives.[58]

In the last decades, the combination of electro synthetic and multicomponent reactions (EMCRs) has been used extensively to synthesize biologically active scaffolds and have become important research fields in medicinal, combinatorial, and organic chemistry. Kazemi-rad et al. developed a new 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives, the electrocatalytic multicomponent transformation reaction of 6-aminouracils (**2**), aromatic aldehydes (**1**) and malononitrile (**3**) in ethanol in an undivided cell in the presence of potassium bromide as an electrolyte in short reaction times and good to high yields (Scheme 6) (70-86%).[59]

R^1 = 4-Cl, 4-OMe, 3-NO$_2$, 4-NO$_2$, 3-Br
R^2 = H, Me
X = O, S

10 Examples
Yields 70-86%
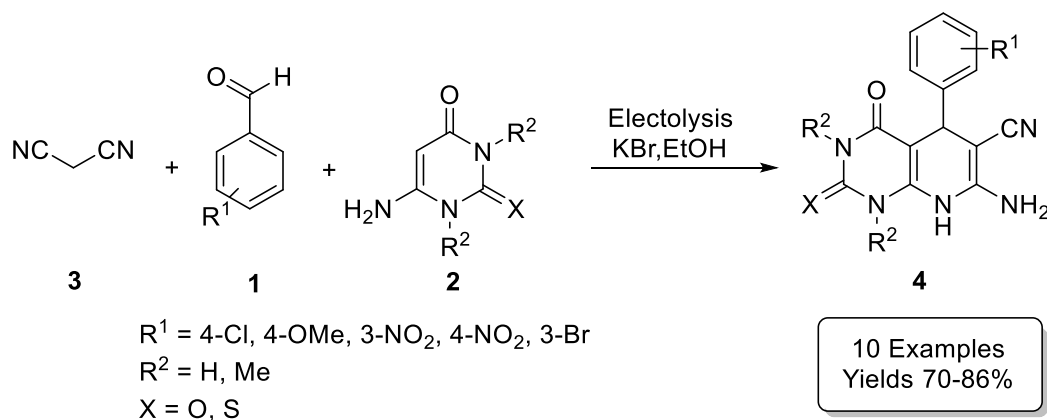
Scheme 6. Synthesis of Pyrido[2,3-*d*]pyrimidines.[59]

Javahershenas and Khalafy represented one-pot three-component reaction of various arylglyoxals (**9**), malononitrile (**3**), and 1,3-dimethyl-6-aminouracil (**2**) gave the desired main products polyfunctionalized pyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives (**11**) in the presence of urea as a cheap and readily accessible organocatalyst in EtOH:H$_2$O (1:1) at 60 °C in good to excellent yields (Scheme 7).[60]


R = H, 4-Cl, 4-OMe, 3,4-OMe$_2$, 4-NO$_2$, 4-Br, 4-Me, 4-OH, 4-F

9 Examples
Yields 65-86%
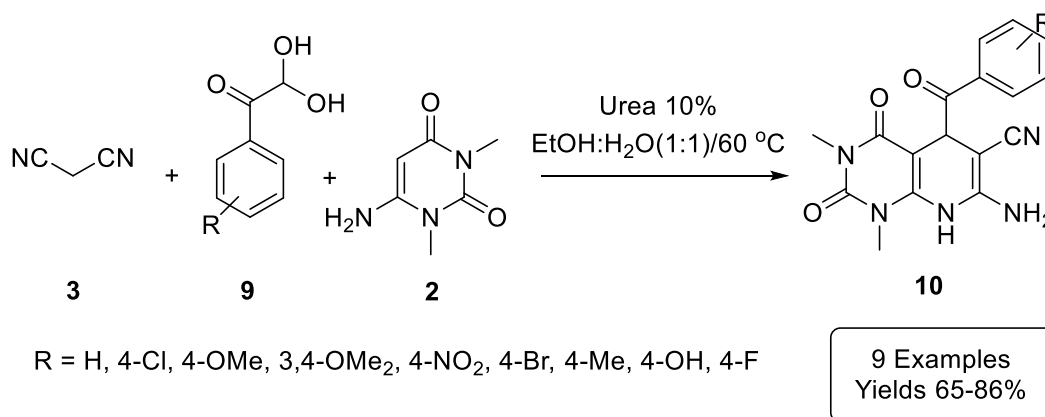
Scheme 7. One-pot three-component reaction of polyfunctionalized pyrido[2,3-*d*]pyrimidine derivatives.[60]

Mohammadpoor-Baltork *et al.* studied an efficient one-step reaction of aromatic aldehydes (**1**), 1,3-dimethyl-6-aminouracil (**2**) and carbonitriles catalyzed by APTADPHS-nSiO$_2$ (triazine diphosphonium hydrogen sulfate ionic liquid supported on functionalized nanosilica) as a reusable catalyst under microwave irradiation and solvent-free conditions that gave fused heteroaromatic1,3-dimethyl-5-aryl-7-(pyridine-3(2)(4)-yl)pyrimidine-2,4(1*H*,3*H*)-diones in moderate to good yields (Scheme 8).[61] Besides, synthesizing the bis-derivatives of pyridylpyrimidines was also efficiently obtained by using dinitriles and dialdehydes. Without any significant loss of its activity can be reused the catalyst at least several times. The easy recovery, reusability, and excellent activity of the catalyst, and easy workup are other noteworthy advantages of this method.

Recently, a clean and straightforward one-pot multicomponent methodology using 6-aminouracils (**2**) was discovered by Dongre and co-workers (Scheme9).[62] It was demonstrated that the interaction of 6-aminouracil (**2**), aromatic aldehydes (**1**), and malononitrile (**3**) led exclusively to 7-amino-2,4-dioxo-5-aryl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitriles (**5**) by using triethylamine (TEA) base as a catalyst in an aqueous ethanol medium under mild conditions. The reaction procedure has many advantages like short reaction time, mild reaction conditions, inexpensive chemicals, an environmentally friendly protocol, and easy isolation of derivatives with excellent yields of bioactive products (85-95%). This multicomponent synthetic protocol uses cheap ingredients like Et$_3$N catalyst and ethanol as the green solvent. All the synthesized compounds with nitrile groups showed comparatively good antibacterial activities.

Pyrido[2,3-*d*]pyrimidines are considered highly important heterocyclic compounds which exhibit a wide variety of biological activities. In another study reported by Aryan and co-workers, the deep eutectic solvents (DESs) was utilized as a media to synthesize a series of diverse pyrido[2,3-*d*]pyrimidine derivatives. A straightforward and efficient multicomponent synthesis of a small library of diverse pyrido[2,3-d]pyrimidine derivatives was reported through the three-component reaction of aromatic aldehydes (**1**), active methylene compound (malononitrile (**3**), methyl acetoacetate (**20**) or ethyl cyanoacetate (**19**)), and aminouracil (**2**, Scheme 10).[63] The products were obtained within relatively short reaction times in good to excellent yields in the presence of in situ prepared choline chloride/urea (1:2) deep eutectic solvents (DESs) as media and promoters. Recently, the use of DESs has received extensive attention as a green solvent alternative to harmful organic solvents and ionic liquids due to the unique properties such as low production price, low

toxicity, negligible vapor pressure, and high biodegradability. This new solvent class, in addition to providing a reaction medium, has in some cases been used as a reactant or even a catalyst for a variety of several synthetic methods. The beneficial factors of this method are simple purification and the ability to reuse deep eutectic solvent. Also, antibacterial and antifungal activities were observed for all compounds synthesized in vitro.
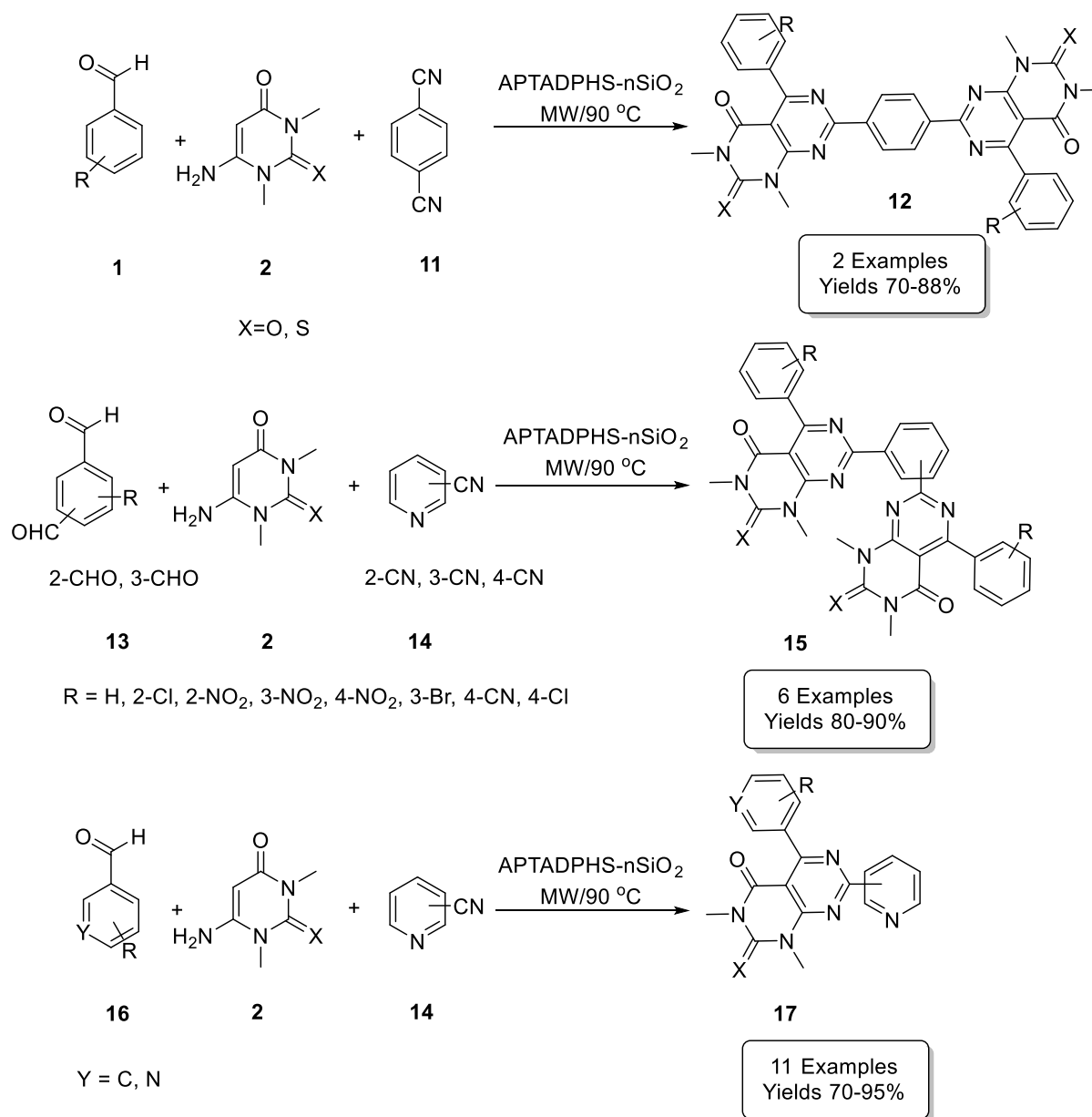
Scheme 8. Multicomponent synthesis of pyridylpyrimidines and their bis-derivatives catalyzed by APTADPHS-nSiO$_2$.[61]

R = H, 4-Cl, 4-OMe, 3-NO$_2$, 4-NO$_2$, 4-Me, 4-OH, 2-NO$_2$

8 Examples
Yields 85-95%
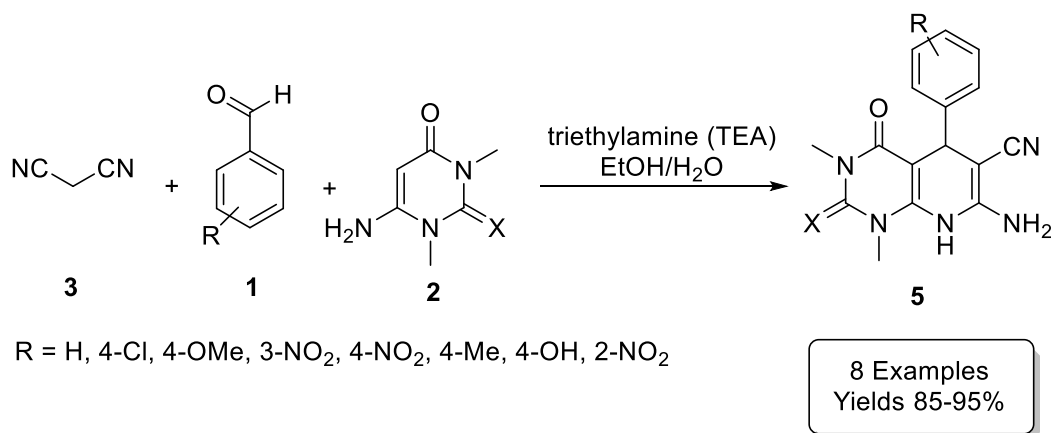
Scheme 9. General procedure for the preparation of pyrido[2,3-*d*]pyrimidines.[62]

R = H, 4-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 4-MeCONHC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$
2,6-C:2C$_6$H$_3$, 3-NO$_2$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-OHC$_6$H$_4$,4-MeC$_6$H$_4$
2-OH-3-OMeC$_6$H$_3$, 2,4-Cl$_2$C$_6$H$_3$, 4-PhCH$_2$OC$_6$H$_4$, 2-Thienyl

16 Examples
Yields 71-96%
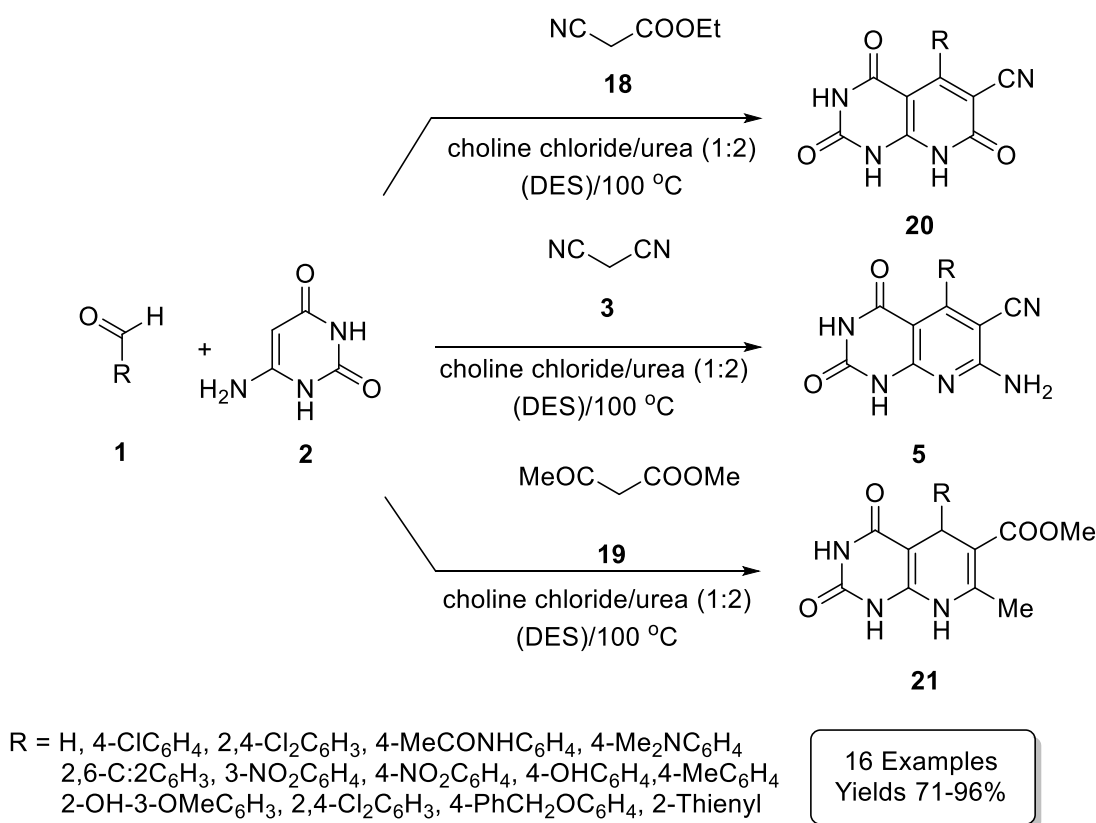
Scheme 10. Synthesis of various pyrido[2,3-*d*]pyrimidine derivatives through a multicomponent reaction.[63]

In 2018, an efficient one-pot, three-component condensation reaction synthesis of 6,8a-dihydropyrido[2,3-*d*]pyrimidine derivatives (**24**) was accomplished through the condensation of (phenylsulfonyl)acetonitrile (**23**), aromatic aldehydes (**1**), and 6-aminouracil (**2**) in glycerol at 80 °C without using any toxic solvent under mild reaction conditions in good to excellent yields (88-95%) by Shaterian et al. (Scheme 11).[64] The method covers domino condensation-cyclization Knoevenagel-Michael addition. The reaction was performed in glycerol as a solvent that is commercially available, cheap, and non-toxic. It could also be successfully recovered and recycled at least for five runs without significant loss in activity.
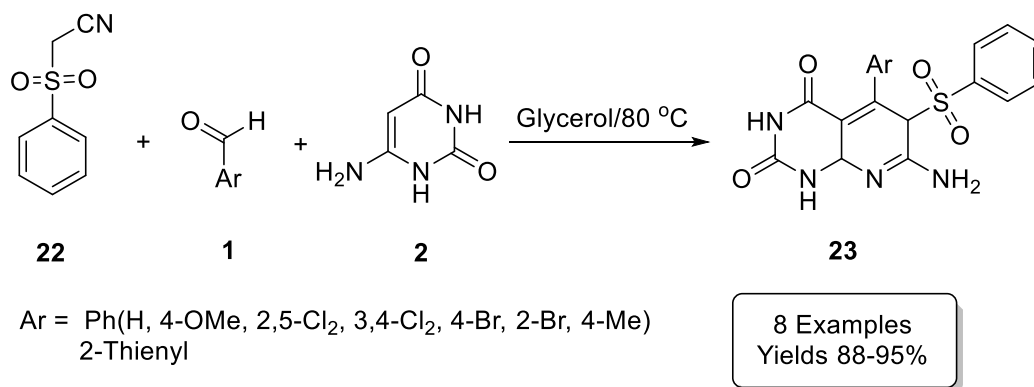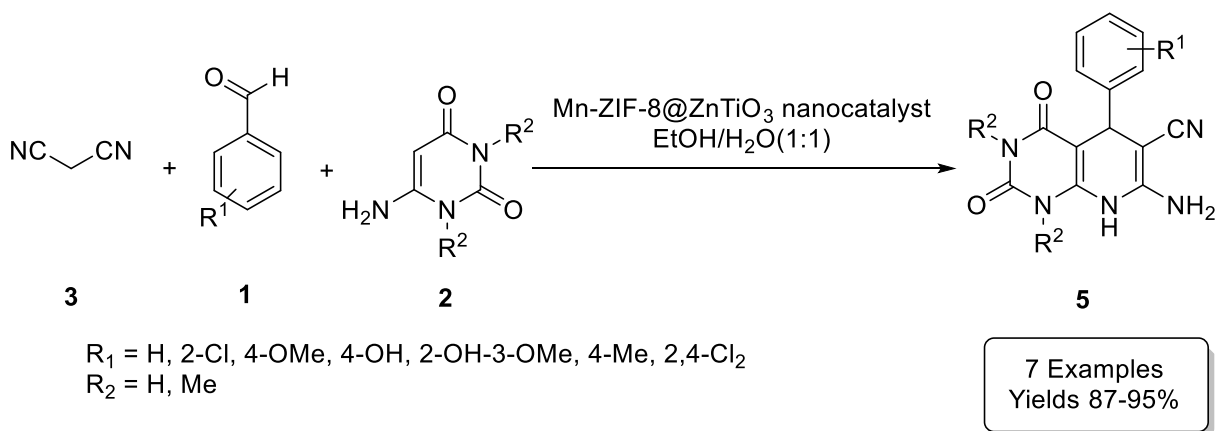
Scheme 11. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives via a three-component reaction.[64]

An eco-friendly and straightforward approach for the glycerol-water assisted catalyst-free synthesis of pyrido[2,3-d]pyrimidine derivatives (**5**) were reported by Anbhule and co-workers through a one-pot, three-component domino reaction of aryl aldehyde (**1**), malononitrile (**3**), and 6-aminouracils (**2**) or 6-amino-1,3-dimethyluracil using glycerol-water (3:1) as green reaction mixture with high yields (Scheme 12).[65] With regard to the green chemistry principles, catalyst-free synthesis with high to excellent yields and use of glycerol–water system as an environmentally, non-corrosive, non-flammable, and inexpensiveness benign reaction condition are the prominent features of this strategy.
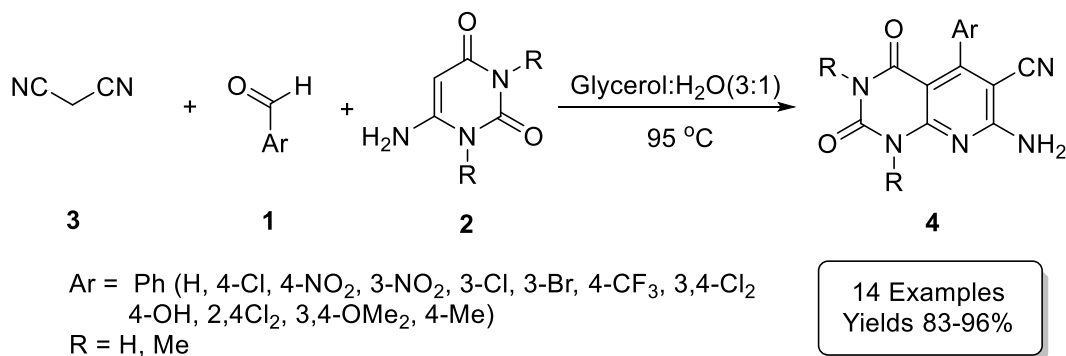
Scheme 12. An efficient protocol for the synthesis of pyrido[2,3-*d*]pyrimidines in glycerol-water medium.[65]

Hashemian *et al.*[66] disclosed the preparation and application of a novel Mn-ZIF-8@ZnTiO₃ nanocomposite by sol-gel method for synthesizing a variety of pyrido [2,3-*d*]pyrimidine derivatives under reflux conditions (Scheme 13). The evolution of catalytic behavior of the nanocrystalline Mn-ZIF-8@ZnTiO₃ was investigated in the three-component condensation of 6-aminouracil (**2**) or 6-amino-1,3-dimethyluracil with aryl aldehydes (**1**) and malononitrile (**3**), affording several pyrido[2,3-d]pyrimidine derivatives (**5**) in water and ethanol at 70 °C in high yields (79-85%).

Scheme 13. One-pot synthesis of pyrido[2,3-*d*] pyrimidine derivatives by using Mn-ZIF-8@ZnTiO$_3$ nanocatalyst.[66]

The Dongre group demonstrated a simple and environmentally benign approach for the one-pot three-component preparation of various of annulated pyrido[2,3-*d*:6,5-*d*]dipyrimidine derivatives (**26**) through the three-component cyclocondensation of aromatic aldehyde (**1**), thiobarbituric acid (**24**), and 6-aminouracil (**2**) catalyzed by DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as an efficient organocatalyst in aqueous ethanol under reflux (Scheme 14).[67] This methodology offered various benefits like excellent yields, short reaction time, environment-friendly procedure, easy isolation of products, and excellent yields (72-89%). DBU is one of the most substantial organocatalysts bases (pKa = 12), which has been used for various organic syntheses due to its cheap, readily available, environmentally friendly, highly active, and non-toxic nitrogen-base catalysts. It is a sterically hindered amidine base, and due to the inherent nucleophilicity of basic nitrogen, it can reduce side reactions.
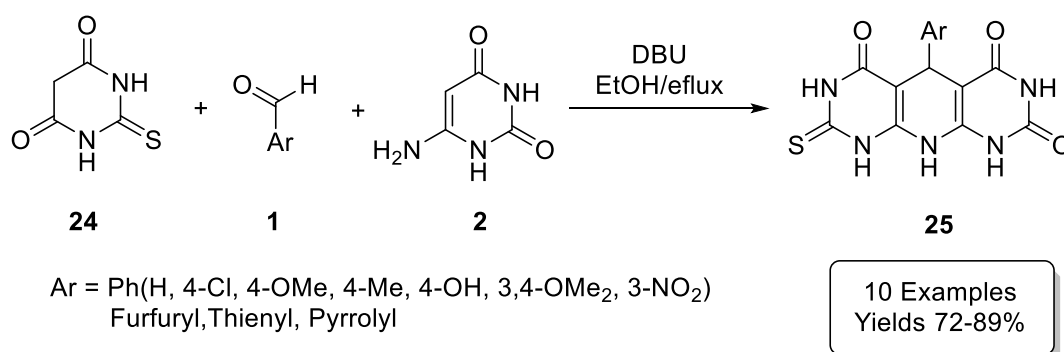
Scheme 14. One-pot synthesis of pyrido[2,3-*d*:6,5-*d*]dipyrimidinec derivatives using DBU.[67]

A clean and practical three-component synthesis of fused indenopyridines (**27**) containing an uracil moiety from benzaldehydes (**1**), 6-aminouracils (**2**), and 2-bromo-1*H*-indane-1,3(2*H*)-dione (**27**) was developed by Bazgir and co-workers in the presence of ammonium acetate in HOAc under reflux conditions. They found that acetic acid is the most suitable reaction media (Scheme 15).[68] The procedure used does not require chromatographic methods and recrystallization and purification methods to extract pure products from the reaction medium.
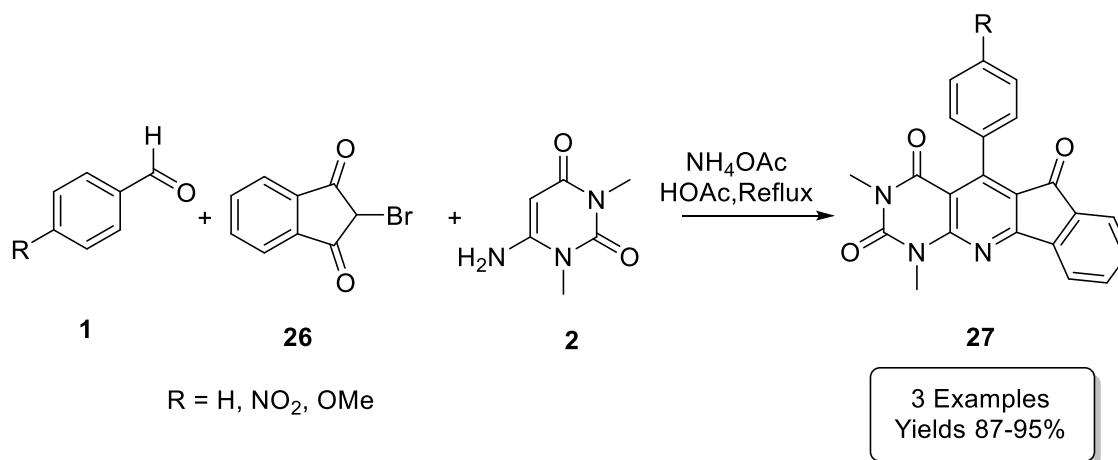
Scheme 15. Three-component synthesis of fused indenopyridines.[68]

Mansoor and his groups developed a mild, facile and straightforward one-step condensation method for the synthesis of privileged of 5-aryl-5,11-dihydro-1*H*-indeno[2',1':5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione derivatives (**29**) from aromatic aldehydes (**1**),1,3-indanedione (**28**) and 6-aminouracil (**2**) in the presence of the catalyst, β-cyclodextrin-propyl sulfonic acid (β-CD-PSA) under solvent-free conditions (Scheme 16).[69]

The hydrophobic cavity of CDs (cyclodextrin) has unique supramolecular properties, so this widespread use of CDs in various organic synthesis areas is of particular interest to chemists. Many kinds of literature have been reported that β-cyclodextrin based polyurethane has been used as an efficient phase transfer and reusable catalyst without significant loss of activity to prepare heterocyclic scaffolds via multicomponent synthesis.
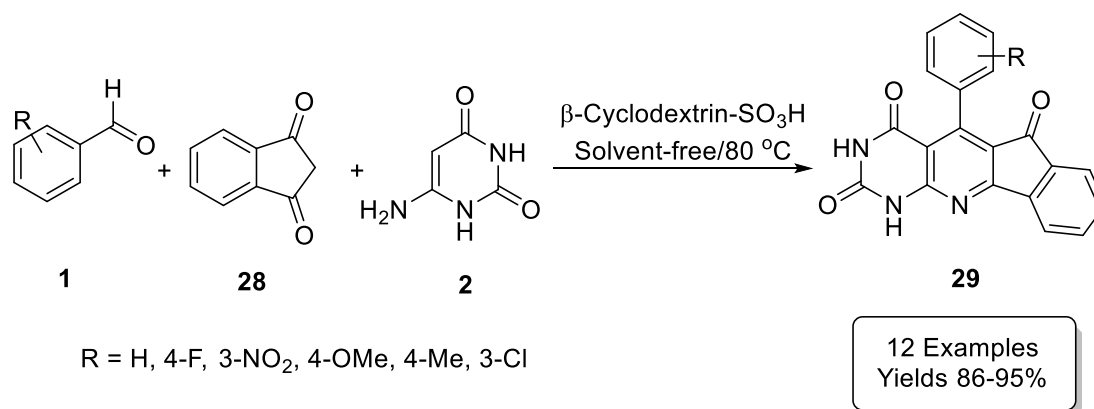
Scheme 16. Synthesis of 5-aryl-5,11-dihydro-1*H*-indeno[2',1':5,6]pyrido[2,3-*d*]pyrimidine-2,4,6-trione.[69]

A review of articles and research has shown that due to phosphorus pentoxide's unique properties and synthetic capabilities, P_2O_5 can be used in organic conversions like in olefin dimerization, Beckmann rearrangement, the formation of 1,1-diacetates and the tetrahydropyranylation of alcohols. A clean and efficient P_2O_5 mediated procedure for the three-component reaction of synthesis of pyrido[2,3-*d*:6,5-*d*]dipyrimidines derivatives (**30**) from aromatic aldehydes (**1**), barbituric acid (**29**)/thiobarbituric acid (**24**), and 1,3-dimethyl-6-aminouracil (**2**) was developed by Anbhule *et al.* in ethanol with good yields (Scheme 17).[70]

Studies on the biological activities of these synthetic compounds showed that all prepared compounds have antituberculosis activity activities against the $H_{37}RV$ strain of *Mycobacterium tuberculosis*.

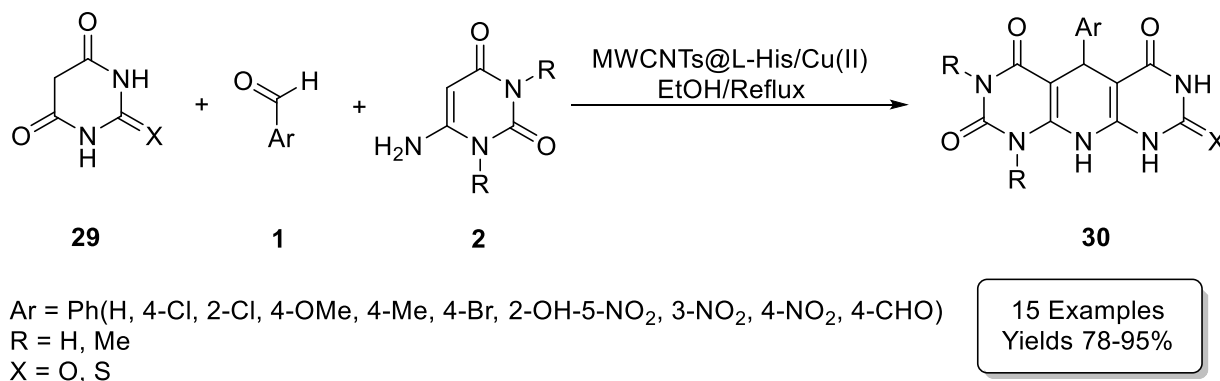Ar = 3-ClC₆H₄, 4-CNC₆H₄, 2-NO₂C₆H₄, 3-Cl C₆H₄
3-NO₂C₆H₄, 2-Cl C₆H₄, 2-Cl C₆H₄, 4-NO₂C₆H₄
2-NO₂C₆H₄, 4-ClC₆H₄, 4-ClC₆H₄

X = O, S

11 Examples
Yields 80-88%
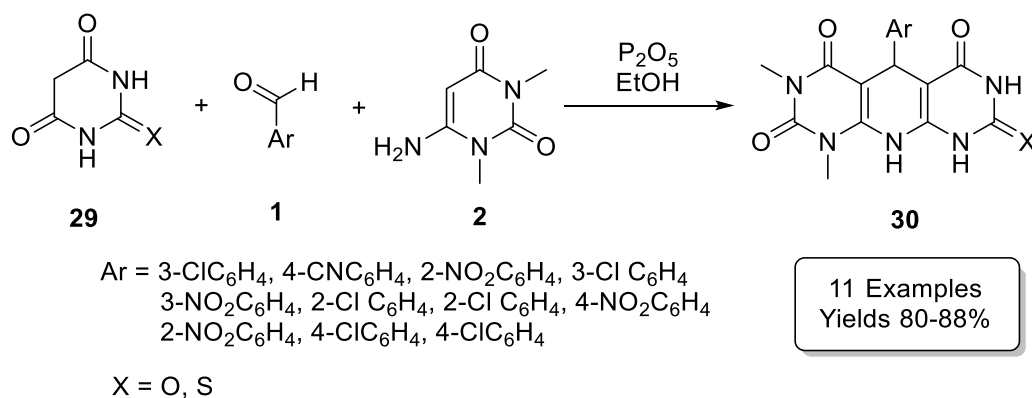
**Scheme 17.** Synthesis and biological evaluation of heterocycle-fused pyrimidine derivatives.[70]

Considering the excellent heterogeneous organometallic catalytic performance of MWCNTs@L-His/Cu(II) reported in the literature, so the Moradi group investigated the three-component reaction of barbituric acid derivatives (**29**), 6-aminouracils (**2**), and various aromatic aldehydes (**1**) in the presence of (MWCNTs@L-His/Cu(II)) for the synthesis of pyrido[2,3-*d*:5,6-*d'*]dipyrimidine derivatives (**3**) under reflux conditions in high to excellent yields (Scheme 18).[71] The catalyst represented high activity in preparing various pyrido[2,3-*d*:5,6-*d'*]dipyrimidine derivatives, offering several benefits, including the catalyst's recoverability, short reaction times, and simple reaction workup, and excellent yields.

In this research, they were prepared a new multi-walled carbon nanotubes (MWCNTs) catalyst through Cu(II) immobilization on *L*-histidine functionalized (MWCNTs@L-His/Cu(II)). It should be noted that the catalyst can be separated from the reaction medium and reused several times without a significant loss of activity.

Ar = Ph(H, 4-Cl, 2-Cl, 4-OMe, 4-Me, 4-Br, 2-OH-5-NO₂, 3-NO₂, 4-NO₂, 4-CHO)
R = H, Me
X = O, S

15 Examples
Yields 78-95%

Scheme 18. Synthesis of pyrido[2,3-*d*:5,6-*d'*]dipyrimidine derivatives in the presence of MWCNTs@L-His/Cu(II).[71]

The group of Pravin[72] discovered a highly efficient regioselective reaction for synthesizing pyrimidine-fused tetrahydropyridines (**34**, **35**, **36**) tethered through a three-component reaction of α,β-unsaturated aldehydes (**26**), cyclic 1,3-dicarbonyls, and 6-aminouracils (**2**) had been demonstrated in the presence of FeCl₃·6H₂O as catalyst under microwave irradiation (Scheme 19). Besides, they prepared a two-component pyrimidine-fused pyridine by replacing cyclic 1,3-diketones and keeping all other conditions the same.
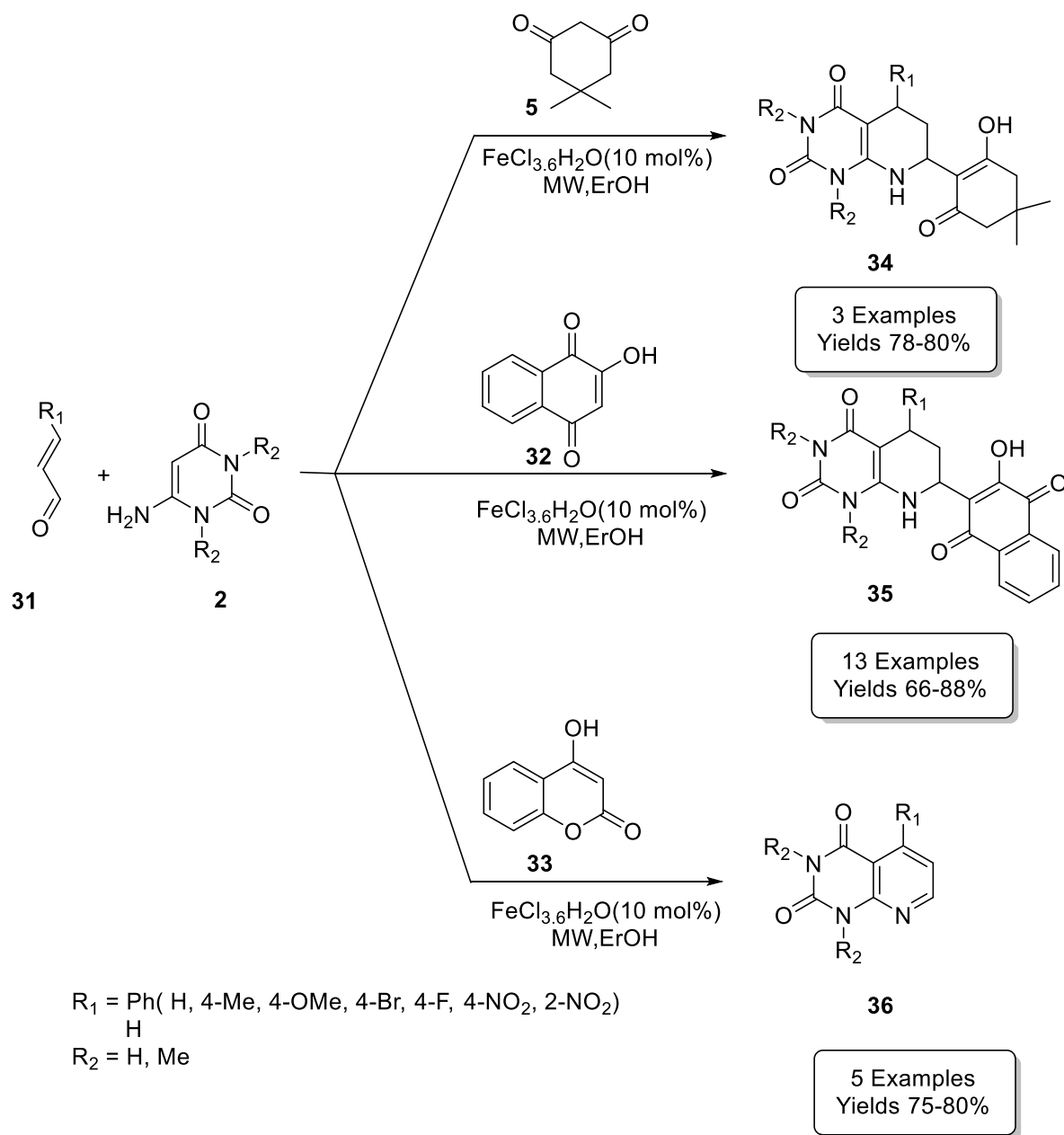
Scheme 19. The one-pot reaction of cyclic 1,3-dicarbonyls, α,β-unsaturated aldehydes, and 6-aminouracils.[72]

In the other report, Chate and co-workers developed regio- and chemoselective multicomponent protocols for the synthesis of biologically active 5-phenyl-5,6-dihydropyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-triones (**38**) based on the selection of specific reaction conditions for the selective production of each of the mentioned products, whereas three-component condensation reaction under the conditions of in water as a green solvent under reflux conditions (Scheme 20).[73] The coupling reaction can produce desired products through a one-pot three-component reaction between benzaldehyde derivatives (**1**) and 6-aminouracil (**2**) with Meldrum's acid (**37**) catalyzed by β-cyclodextrin as a green catalyst in an aqueous medium.

In supramolecular and host-guest chemistry, some of the most useful host molecules are the cyclodextrins (CDs). They are torus-shaped cyclic oligosaccharides with the ability to form host-guest complexes through a hydrophobic interior cavity. Substrates are bound to form desired products, often in a highly selective fashion. The formation of complexes depends on the size, shape, and hydrophobicity of the

guest molecule. The used β-cyclodextrin catalyst was recuperated and the process was repeated several times, devoid of considerable loss of catalytic activity, a crucial green synthesis parameter.[74]
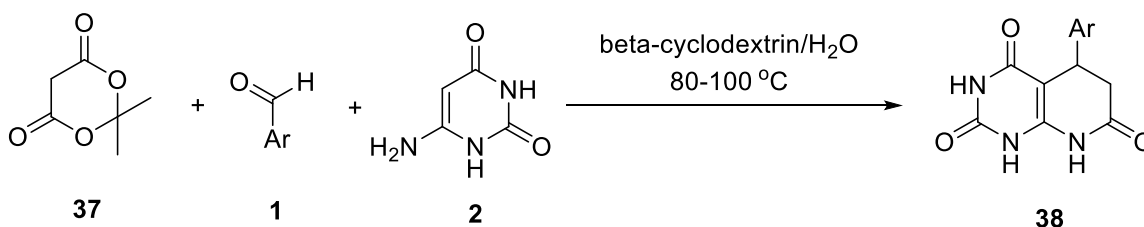
Ar = Ph (H, 4-Cl, 2,6-Cl₂, 2-OMe, 4-OMe, 4-Br, 2-OH, 4-NO₂, 3-OH, 4-OH, 2-OH
2-OH-3-OMe, 3-OMe-4-OH, 4-iPr), 3-Formylindole, 2-Thienyl

20 Examples
Yields 79-96 %

Scheme 20. Synthesis of pyrido[2,3-*d*]pyrimidine trione framework.[73]

3. Synthesis of Pyrimido-pyrimidine Compounds

In the other report, Siddiqui and co-workers[75] described a multicomponent approach for the synthesis of 1-methyl-5-phenylbenzo[*g*]pyrimido[4,5-*b*]quinoline-2,4,6,11(1*H*,3*H*)-tetraone (**39**) based on a nano ZnO tandem reaction of from various aromatic aldehydes (**1**), 2-hydroxynaphthalene-1,4-dione (**33**), and 6-aminouracil (**2**) in a CTAB-water admicellar system at 80 °C (Scheme 21). Catalyst can be recovered efficiently and reused several times to synthesize the desired product, an essential green Synthesis parameter.
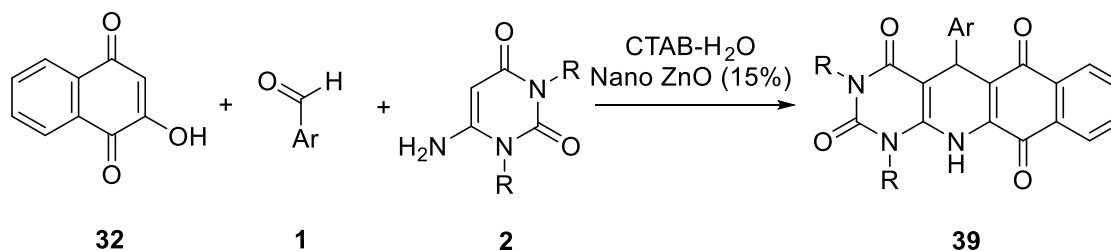
Ar = 4-ClC₆H₄, 4-BrC₆H₄, 4-NO₂C₆H₄, 3-MeC₆H₄
2-MeC₆H₄, 4-OMeC₆H₄, 4-MeC₆H₄, 4-PhC₆H₄
R = H, Me

12 Examples
Yields 89-95%

Scheme 21. Synthesis of 1-methyl-5-phenylbenzo[*g*]pyrimido[4,5-*b*]-quinoline-2,4,6,11(1*H*,3*H*)-tetraone.[75]

Choudhury and co-workers demonstrated a facile and green pathway to prepare several condensed 1,4-dihydropyridines fused with 2-hydroxynaphthalene-1,4-dione (**33**) under microwave heating conditions via Knoevenagel-Michael addition (Scheme 22).[76] They have reported the three-component reaction of 2-hydroxynaphthalene-1,4-dione (**33**), aldehydes (**1**), and 6-aminouracil derivatives (**2**) in acetic acid/water (1:1;v/v) under microwave irradiation. Using these tunable reaction conditions, a series of polycyclic fused N-heterocycles (**39**) has been synthesized.

R^1 = H, 4-Me, 4-OMe, 4-F, 4-iPr, 4-CN, 4-Cl,3-Br
      2-Cl, 3-NO$_2$, 2-OMe,4-NO$_2$, 2,6-Me$_2$, Naphtyl
R^2 = H, Me

22 Examples
Yields 64-96%
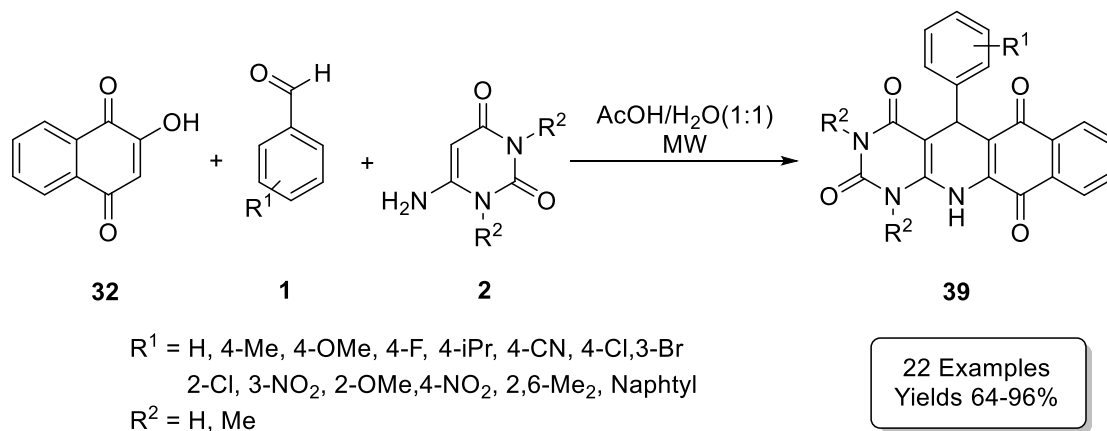
Scheme 22. Synthesis of benzo[g]pyrimido[4,5-b]quinolone derivatives.[76]

14 Examples
Yields 62-86%

14 Examples
Yields 66-85%

Ar = H, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-MeC$_6$H$_4$
       2-MeC$_6$H$_4$, i-Pr, 2-Pyrrolyl, 2-Thienyl
R^1 = H, Me
R^2 = CN, COOEt, CONH$_2$
R^3 = H, Me
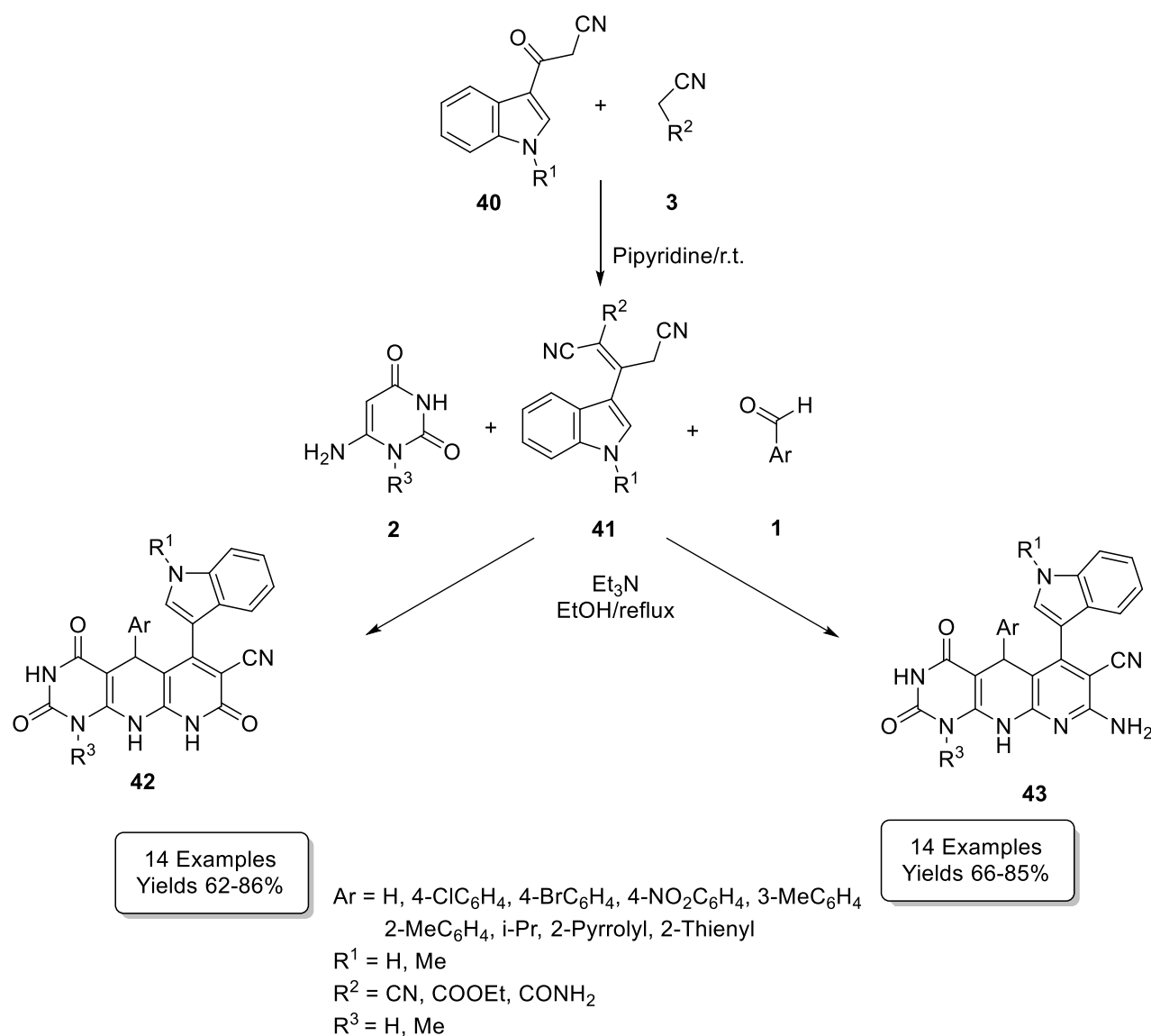
Scheme 23. Synthesis of pyrimido[4,5-b][1,8]naphthyridine-7-carbonitrile derivatives.[77]

In another synthetic route developed by Naidu *et al.*, the indole derivatives were employed to synthesize the novel hexahydropyrimido[4,5-*b*][1,8]-naphthyridine derivatives (**42**) and (**43**) in ethanol in the absence of a catalyst at room temperature (Scheme 23).[77] An efficient protocol has been developed for three-component domino heteroannulation and synthesis of the unsymmetrical coupling reaction by a one-pot three-component reaction of an aromatic aldehyde (**1**) and a 6-aminouracil derivative (**2**), a 2-cyano-3-(1*H*-indol-3-yl)-pent-2-enedinitrile or ethyl-2,4-dicyano-3-(1*H*-indol-3-yl)but-2-enoate derivative (**41**). They prepared indole derivatives (**41**), one of the starting materials, through the reaction of the corresponding 3-(cyanoacetyl)indoles (**40**) with acetonitrile derivatives (**4**).

This synthetic route uses 6-amino-1,3-dimethyluracil (**1**), *N,N*-dimethylformamide dimethyl acetal (**46**), 1-phenyl-3-(4-substituted-phenyl)-4-formyl-1*H*-pyrazoles (**45**) and aromatic aniline (**44**), as starting materials for rapid access of the diverse pyrazolo-pyrimido[4,5-*d*]pyrimidines (**47**) in ionic liquid conditions by Chandramouli and co-workers (Scheme 24).[78] An efficient, four-component sequential protocol, the reaction proceeded in the presence of [Bmim]FeCl₄ as a "green" reaction medium to promote eco-friendly transformations with unique reactivity and selectivity and both of recyclability and reusability without any loss. All the synthesized desired products were evaluated for their antibacterial, biofilm inhibition, intracellular ROS accumulation, and protein leakage activities.
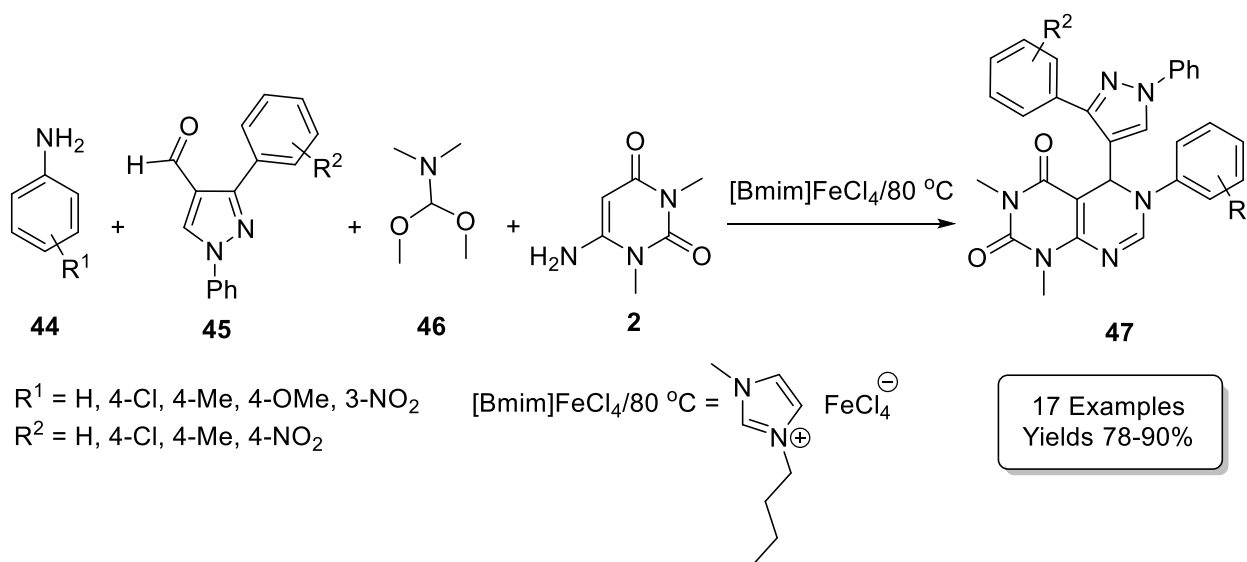
Scheme 24. Synthesis of pyrazolo-pyrimido[4,5-*d*]pyrimidine derivatives in an ionic liquid.[78]

Shiri and co-workers efficiently carried out a new intramolecular cyclization method via the one-pot reaction 2-chloroquinoline-3-carbaldehydes (**48**), 6-aminouracils (**2**), and dimedone (**5**) for the synthesis of novel functionalized 4*H*-pyrano[2,3-*b*]quinoline (**50**) and 1,4-dihydrobenzo[*b*][1,8]-naphthyridine derivatives (**49**) using *L*-proline as a mild organocatalyst (Scheme 25). [79]

R₁ = H, 8-Me, 6-Br, 6-Cl₂, 6-Me, 6-OMe
R₂ = H, Me

3 Examples
Yields 79-87%

4 Examples
Yields 87-93%
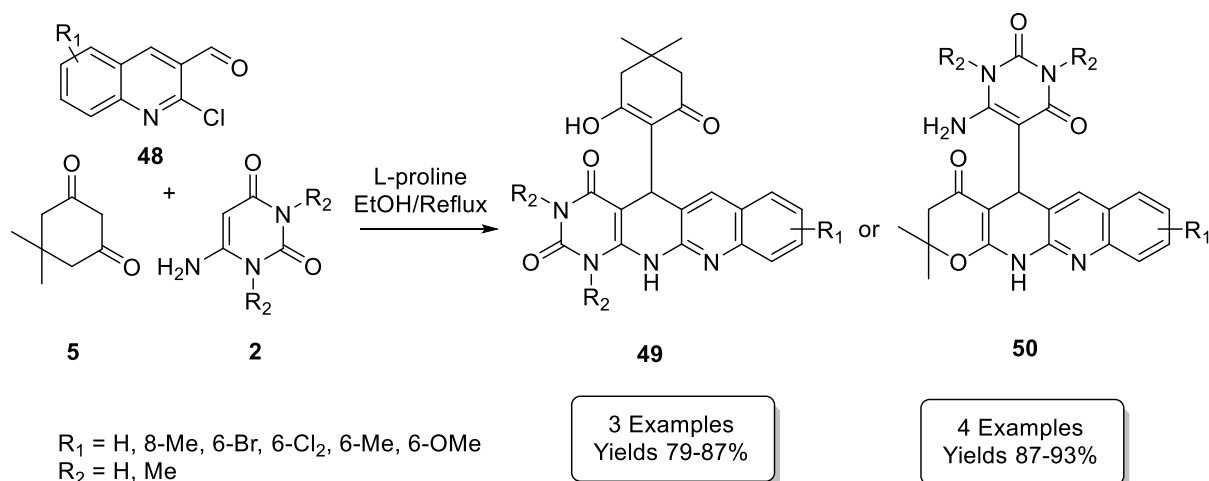
Scheme 25. Synthesis of novel functionalized 4*H*-pyrano[2,3-*b*]quinoline and 1,4-dihydrobenzo[*b*][1,8]naphthyridine derivatives.[79]

In 2014, an effective synthetic route to pyrimido[4,5-*d*]pyrimidine derivatives had been recently proposed by Shirini *et al.* in the presence of Zn (BDC)-MOFs (BDC (1,4-Benzenedicarboxylic acid); MOFs (Metal–organic frameworks)) under ultrasound irradiation in the absence of any solvent. (Scheme 26).[80] The nanocatalyst gave the target products high yields (85-98%) during short reaction times (5-10 min). In continuation, the authors investigated the reaction of *N,N'*-disubstituted-6-aminouracil (**2**), isothiocyanate (**51**) with a variety of aldehydes (**1**) under the optimized conditions. These results revealed the efficiency of these processes in preparing the desired products an efficient method for the synthesis of pyrimido[4,5-*d*]pyrimidine derivatives using ultrasound irradiation in the presence of Zn(BDC)-MOF as the catalyst. The Zn (BDC)-MOF catalyst proved to be thermally and chemically stable, heterogeneous, easily separable, and recyclable up to three times in this method.

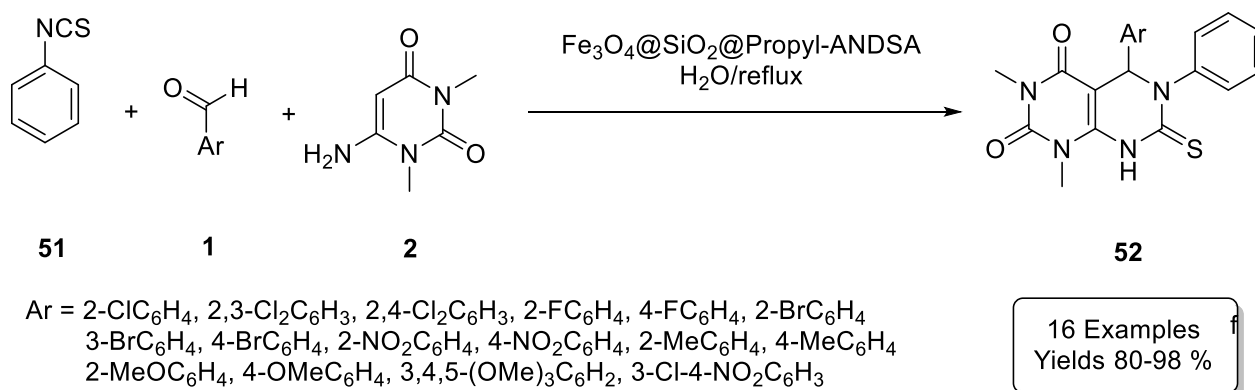Ar = C₆H₅, 4-ClC₆H₄, 2-ClC₆H₄, 4-BrC₆H₄, 2-BrC₆H₄, 4-NO₂C₆H₄
4-MeC₆H₄, 2-MeC₆H₄, 4-OHC₆H₄, 4-OMeC₆H₄, 4-FC₆H₄
R = H, Me

13 Examples
Yields 85-98 %
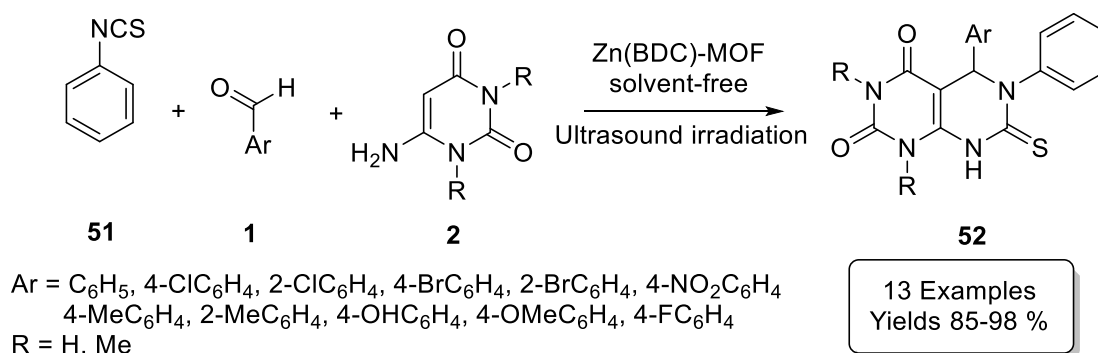
Scheme 26. Synthesis pyrimido[4,5-*d*]pyrimidine derivatives under ultrasound Irradiation.[80]

This methodology was extended in 2017 by Ghorbani-Vaghei[81], producing substituted pyrimido[4,5-*d*]pyrimidines. In this case, 7-aminonaphthalene-1,3-disulfonic acid (ANDSA)-functionalized magnetic Fe₃O₄@SiO₂ particles were employed as a hetrerogeneous catalyst. They carried out an efficient and one-pot multicomponent procedure for the synthesis of substituted pyrimido[4,5-*d*]pyrimidines (**52**) via reaction of *N,N'*-dimethyl-6-aminouracil (**2**), isothiocyanate (**51**), and aromatic aldehydes (**1**) in water as a

green solvent and without using any other harmful organic reagents under the optimized conditions (Scheme 27).

Ar = 2-ClC_6H_4, 2,3-Cl_2C_6H_3, 2,4-Cl_2C_6H_3, 2-FC_6H_4, 4-FC_6H_4, 2-BrC_6H_4
3-BrC_6H_4, 4-BrC_6H_4, 2-NO_2C_6H_4, 4-NO_2C_6H_4, 2-MeC_6H_4, 4-MeC_6H_4
2-MeOC_6H_4, 4-OMeC_6H_4, 3,4,5-(OMe)_3C_6H_2, 3-Cl-4-NO_2C_6H_3

16 Examples f
Yields 80-98 %

Scheme 27. Synthesis of new pyrimido[4,5-*d*]pyrimidine derivatives using nanoparticles as a catalyst.[81]

Another example of using 6-aminouracil derivatives (**2**) as cross-coupling partners is shown in Scheme 28, in which MIL-53(Fe) porous metal-organic framework (MOFs) was utilized.[82] The MIL-53 (Fe) structure results from the formation of the Fe-oxo bond between Fe (III) and the terephthalic acid carboxylic group as an organic linker. In this case, a one-pot synthetic protocol was used for the synthesis of pyrimido[4,5-*d*]pyrimidine derivatives. The approach is based on th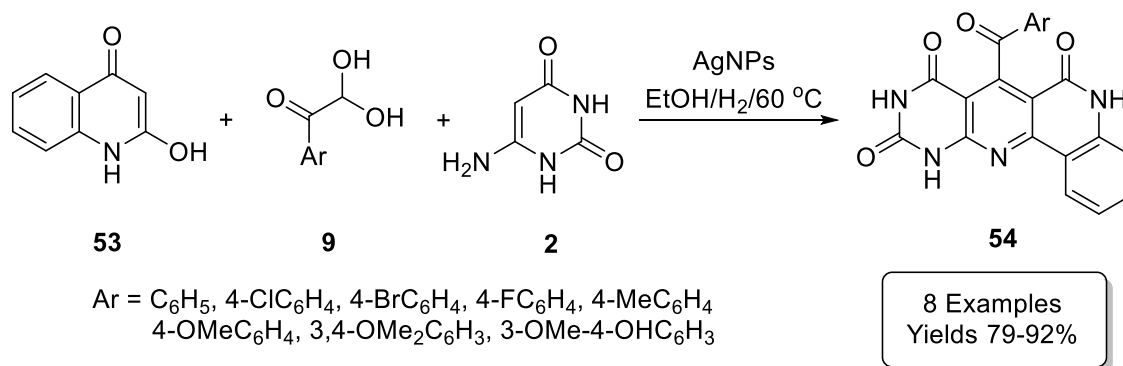e reaction of isothiocyanate (**51**), aromatic aldehydes (**1**), and 6-aminouracil and/or *N,N*-dimethyl-6-aminouracil in the presence of MIL-53(Fe) at 110 °C under solvent-free conditions in good to excellent product yields during acceptable reaction times.

Ar = C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, 4-NO_2C_6H_4, 4-MeC_6H_4, 4-OHC_6H_4
4-OMeC_6H_4, 4-NO_2C_6H_4, 2-NO_2C_6H_4, 4-FC_6H_4
R = H, Me

13 Examples
Yields 86-98 %
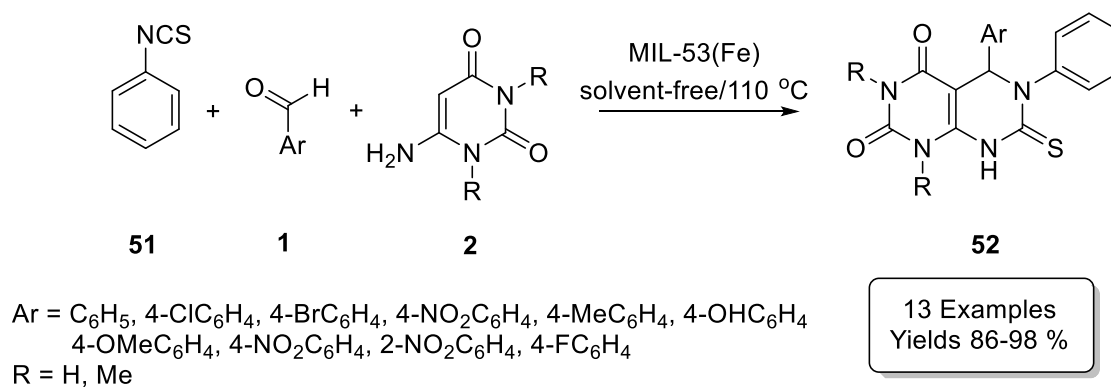
Scheme 28. Synthesis of pyrimido[4,5-*b*]quinolones in the presence of Fe_3O_4@SiO_2-SnCl_4.[82]

A simple method for the preparation of pyrimido[4,5-*b*][1,6]naphthyridines (**54**) was reported by Poursattar Marjani.[83] The one-pot, three-component condensation reactions were carried out using arylglyoxal monohydrates (**9**), 6-aminouracil (**2**) and 4-hydroxyquinoline-2(1*H*)-one (**53**) in the presence of AgNPs (10 ppm) in H_2O/EtOH (1:1) as a robust and green nanocatalyst at 60 °C in 79-92% yields (Scheme 29).

53　　　　**9**　　　　**2**　　　　　　　　　　　　　　**54**

Ar = C$_6$H$_5$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$
4-OMeC$_6$H$_4$, 3,4-OMe$_2$C$_6$H$_3$, 3-OMe-4-OHC$_6$H$_3$

8 Examples
Yields 79-92%

Scheme29. The synthesis of pyrimido[4,5-*b*][1,6]naphthyridines.[83]

Recently, the group of Baruah extended this reactivity, reporting a direct reaction of 6-aminouracils (**2**) with aldehydes (**1**) and secondary amines (**55**) as starting components, catalyzed by acetic acid via domino aza-Michael reaction at room temperature (Scheme 30).[84] First, they synthesized intermediate (**56**) and were able to convert it to the desired pyrimido[4,5-*d*]-pyrimidine products (**57**) by using I$_2$-TBHP at room temperature in ethanol through an intramolecular cyclization.

55　　　　**1**　　　　**2**　　　　　　　　　　　　　　**56**
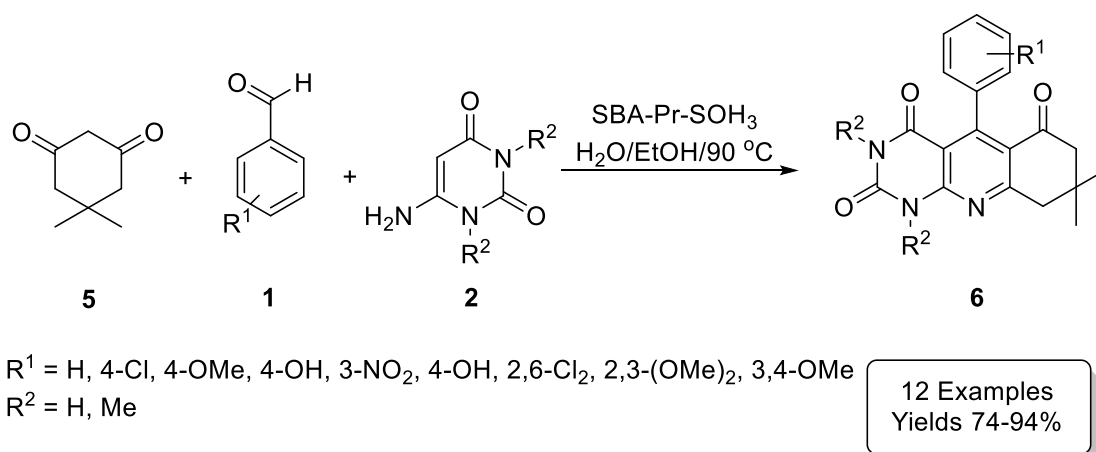
R^1 = H, Ph(C$_6$H$_5$, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-MeC$_6$H$_4$, 2-ClC$_6$H$_4$
　　4-OMeC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3,4-(OMe)$_2$C$_6$H$_4$), 2-Thienyl
R^2 = H, Me

I$_2$(10 mol%
TBHP(1.5 eq.)
Etoh,RT

57

20 Examples
Yields 80-94%
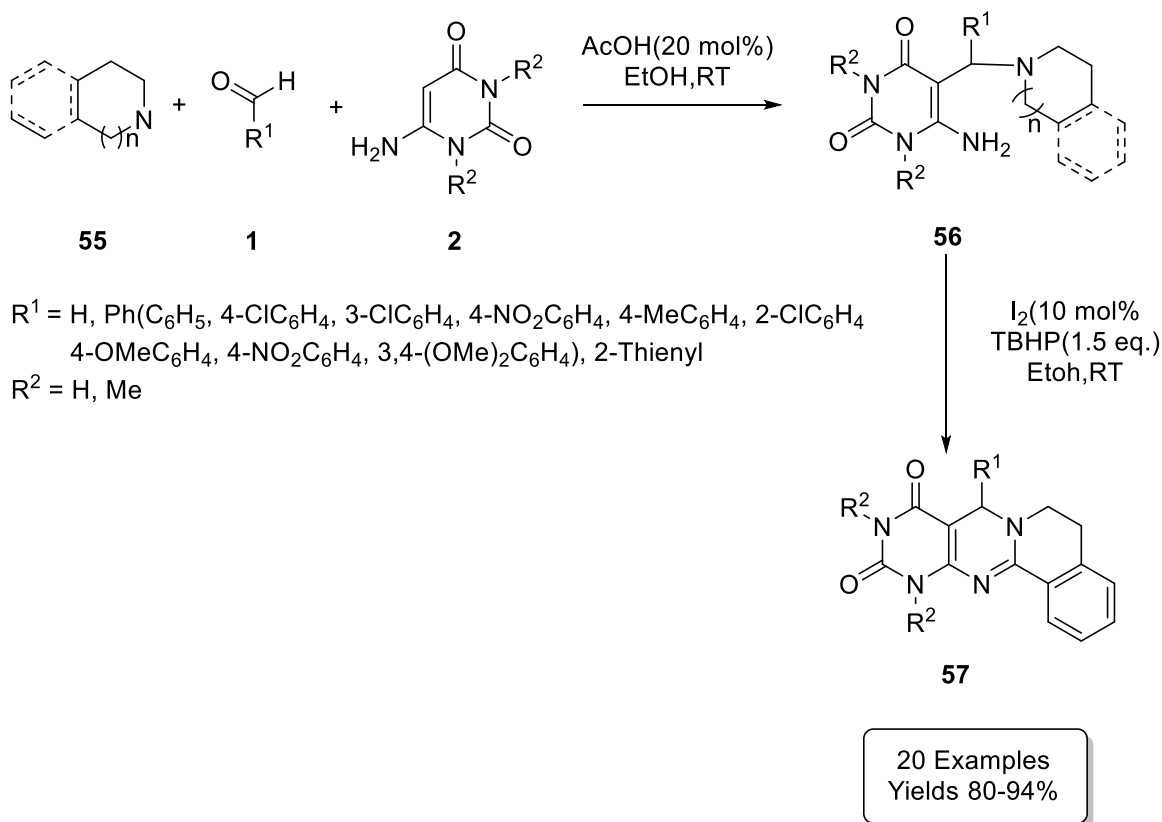
Scheme 30. Synthesis of pyrimido[4,5-*d*]pyrimidines.[84]

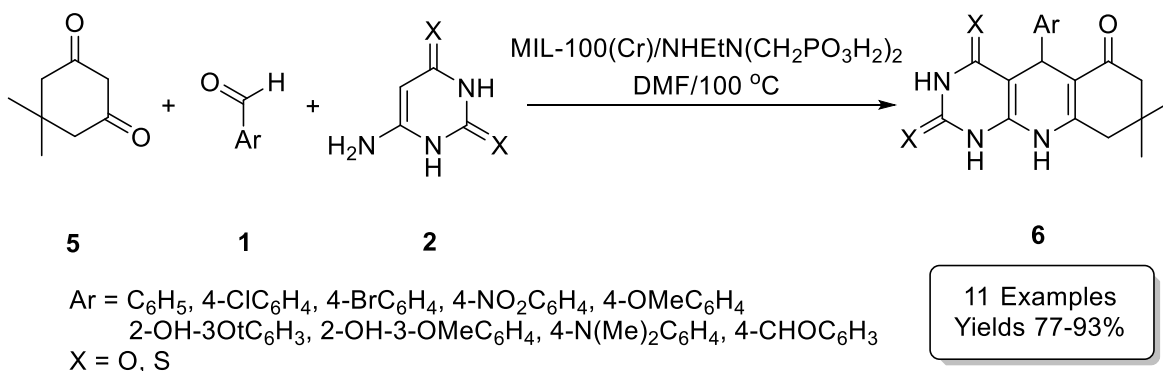In 2017 [85] group of Mohammadi Ziarani showed a simple and efficient method for synthesizing tetrahydropyrimido[4,5-*b*]quinoline scaffolds (**6**) via a three-component reaction (Scheme 31). They accomplished the one-pot condensation of aromatic aldehydes (**1**), dimedone (**5**), and 6-aminouracil derivatives (**2**) in the presence of a catalytic amount of sulfonic acid functionalized nanoporous silica (SBA-15-

Pr-SO$_3$H) in high yields is described. Some synthesized compounds had antibacterial and antifungal activities measured against Gram-positive, Gram-negative bacteria, and fungi.

R^1 = H, 4-Cl, 4-OMe, 4-OH, 3-NO$_2$, 4-OH, 2,6-Cl$_2$, 2,3-(OMe)$_2$, 3,4-OMe
R^2 = H, Me

12 Examples
Yields 74-94%

Scheme 31. One-pot synthesis of tetrahydropyrimido[4,5-*b*]quinoline derivatives using sulfonic acid functionalized SBA-15.[85]
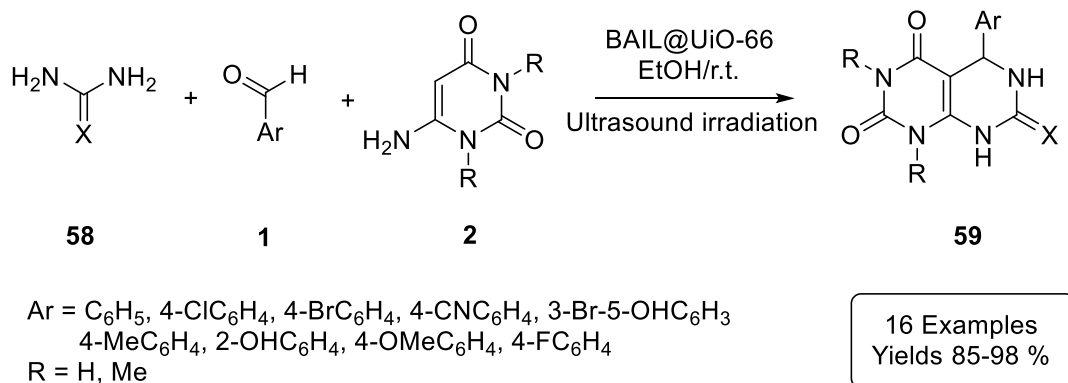
In 2017, Sepehrmansouri *et al.* synthesized a variety of functionalized pyrimido[4,5-b]quinolone derivatives in high yields at reflux conditions (Scheme 32).[86] They prepared a novel ethylenediamine (En) based metal-organic frameworks (MOFs) of Cr-MOFs, En/MIL-100(Cr), and containing phosphorous acid tags, and applied for Knoevenagel-Michael condensation reaction the synthesis of new series of N-heterocyclic compounds. For preparing MIL-100(Cr)/NHEtN(CH$_2$PO$_3$H$_2$)$_2$ as the MOF catalyst, they used the condensation reaction of MIL-100(Cr)/NHEtNH$_2$, paraformaldehyde, phosphorous acid, hydrochloric acid, and EtOH as solvent under reflux condition. Also, they reported the reaction of dimedone (**5**) and various aldehydes (**1**) with uracil derivatives compound (X= S, O). In multivariate MOFs, multiple aspects such as nuclei, organic, and linker can be integrated into one framework, providing the opportunity to model complex porous MOFs' in a logical approach.

Ar = C$_6$H$_5$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-OMeC$_6$H$_4$
     2-OH-3OtC$_6$H$_3$, 2-OH-3-OMeC$_6$H$_4$, 4-N(Me)$_2$C$_6$H$_4$, 4-CHOC$_6$H$_3$
X = O, S

11 Examples
Yields 77-93%

Scheme 32. Synthesis of pyrimido[4,5-*b*]quinolone derivatives using MIL-100(Cr)/NHEtN(CH$_2$PO$_3$H$_2$)$_2$.[86]

Mirhosseini-Eshkevari and co-workers[871] developed an excellent strategy for preparing pyrimido[4,5-*d*]pyrimidines (**59**), using TEDA-BAIL@UiO-66, a novel catalyst, in EtOH under ultrasound irradiation with high yields. Privileged structures useful in medicinal chemistry were obtained. This reaction is done through a one-

pot, the telescoped reaction via the three-component reactions of 6-aminouracils (**2**), substituted aromatic aldehydes (**1**), and urea derivatives (**58**) in the presence of triethylenediamine Brønsted acidic ionic liquid supported in Zr metal-organic framework (TEDA-BAIL@UiO-66) as a novel catalyst under ultrasound irradiation (Scheme 33).

Ar = C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, 4-CNC_6H_4, 3-Br-5-OHC_6H_3
4-MeC_6H_4, 2-OHC_6H_4, 4-$OMeC_6H_4$, 4-FC_6H_4
R = H, Me

16 Examples
Yields 85-98 %

Scheme 33. Synthesis of pyrimido[4,5-*d*]pyrimidine derivatives using BAIL@UiO-66 under ultrasound irradiation.[87]

An interesting One-pot multicomponent cascade reaction with azo and sulfonated aldehydes (**1**), 6-amino-1,3-dimethyluracil (**2**), and dimedone (**5**) or 1,3-cyclo-hexadione in the presence of choline chloride/oxalic acid (ChCl/Oxa) at 80 °C affords access to azo and sulfonated pyrimido[4,5-*b*]quinoline derivatives in high yields (Scheme 34).[88] The reaction was proceeded in deep eutectic solvents (DESs) as green solvents to it provided as a new prominent family of the reaction medium, due to they are very cheap, readily accessible materials, non-toxic, and non-flammable.

Ar =

R^1 = H, 2-Cl, 4-Cl, 3-OH
R^2 = 2-R, 3-R, 4-R
R^3 = H, OMe
R^4 = H, Me

R=

12 Examples
Yields 92-98%
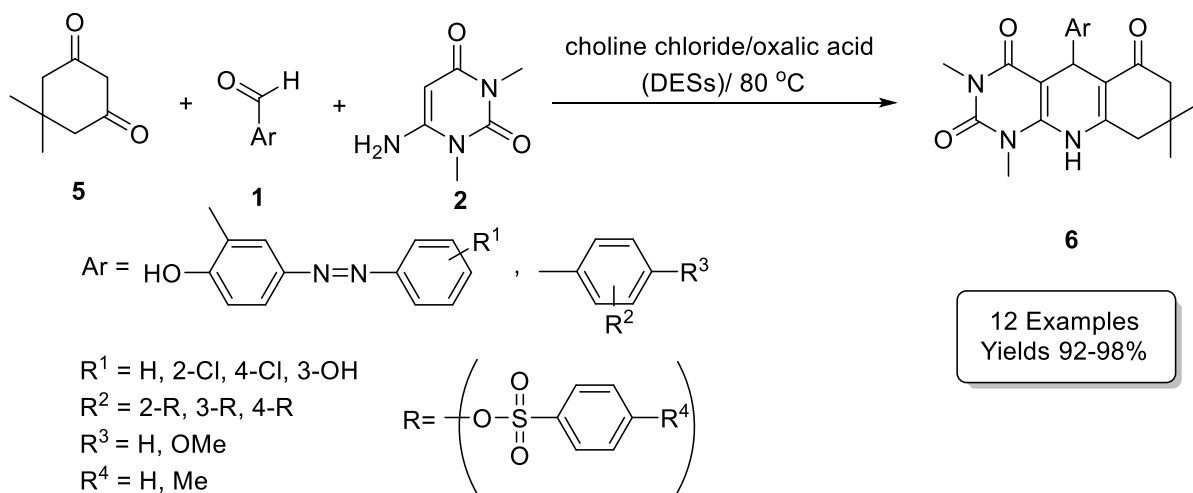
Scheme 34. Synthetic pathway for the synthesis of azo and sulfonated pyrimido[4,5-*b*]quinolines.[88]

Researchers have focused their attention on bis-heterocyclic compounds in the last decades due to various biological and pharmacological activities. Bayat *et al.* reported a one-pot, three-component synthesis of variety of bis-heterocycles such as bis(pyrimido[4,5-*b*]quinolone), bis(chromeno[3',4':5,6]pyrido[2,3-*d*]pyrimidine), bis(pyrido[2,3-d:6,5-*d'*]dipyrimidine), and bis(benzo[*g*]pyrimido[4,5-*b*]quinolone) derivatives

(Scheme 35).[89] They were synthesized via one-pot, the multicomponent reaction of various 6-aminouracils (**2**) or 6-aminothiouracils, terephthalaldehyde, and various active methylene 4-hydroxycoumarin (**33**), dimedone (**5**), 2-hydroxynaphthalene-1,4-dione (**32**), barbituric acid (**29**), and thiobarbituric acid (**24**) in EtOH as a solvent at reflux conditions without a catalyst.

A variety of bis-heterocycles such as bis(pyrimido[4,5-b]quinolone), bis(chromeno[3 ',4':5,6]pyrido[2,3-d]pyrimidine), bis(pyrido[2,3-d:6,5-d′]dipyrimidine), and bis(benzo[g]pyrimido[4,5-b]quinolone) derivatives (**61**) were synthesized via one-pot, multicomponent reaction of various 6-aminouracil derivatives (**2**), terephthalaldehyde (**60**), and methylene active compounds such as 4-hydroxycoumarin (**33**), dimedone (**5**), 2-hydroxynaphthalene-1,4-dione (**32**), barbituric acid (**29**), and thiobarbituric acid (**24**) in EtOH as a solvent under reflux.
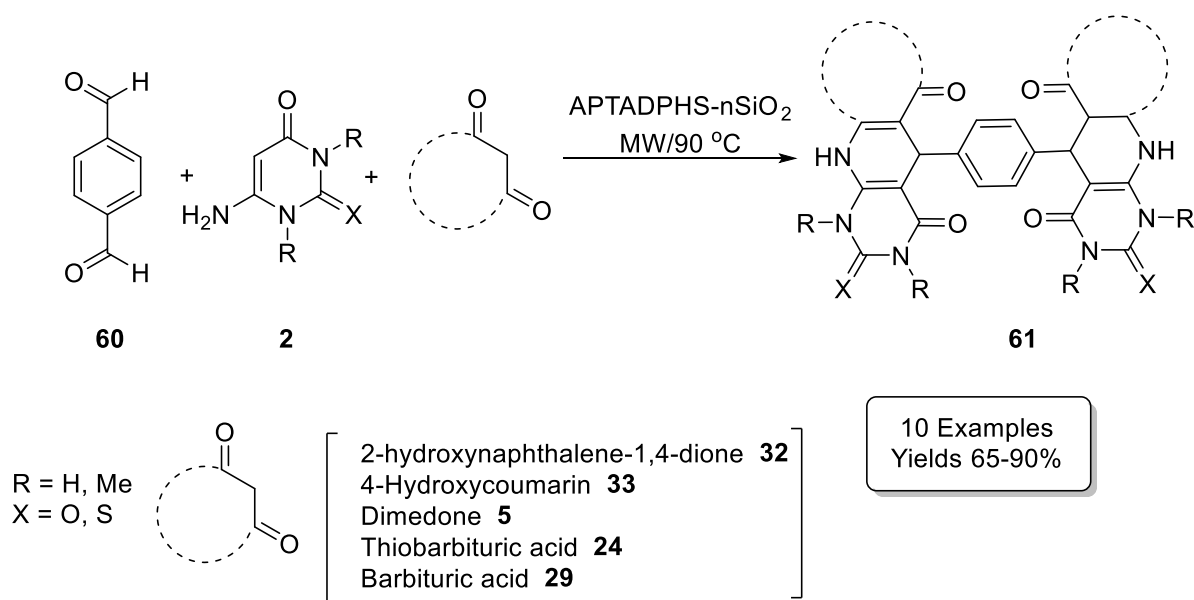

Scheme 35. One-pot, multicomponent synthesis of bis-heterocycles.[89]

4. Synthesis of Pyrrolo-pyrimidine Compounds

The one-pot condensation of the one-pot reaction of 1,3-dimethylbarbituric acid (**29**) and arylglyoxal (**9**) with aminouracil **2** in the presence of TBAB (5 mol%) in ethanol at 50 °C for the synthesis of the novel an efficient method for the synthesis of pyrrolo[2,3-d]pyrimidine derivatives (**63**), has also been investigated by Javahershenas and Khalafy (Scheme 36).[90]

In another study, this group reported an efficient procedure for the reaction of arylglyoxals (**9**) with 6-amino-1,3-dimethyluracil (**2**) and 4-hydroxycoumarin (**33**), in the presence of *L*-proline in acetic acid under reflux conditions, affording polyfunctionalized pyrrolo[2,3-d]pyrimidine derivatives (**64**) in high yields (Scheme 37).[91]
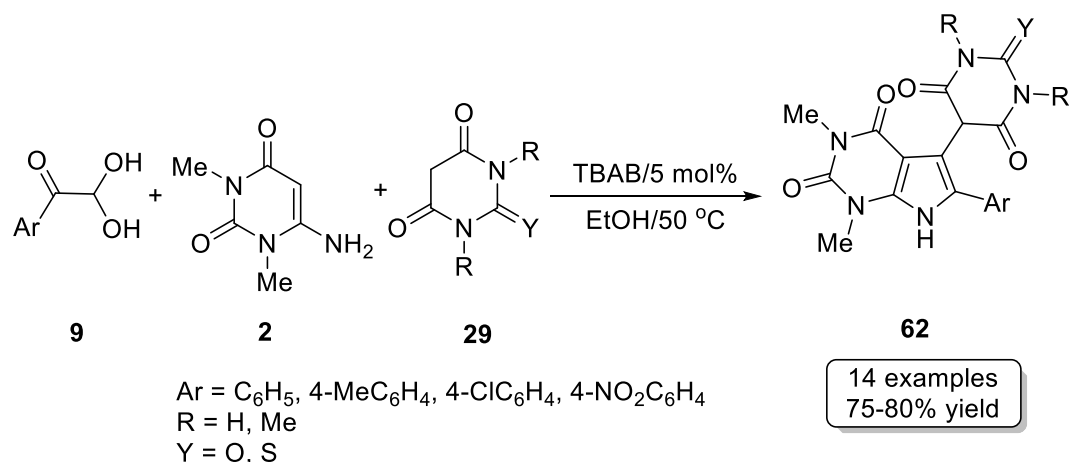
Scheme 36. Three-component synthesis of polyfunctionalized fused pyrroles.[90]
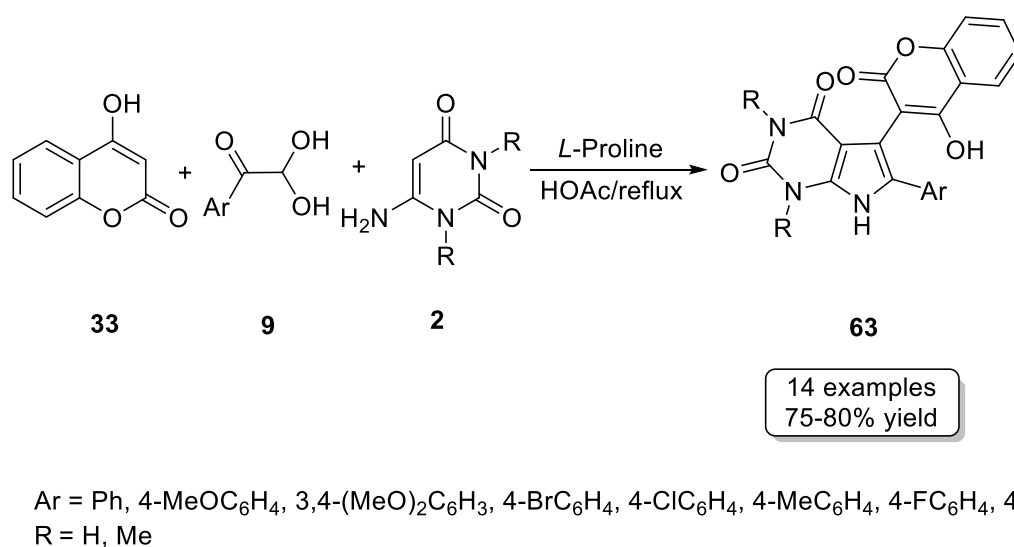
Scheme 37. Three-component synthesis of pyrrolopyrimidine.[91]

The mechanism proposed by the authors is as follows: to form the final product, first through a Knoevenagel condensation reaction of 4-hydroxycoumarin with aryglyoxal under loss of a water molecule leads to the formation of intermediate C. The organo-catalyst L-proline helps to attack by activating arylglyoxal. Then, by Michael addition 6-aminouracil (**2**) to intermediate C, followed by intramolecular heterocyclization through condensation. The proposed mechanism is shown in Scheme 38.

A one-pot, three-component reaction of 1,4-phenylene-bis-glyoxal (**65**), 6-aminouracils (**2**), and dimedone (**5**) or barbituric acid derivatives 29 in the presence of tetrapropylammonium bromide (5 mol%) in ethanol under reflux conditions gave a series of new bis-pyrrolo[2,3-*d*]pyrimidine derivatives (**66, 64**) in high yields (Scheme 39).[92]
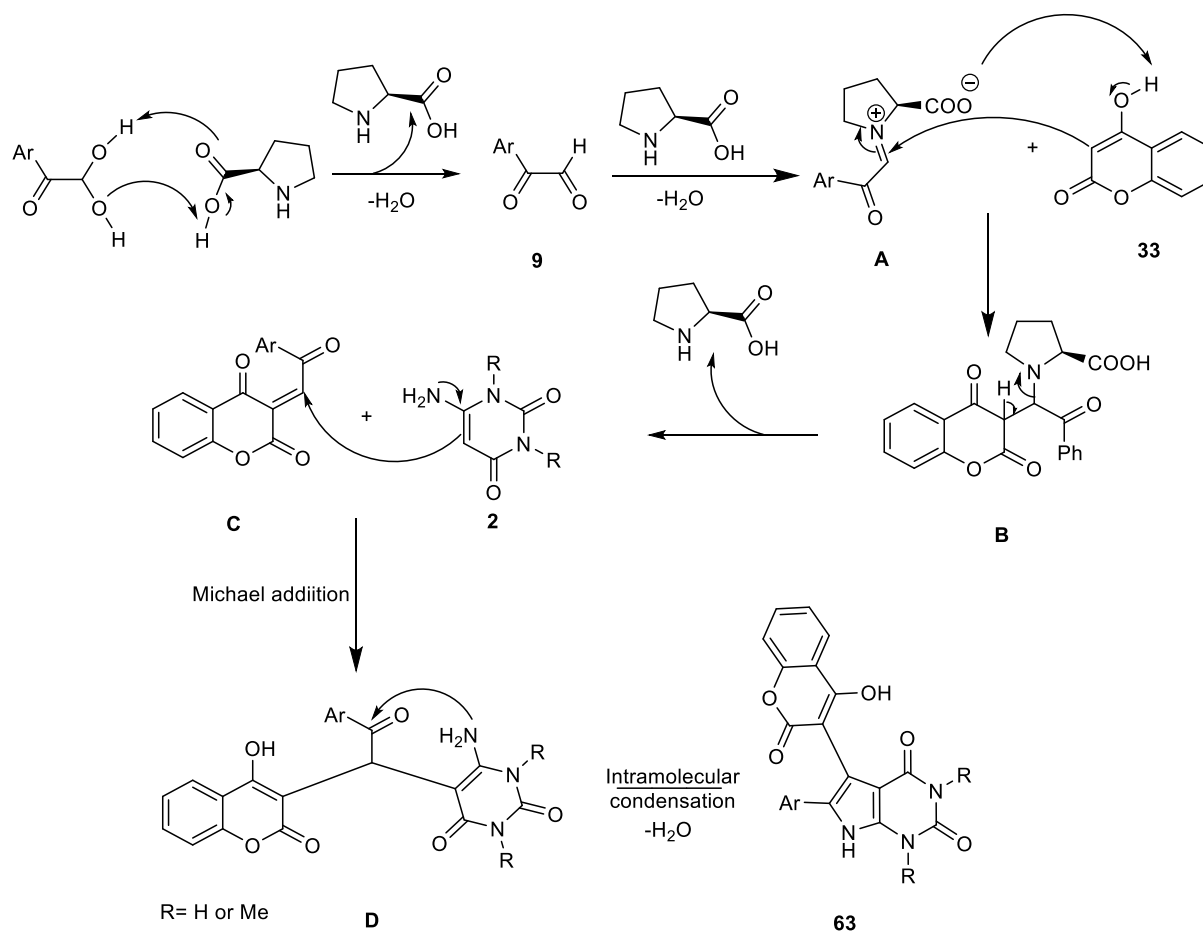
Scheme 38. The proposed mechanism for the one-pot three-component reaction.
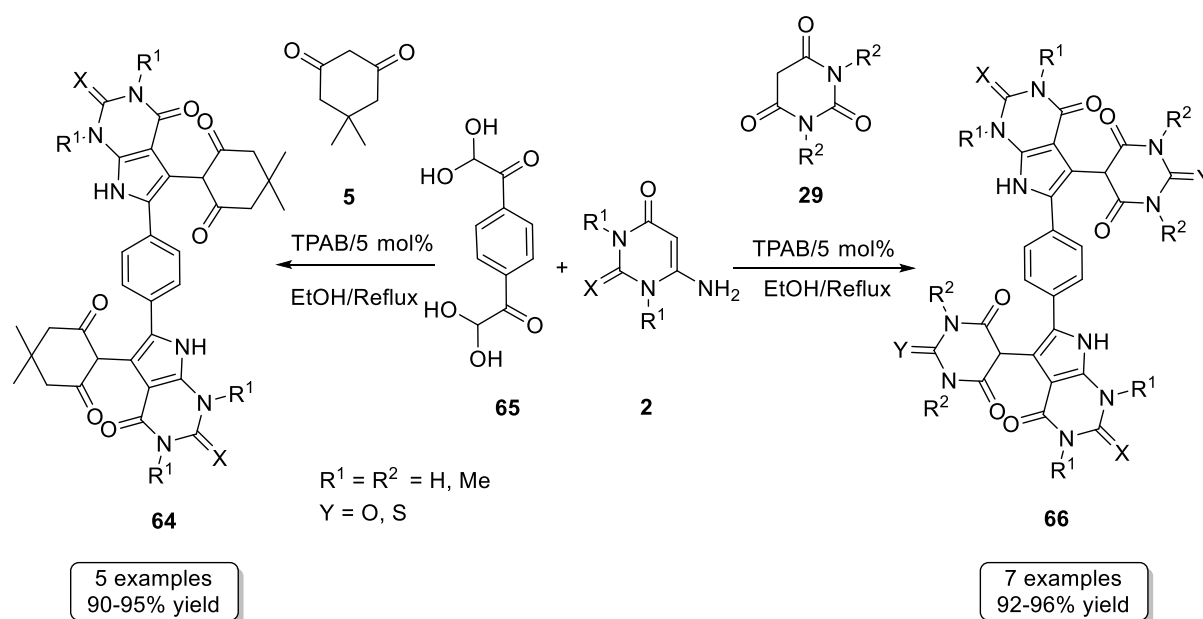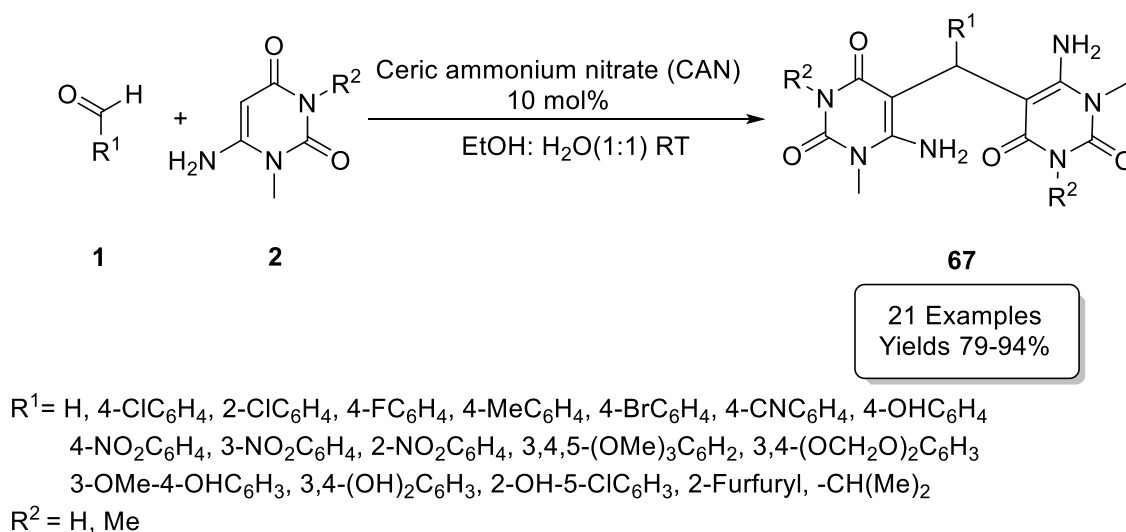

Scheme39. Three-component Synthesis of a Series of Bis-pyrrolo[2,3-*d*]pyrimidine.[92]

Recently, the synthesis of polyfunctionalized pyrrolo[2,3-*d*]pyrimidine derivatives was reported in a review.[49]

5. Synthesis of 6-Aminouracil Arylmethane Derivatives

Brahmachari and Banerjee reported a simple, facile, and convenient, practical method for the one-pot synthesis of biologically relevant alkyl/aryl/heteroaryl-substituted bis(6-aminouracil-5-yl)methane scaffolds (**67**). (Scheme 40).[93] They have demonstrated an elegant and efficient approach for the synthesis by using ceric ammonium nitrate (CAN) as a commercially available and eco-friendly catalyst via a pseudo-three-component condensation reaction aldehydes (**1**) and 6-aminouracils (**2**) in aqueous ethanol at room temperature.
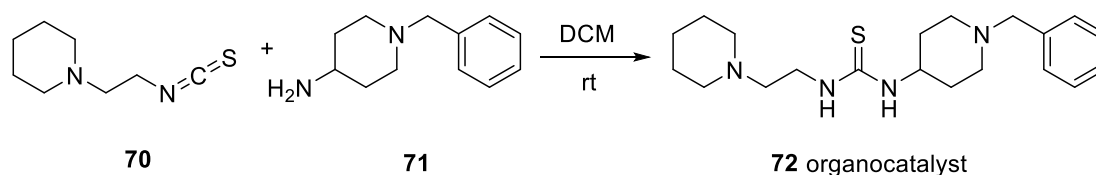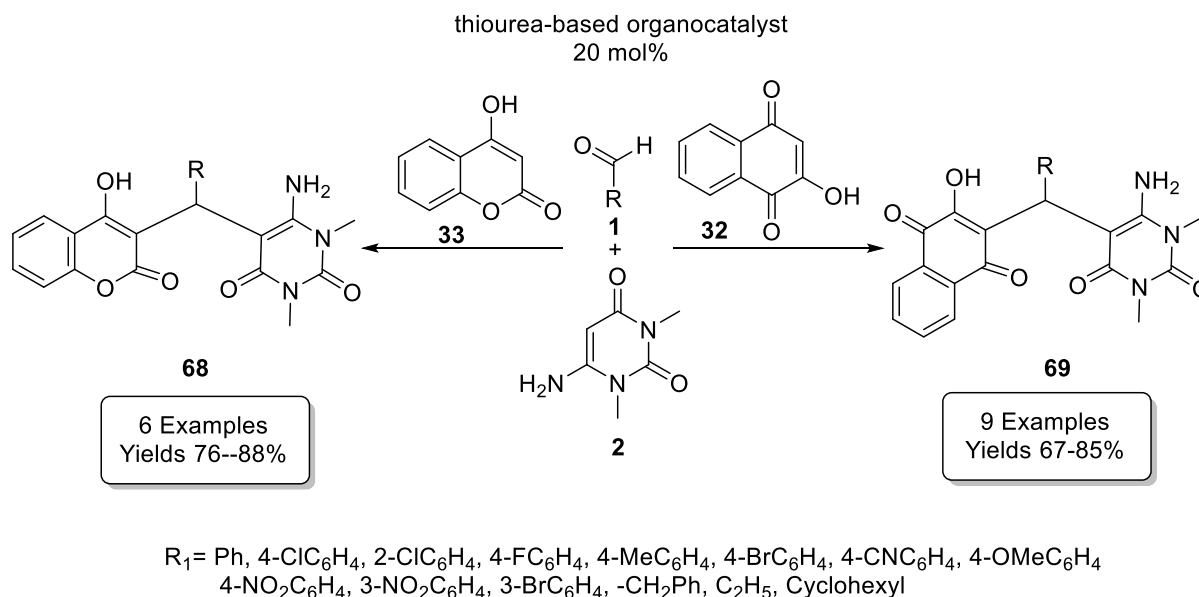

R^1= H, 4-ClC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-CNC$_6$H$_4$, 4-OHC$_6$H$_4$
4-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 3,4,5-(OMe)$_3$C$_6$H$_2$, 3,4-(OCH$_2$O)$_2$C$_6$H$_3$
3-OMe-4-OHC$_6$H$_3$, 3,4-(OH)$_2$C$_6$H$_3$, 2-OH-5-ClC$_6$H$_3$, 2-Furfuryl, -CH(Me)$_2$
R^2 = H, Me

Scheme 40. Synthesis of substituted bis(6-aminouracil-5-yl)methanes.[93]

Bharti and Parvin proposed a one-pot multicomponent procedure to produce a series of trisubstituted methane derivatives (**68**, **69**) by the reaction of aldehyde, 1,3-dimethyl-6-aminouracil (**2**), and 2-hydroxynaphthalene-1,4-dione (**32**)/4-hydroxycoumarin (**33**) using a bifunctional thiourea-based organocatalyst with the optimized reaction conditions in an aqueous medium (Scheme 41).[94] The use of the organocatalyst and water as a solvent, without the need for column chromatographic purification, are the notable features of this methodology.

Typical experimental procedure for synthesizing bifunctional thiourea-based organocatalyst I: First, 4-amino-1-benzyl piperidine (0.5mmol) was dissolved in 2 mL dichloromethane and cooled to 0 °C. Then, 2-piperidinoethyl isothiocyanate (0.5 mmol) was added into the reaction mixture and stirred at room temperature until completion of the reaction, as judged by TLC. The reaction mixture was cooled, and the solid was filtered off and washed with ethanol to afford the desired bifunctional thiourea-based organocatalyst.

The plausible mechanism for the formation of tri-substituted methane derivatives (**69**) is schematically presented in Scheme 42. The hydroxy group in 4-position of 4-hydroxycoumarin (**33**) is vital for the reaction; aldehyde initially reacts with 4-hydroxycoumarin (**33**) via aldol condensation followed by dehydration to give intermediate **A**. Since 6-amino-1,3-dimethyluracil (**2**) is a softer nucleophile than 4-hydroxycoumarin (**33**), the former will undergo a 1,4-addition reaction preferentially. Then the third component undergoes Michael

addition followed by tautomerization to provide the corresponding tri-substituted methane derivatives (**69**). The basic functionalities present in catalyst activates nucleophiles and the C=O group by a double hydrogen bonding interaction. When aminouracil cyclization did not occur, this may be due to the presence of a carbonyl group (amide) conjugated to the enamine moiety of compound (**2**), which reduces the nucleophilicity of the amino group.

R_1= Ph, 4-ClC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-CNC$_6$H$_4$, 4-OMeC$_6$H$_4$
4-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 3-BrC$_6$H$_4$, -CH$_2$Ph, C$_2$H$_5$, Cyclohexyl
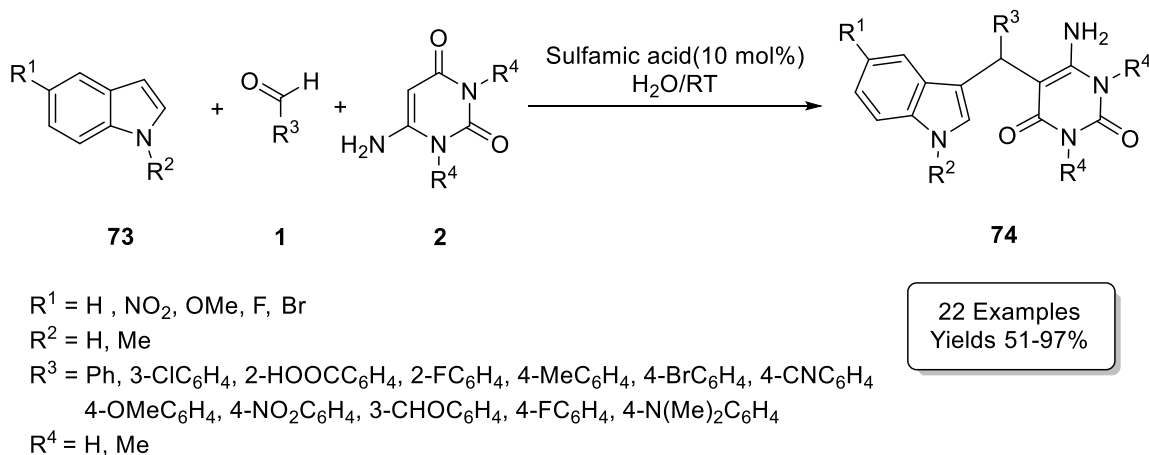
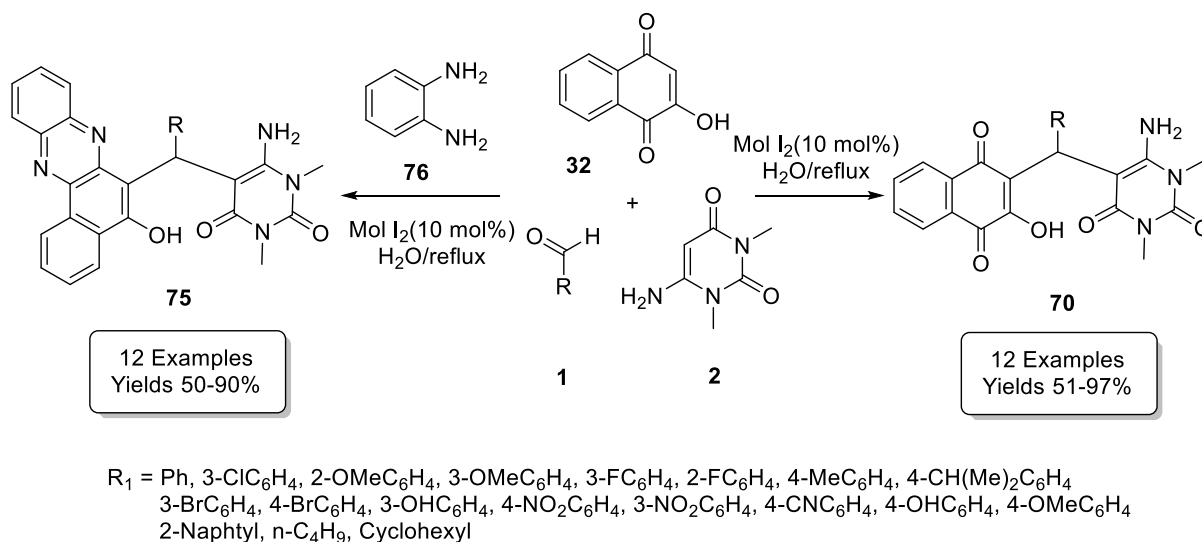**Scheme 41.** Synthesis of tri-substituted methane derivatives.[94]
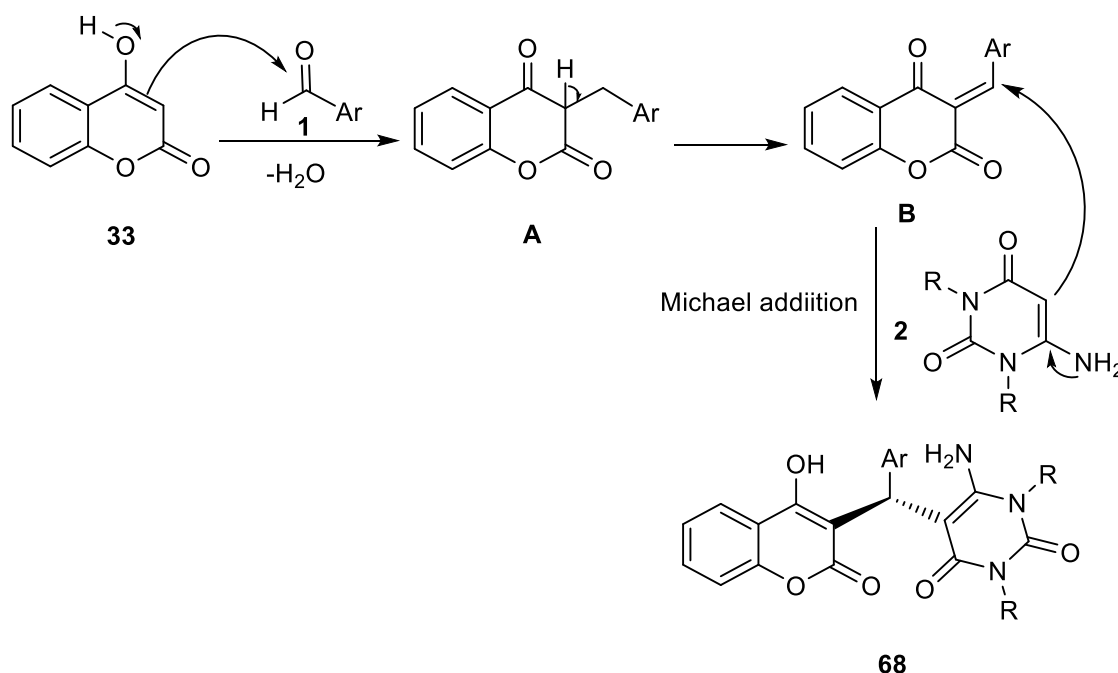
Scheme 42. Plausible reaction mechanism.

The Brahmachari group[95] also developed another synthetic protocol for efficiently synthesized a new series of biologically-interesting diverse and functionalized 5-((1*H*-indol-3-yl)(aryl)methyl)-6-aminopyrimidine-2,4(1*H*,3*H*)-dione derivatives (**74**) through the one-pot three-component coupling reaction of substituted aromatic aldehydes (**1**), 6-aminouracil derivatives (**2**), and indoles (**73**) in the presence of sulfamic acid as a low-cost and eco-friendly catalyst in the water at room temperature under mild reaction conditions (Scheme 43). It was shown that this versatile synthon could be used as intermediates to generate a series of pharmaceutically active heterocycles such as the target molecules in high yields.

R^1 = H , NO_2, OMe, F, Br
R^2 = H, Me
R^3 = Ph, 3-ClC$_6$H$_4$, 2-HOOCC$_6$H$_4$, 2-FC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-CNC$_6$H$_4$
       4-OMeC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-CHOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-N(Me)$_2$C$_6$H$_4$
R^4 = H, Me

22 Examples
Yields 51-97%

Scheme 43. Sulfamic Acid-Catalyzed One-Pot Synthesis of a New Series of Biologically Relevant Indole-Uracil Molecular Hybrids.[95]

Parvin and his team one-pot three-component reaction of 2-hydroxynaphthalene-1,4-dione (**32**), 6-amino-1,3-dimethyluracil (**2**), and aldehydes (**1**) under reflux has been elaborated based on molecular iodine as a catalyst due to the rapid access to the biological activity of aminouracil-tethered trisubstituted methanes (**70**) (Scheme 44).[96] In following, under the same reaction conditions, they could be synthesized of aminouracil-tethered tri-substituted methane derivatives (**75**) via the four-component reaction of 2-hydroxynaphthalene-1,4-dione (**32**), *o*-phenylenediamine (**76**), aldehydes (**1**), and aminouracil derivatives (**2**).

12 Examples
Yields 50-90%

12 Examples
Yields 51-97%

R_1 = Ph, 3-ClC$_6$H$_4$, 2-OMeC$_6$H$_4$, 3-OMeC$_6$H$_4$, 3-FC$_6$H$_4$, 2-FC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-CH(Me)$_2$C$_6$H$_4$
       3-BrC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-OHC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 4-CNC$_6$H$_4$, 4-OHC$_6$H$_4$, 4-OMeC$_6$H$_4$
       2-Naphtyl, n-C$_4$H$_9$, Cyclohexyl

Scheme 44. Molecular I$_2$-catalyzed MCRs for the synthesis of amino uracil-tethered tri-substituted methanes.[96]

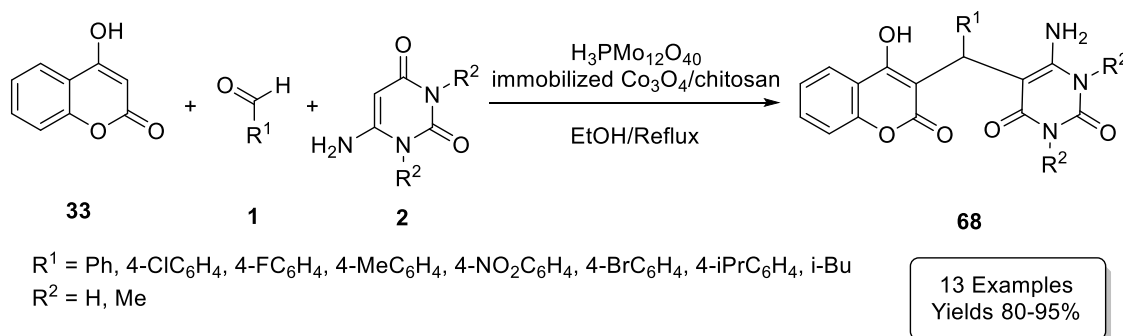Substituents dependent an efficient procedure for the synthesis of coumarin-based unsymmetrical trisubstituted methanes (**77**) was described by Basumatary and colleagues (Scheme 45).[97] The reaction involves the interaction of 4-hydroxycoumarin (**33**), aryl aldehydes (**1**), and 6-aminouracil (**2**) in the presence of L-proline. They reported the application of *L*-proline derived aminothiourea as a multifunctional catalyst in multicomponent reactions for the first time. The prototype of desired molecules has been shown to have acetylcholinesterase inhibitory properties.

R$_1$ = H, Cl, Br
R$_2$ = Ph, 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 2-OMeC$_6$H$_4$, 4-OMeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$
   3-NO$_2$-4-ClC$_6$H$_3$, 2-BrC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-NO$_2$C$_6$H$_4$
   4-CNC$_6$H$_4$, 3-Cl-4-OMeC$_6$H$_3$, pyridin-3-yl, benzo[*d*][1,3]dioxole-5, COOEt, n-Pr

21 Examples
Yields 81-98%
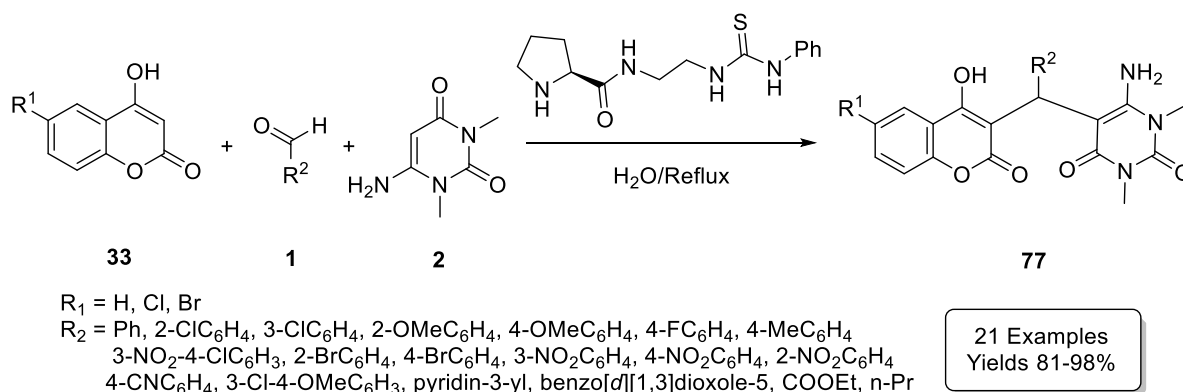
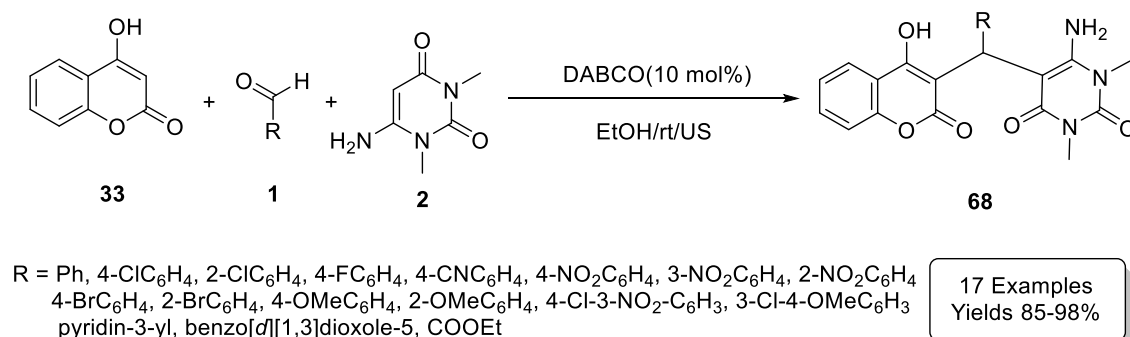**Scheme 45.** Synthesis of coumarin based trisubstituted methanes.[97]

Safari *et al.* applied an efficient three-component reaction of aromatic aldehydes (**1**), 6-aminouracil (**2**)/6-amino-1,3-dimethyluracil (**2**), and 4-hydroxycoumarin (**33**) in the presence of a novel heterogeneous and the magnetically recoverable nanocomposite of catalyst H$_3$PMo$_{12}$O$_{40}$-immobilized Co$_3$O$_4$/chitosan led to a synthesis of a new class of pyrimidinedione derivatives (**68**) under reflux conditions (Scheme 46).[98] Based on results and data, it turned out that Keggin-type 12-molybdophosphoric acid was immobilized with super-paramagnetic Co$_3$O$_4$ nanoparticles into the network cross-linked chitosan.

R^1 = Ph, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-BrC$_6$H$_4$, 4-iPrC$_6$H$_4$, i-Bu
R^2 = H, Me

13 Examples
Yields 80-95%

Scheme 46. Three-component synthesis of pyrimidinedione derivatives catalyzed by Co$_3$O$_4$/CS/PMo nanocomposite.[98]

The Bez group demonstrated a simple and straightforward strategy for the synthesis of several coumarin-based trisubstituted methanes (TRSMs) derivatives (**68**) as biologically active nitrogen-containing heterocyclic compounds (Scheme 47).[99] Besides, the experimental studies on anthelmintic showed efficacy against helminth parasites, *Raillietina echinobothrida* and *Syphacia obvelata* due to some of the TRSMs with substituents in the para position of the phenyl ring, showed significant anti-inflammatory activity compared to

conventional drugs showed significant anthelmintic activity in comparison to the commonly used drugs such as praziquantel and albendazole. The authors synthesized the final products employing a green highly efficient sonochemical multicomponent reaction of diverse aldehydes (**1**) with 1,3-dimethyl-6-aminouracil (**2**), and 4-hydroxycoumarin (**33**) in the presence of a catalytic amount of DABCO at room temperature.

R = Ph, 4-ClC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-CNC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 2-NO$_2$C$_6$H$_4$
4-BrC$_6$H$_4$, 2-BrC$_6$H$_4$, 4-OMeC$_6$H$_4$, 2-OMeC$_6$H$_4$, 4-Cl-3-NO$_2$-C$_6$H$_3$, 3-Cl-4-OMeC$_6$H$_3$
pyridin-3-yl, benzo[*d*][1,3]dioxole-5, COOEt

17 Examples
Yields 85-98%

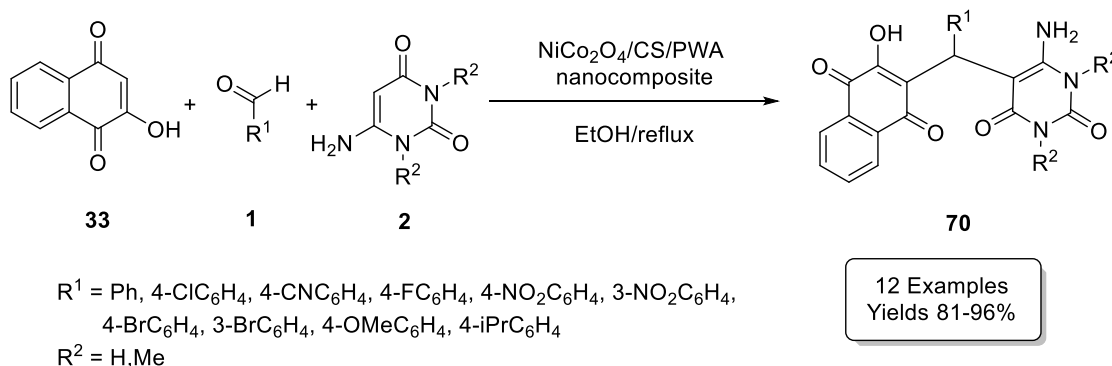**Scheme 47.** Synthesis of coumarin based unsymmetrical TRSMs.[99]

Zare *et al.* synthesized a novel nanorod-structured organic-inorganic hybrid material, namely nanorod-[SiO$_2$-Pr-Im-SO$_3$H][TFA](N-[SPIS][TFA]). Therefore, they demonstrated for the efficient synthesis of several the preparation of (6-amino-1,3-dimethyluracil-5-yl)-(2-hydroxynaphthalene-1,4-dione-3-yl)methanes (**70**) by the one-pot multicomponent reaction of 6-amino-1,3-dimethyluracil, 2-hydroxynaphthalene-1,4-dione (**33**), and aryl aldehydes (**1**) in the presence of a catalyst (Scheme 48).[100] Similar to this approach, the authors disclosed the rapid reaction access to a range of novel bis(6-amino-1,3-dimethyluracil-5-yl)methanes (**78**) under eco-friendly via the pseudo-three-component reaction of 6-amino-1,3-dimethyluracil (**2**) and aryl aldehydes (**1**).

78
6 Examples
Yields 94-97%

70
4 Examples
Yields 79-86%

R$_1$ = Ph, 4-ClC$_6$H$_4$, 4-OMeC$_6$H$_4$, 3-OMeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2,5-OMe$_2$C$_6$H$_3$
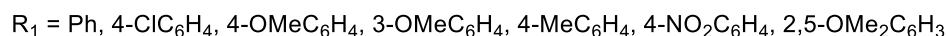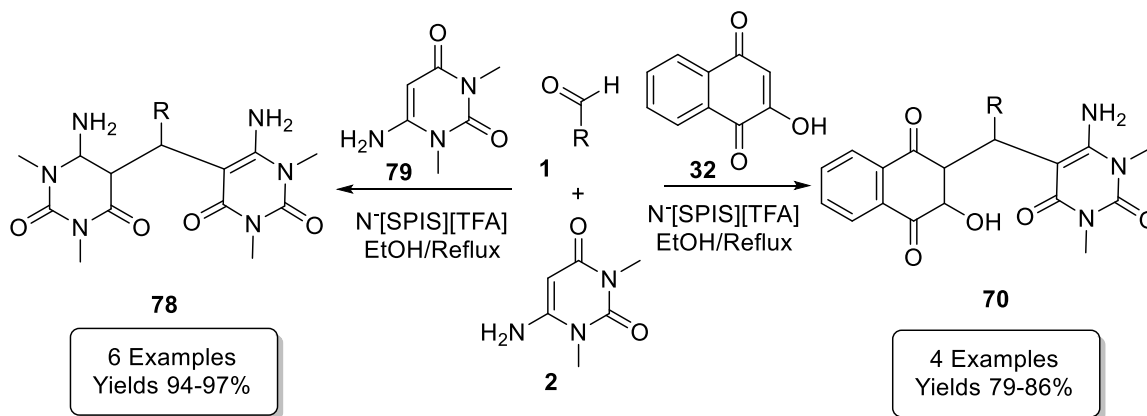
Scheme 48. Synthesis of of bis(6-amino-1,3-dimethyluracil-5-yl)methanes.[100]

In this research, Safari *et al.*[101] investigated a cyclization cascade with a catalyst an efficient, robust, recoverable and magnetic nanocomposite, containing 12-phosphotungstic acid-functionalized chitosan@NiCo$_2$O$_4$ NPs (PWA/CS/NiCo$_2$O$_4$) for the construction of for the synthesis of the pyrimido[4,5-b]quinoline-tetraone skeleton (**70**) (Scheme 49). They developed a three-component one-pot cyclo

condensation reaction of aromatic aldehydes (**1**), 6-aminouracil (**2**), 6-amino-1,3-dimethyluracil with 2-hydroxynaphthalene-1,4-dione (**33**) under reflux conditions in the presence of novel magnetic nanocomposite as a reusable catalyst by using ethanol as a green solvent. The structure and characterization of the recoverable magnetic nanocatalyst have been done by using various spectroscopic techniques, which include Fourier transform infrared spectrophotometry (FT-IR), scanning electron microscopy (SEM), X-ray diffraction (XRD), energy-dispersive X-ray spectroscopy (EDX), and vibrating sample magnetometry (VSM) analysis methods. The obtained magnetic nanocomposite showed excellent catalytic activity as a new heterogeneous catalyst and separated from the reaction system with a simple external magnet. It is also confirmed that $H_3PW_{12}O_{40}$/chitosan/$NiCo_2O_4$ could be reused without any significant loss in its activity.

R^1 = Ph, 4-ClC_6H_4, 4-CNC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-BrC_6H_4, 3-BrC_6H_4, 4-$OMeC_6H_4$, 4-$iPrC_6H_4$
R^2 = H,Me

12 Examples
Yields 81-96%

Scheme49. Synthesis of pyrimido[4,5-b]quinoline-tetraone derivatives using the $NiCo_2O_4$/CS/PWA nanocomposite.[101]

6. Conclusions

Researchers' significant attention has been paid to the design and development of the synthesis of numerous heterocyclic compounds containing nitrogen atoms in the central core due to valuable pharmaceutical and biological activities. A topic of intense research throughout the areas of medicinal and biomolecular chemistry is the synthesis of new uracil derivatives. This review has highlighted the recent progress of the multicomponent functionalization of 6-aminouracil as a significant starting material and a vital nucleus in synthesizing complex heterocyclic scaffolds with ease ecologically viable fashion. In fact, in modern organic synthesis, these MCRs have rigorously proven to be brilliant, powerful tools for synthesizing diverse and complex molecular systems, including various heterocyclic and natural products in a single one-pot operational step. It is needless to mention that there remains a vast opportunity to develop and design various sustainable strategies to perform the reaction under mild conditions, in high efficiency, and selectivity and greenness of the respective procedures. The authors apologize for the research which has not been mentioned in this review for one reason or another. This review has tried to summarize the latest research on the application of 6-aminouracil in multicomponent reactions to synthesize a variety of novel substituted heterocyclic compounds between 2015 and 2020.

7. Acknowledgements

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