*Review*

# Catalyzed Methods to Synthesize Pyrimidine and Related Heterocyclic Compounds

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**Abstract:** This review covers articles published in the period from 2010 to mid-2022 on synthetic
advances in the formation of pyrimidine and related heterocyclic compounds. Special emphasis
has been given to the different types of cycloadditions, taking into account the number of their
components and leading to the formation of the pyrimidine ring. Due to the large number of
publications on the Biginelli reaction and related reactions, this will be dealt with in a separate review
in the near future.

**Keywords:** pyrimidines; multicomponent reactions; cycloadditions; *N*-heterocycles

## 1. Introduction

Compounds with pyrimidine rings and analogs have attained considerable interest
in the last years because of their properties [1–5]. In this review, we focus on the latest
syntheses of these compounds, emphasizing those that use cyclization reactions and cy-
cloadditions of two or more components. We are interested in those pyrimidines and
analogous compounds such as pyrimidinones, pyrimidinethiones and other pyrimidine-
related scaffolds. The synthesis of pyrimidines with substituted or decorated rings is
only considered when the principal functionalization is included in the starting compo-
nents and is involved in the cyclization or cyclocondensation processes. Works whose
primary objective is to modify the substitution of an already formed pyrimidine ring are
not described.

In addition, we consider those less well-known reactions with the formation of new
rings by expansion or contraction of other types of rings. In this review, we analyze
the synthetic aspect of these compounds as a principal point of view. Their biological
and medical applications have been well described in a plethora of reviews in the last
years [6–12]. We summarize the published findings reported mainly from 2010 to mid-2022.
It is worth noting the growing number of emerging publications in this field in the last
years [13]. Owing to the number of reports about pyrimidine derivatives, we apologize to
researchers whose important publications might be left out.

The multicomponent approach (MCR) is especially appealing to form the pyrimidine
core and other heterocyclic compounds [14–16]. Much diversity can be readily achieved sim-
ply by varying the reacting components. The two most known multicomponent reactions
to form *N*-containing heterocycles are Hantzsch's (1881) [17] dihydropyridine synthesis
and Biginelli's (1893) [18] 3,4-dihydropyrimidin-2(1H)-one synthesis to form pyrimidine
frameworks. These reactions were reported a long time ago; however, after years with much
interest [19] and later with a discreet number of publications, the Biginelli reaction has been

intensively studied in the last two decades [20,21]. The principal reason is the large number of applications of synthesized dihydropyrimidinone and related compounds [22]. Most of the applications of these products are in the field of biochemistry and medicine [23,24]. More information on the Biginelli-type reaction will be given in a following review. We now focus on other types of strategies for forming the pyrimidine core.

## 2. Strategies to Compose the Pyrimidine Core

By analyzing the pyrimidine framework, one can consider diverse options of cycloadditions to form pyrimidine rings. We distinguish them considering the number of components and the atomic composition of each of the fragments. The corresponding reactions are revised below. Figure 1 depicts the numbers of the schemes corresponding to each type, where the reactions are described.
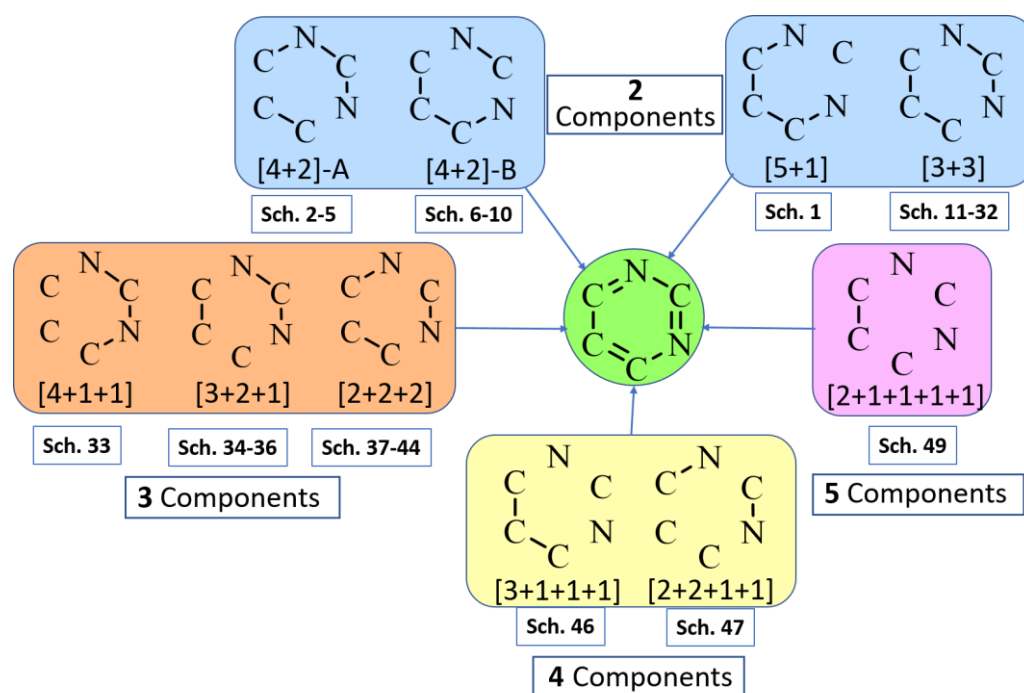


**Figure 1.** Formation of pyrimidine core from diverse numbers of components.

### 2.1. Two-Component Cycloadditions

The usefulness of these strategies to form the pyrimidine core can be found in the literature [25]. As a matter of fact, in the period considered in this review, a large number of examples have been reported starting from two components [26–65]. In the following schemes, information is given on those reactions which can be included in this group. The classification has been made according to the four types considered in Figure 1, for two-component reactions, starting with the one with the largest components [5+1].

#### 2.1.1. [5+1] Cycloadditions

The [5+1] annulation of enamidines **2** with *N,N*-dimethylformamide dialkyl acetals **4** has been described. This process leads to the synthesis of tri- and tetrasubstituted pyrimidine derivatives **3** under catalyst- and solvent-free reaction conditions (Scheme 1) [26]. These intermediate enamidines **2** were prepared from functionalized silanes, organolithium compounds and two nitriles. Furthermore, the [5+1] annulation of enamidines using orthoesters **5** with a catalytic amount of ZnBr$_2$ was also considered, yielding polysubstituted pyrimidines (Scheme 1) [26].
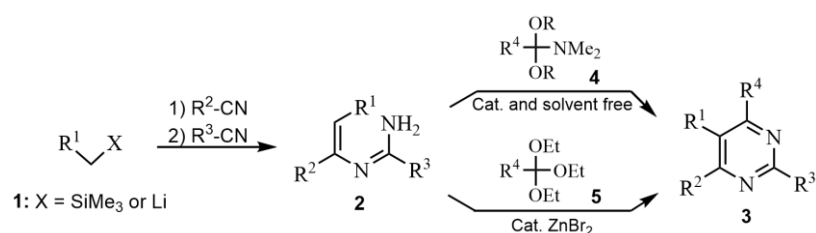
**Scheme 1.** Synthesis of tri- and tetrasubstituted pyrimidine derivatives **3**.

The diversity of two-or-more-component pyrimidine syntheses starting from alkynes has been well documented [27]. Some examples are described below.

### 2.1.2. [4+2] Cycloadditions

An original route to prepare multifunctionalized pyrimidines involved in the in situ generation of ketimines from alkynes and sulfonyl azides. Thus, the synthesis of a novel class of sulfonamide pyrimidine derivatives **10** via a copper-catalyzed tandem reaction of trichloroacetonitrile, 1,1,3,3-tetramethylguanidine (**6**), sulfonyl azides and terminal alkynes **7** has been described with high yields (up to 87%) [28]. The intermediates **8** and **9** via a [4+2]-A condensation gave the targeted pyrimidines **10** (Scheme 2).
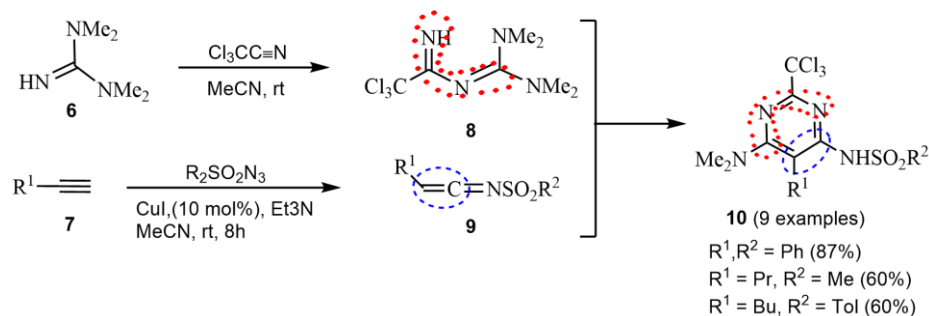


**Scheme 2.** Synthesis of sulfonamide pyrimidines **10** from trichloroacetonitrile, 1,1,3,3-tetramethylguanidine (**6**), sulfonyl azides and terminal alkynes **7**.

A methodology [4+2]-A to prepare 2-trifluoromethylpyrimidines **14** has been developed based on a cyclization reaction of 2-trifluoromethyl 1,3-diazabutadienes **13** [29]. These intermediates were prepared by the condensation of trifluoroacetamidine **11** and amide acetals **12** or with chloromethaniminium salt derived from *N*,*N*-dimethylbenzamide with phosphorus oxychloride. The cycloaddition reactions of these 2-trifluoromethyl-1,3-diazabutadienes **13** with dimethyl acetylenedicarboxylate and phenylacetyl chloride provided 2-trifluoromethylpyrimidine derivatives **14** and **15** in a regular to moderate overall yield (Scheme 3).

A particular case of [4+2] cycloaddition involves triazines using a Diels–Alder-type reaction. Recently, a review on triazines, their syntheses and inverse electron-demand Diels–Alder reactions, focusing on the application of obtaining heterocycles with nitrogen, has been published [30]. As an example of their usefulness, a series of 4,5 disubstituted-or-4-monosubstituted-pyrimidine **18** was obtained by an organocatalytic inverse electron-demand Diels–Alder reaction of a variety of ketones **16** with 1,3,5-triazine **17** through enamine catalysis. Good yields and high levels of regioselectivity were reported (Scheme 4) [31].
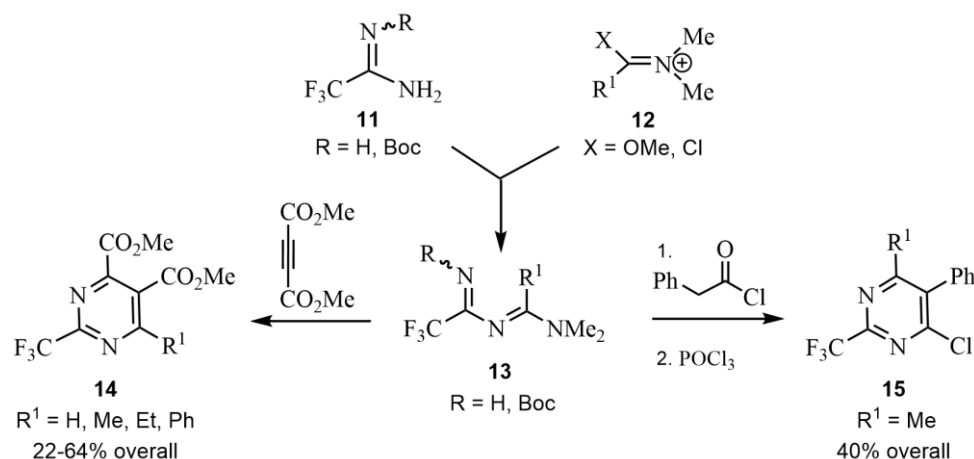
**Scheme 3.** Synthesis of 2-trifluoromethylpyrimidines **14** and **15**.
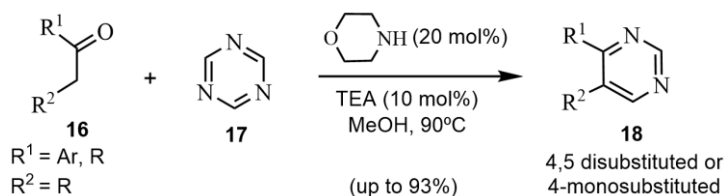


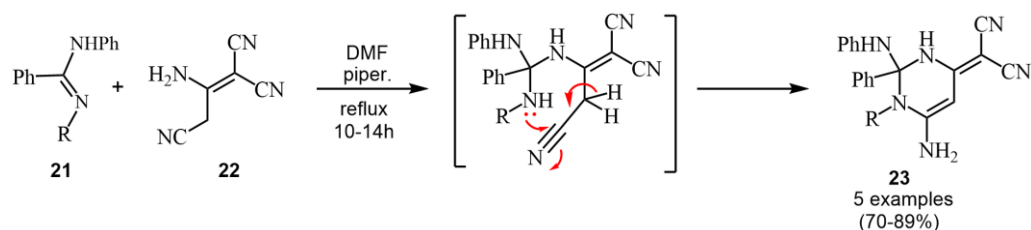**Scheme 4.** Synthesis of pyrimidines **18** from ketones **16** and triazines **17**.

More recently, a similar strategy, but with TFA-catalyzed reactions of electron-deficient 1,3,5-triazines **19** and aldehydes/ketones **16**, was described [32]. Highly functionalized pyrimidines **20** were obtained as products in fair-to-good yields. The reaction mechanism was carefully studied by the combination of experimental and computational studies. The reactions involved a cascade of stepwise inverse electron-demand hetero–Diels–Alder reactions, followed by retro-Diels–Alder reactions and the elimination of water. Both Diels–Alder reactions required TFA. The yields were higher when cyclic ketones were used. (Scheme 5).
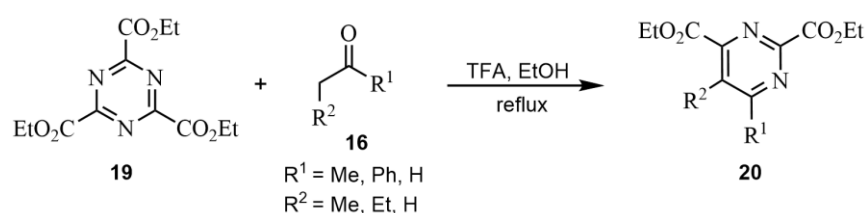


**Scheme 5.** Synthesis of pyrimidines **20** from substituted triazines **19** and ketones **16**.
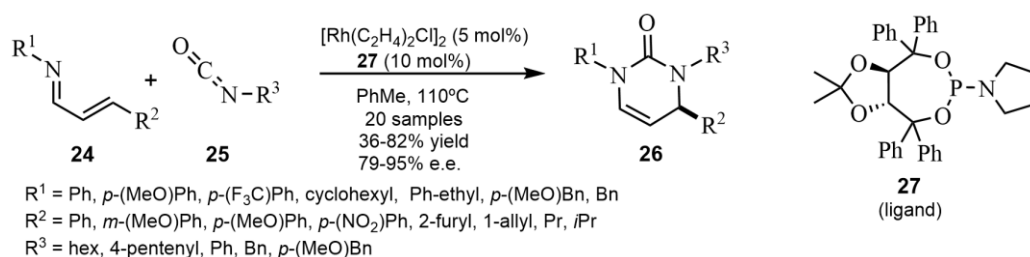
Amidines are another group of compounds that can be used in cyclization reactions of two or more components. Substituted amidines are useful intermediates in the synthesis of many heterocyclic compounds, not only for pyrimidines. Consequently, several reviews have been devoted to the application of amidines as condensation agents to form heterocyclic rings [33,34].

Amidines can react with malononitrile dimer in a [4+2]-B cyclocondensation, as reported by Aly's group [35]. The reaction occurred via an amination process followed by cyclization to give racemic 6-aminopyrimidine compounds **23**, which were catalyzed with piperidine in DMF. Amidine compounds **21** that have aryl groups with electron-donating or electron-withdrawing substituents on the benzene ring were selected to examine their respective effect on the course of the reaction. The yield was higher in the case of electron-donating substituents, *p*-methoxy (89%), than for the withdrawing nitro group (70%) (Scheme 6).
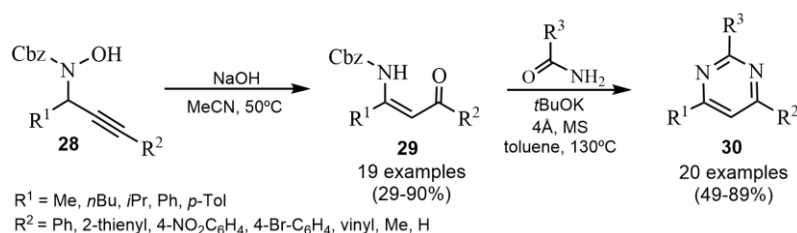
**Scheme 6.** Synthesis of pyrimidines **23** from amidines and malononitrile dimer.

An enantioselective rhodium-catalyzed [4+2]-B cycloaddition was performed from α,β-unsaturated imines **24** and isocyanates **25**, obtaining pyrimidinones **26** with a high enantioselectivity and moderate-to-good yields. The reaction was catalyzed by a phosphoramidite–Rh complex, affording a substitution pattern complementary to that of Biginelli adducts (Scheme 7) [36].



$R^1$ = Ph, *p*-(MeO)Ph, *p*-(F$_3$C)Ph, cyclohexyl, Ph-ethyl, *p*-(MeO)Bn, Bn
$R^2$ = Ph, *m*-(MeO)Ph, *p*-(MeO)Ph, *p*-(NO$_2$)Ph, 2-furyl, 1-allyl, Pr, *i*Pr
$R^3$ = hex, 4-pentenyl, Ph, Bn, *p*-(MeO)Bn

**Scheme 7.** Synthesis of pyrimidinones **27** from α,β-unsaturated imines **24** and isocyanates **25**.

An [4+2]-B condensation starting from β-enaminones was described by Campagne´s group [37]. These authors achieved, with (*Z*)-selectivity, several *N*-Cbz-β-enaminones **29** through a novel base-catalyzed isomerization from propargylic *N*-hydroxylamines **28**. The use of NaOH as a base was crucial to improve the yield of the reaction. The role of the $R^2$ substituent was also important. In fact, for $R^2$ = *t*Bu, Ph, *p*-Tol, a propargylic by-product was formed in significant proportion. The usefulness of these enaminones was to obtain 2,4,6-trisubstituted pyrimidines **30**, as they could be condensed with various carboxamides, under basic conditions, in gram scale, in moderate-to-good yields (Scheme 8).



$R^1$ = Me, *n*Bu, *i*Pr, Ph, *p*-Tol
$R^2$ = Ph, 2-thienyl, 4-NO$_2$C$_6$H$_4$, 4-Br-C$_6$H$_4$, vinyl, Me, H

**Scheme 8.** Synthesis of pyrimidines **30** from β-enaminones **29**.

Later, amino acid-derived carboxamides were also employed in this reaction, providing chiral pyrimidine derivatives **34** and **35** in modest yields. The obtained pyrimidines were studied with NMR and DFT methods (Scheme 9) [38].
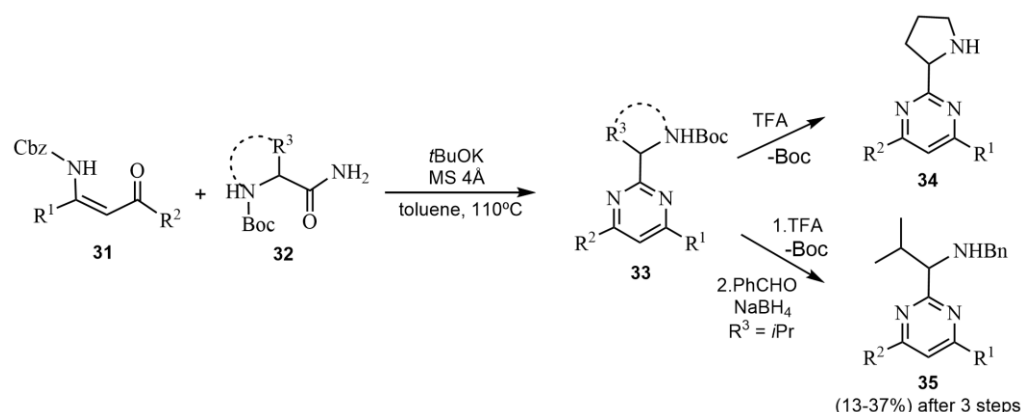
**Scheme 9.** Synthesis of pyrimidines **34** and **35** from amino acid-derived carboxamides.

Anderson and Boger [39] published a systematic study of the inverse electron-demand Diels–Alder reactions of 1,2,3-triazines. The study revealed not only that the reactivity may be predictably modulated by a C-5 substituent (R = CO$_2$Me > Ph > H), but also that the application of this methodology is broadened to heterocyclic ring systems as pyrimidine derivatives. In this case, from 1,2,3-triazines, pyrimidine formation follows a [4+2]-B cycloaddition. In a subsequent work, amidines were found to undergo a powerful cycloaddition to 1,2,3-triazines bearing electron-donating substituents at C5, to provide 2,5-disubstituted pyrimidines **42** in excellent yields (42–99%) (Scheme 10) [40]. Even selected ynamines and enamines were capable of cycloadditions with **36**, but not with **37** or **38**, to provide other trisubstituted pyridines in modest yields (37–40% and 33%, respectively).
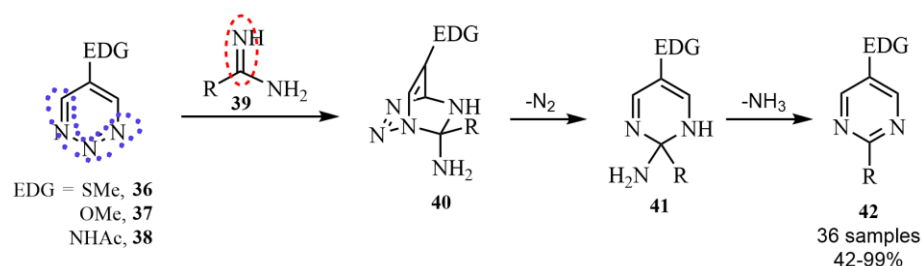


**Scheme 10.** Inverse electron-demand Diels–Alder reactions of 1,2,3-triazines **36**–**38** with amidines **39**.

### 2.1.3. [3+3] Cycloadditions

We cannot deal with the synthesis of pyrimidines by [3+3] cycloaddition without describing the classical Pinner reaction [41]. This synthesis entails the condensation of 1,3-dicarbonyl compounds, formerly ketones, with amidines (Scheme 11).
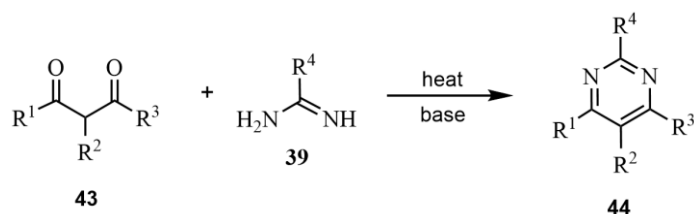


**Scheme 11.** Classical Pinner synthesis.

A modified Pinner reaction is described by Vidal et al. with a β-keto ester instead of 1,3-diketone. The procedure was improved under ultrasound (US) irradiation. Fully substituted pyrimidines were obtained by tosylation of the free hydroxyl of the obtained pyrimidine derivatives, which allowed further Suzuki cross-coupling reactions (Scheme 12) [42].
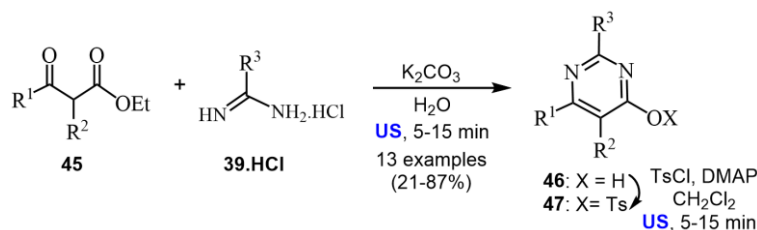
**Scheme 12.** Modified Pinner reaction with β-keto esters **45** and amidines **39**.

Other variations of the original reaction have been described [43]. Thus, using 1,3-dicarbonyl equivalents as precursors, several syntheses of pyrimidines have been reported using a Pinner-like synthesis. Cho's group [44] condensed β-bromo-α,β-unsaturated ketones with benzamidine or acetamidine under $Cu^0$ catalysis to provide the corresponding pyrimidines in fair yields. Most of the samples were fused pyrimidines, which do not fall within the scope of this study. Previously, this group carried out the same synthesis with β-bromo-α,β-unsaturated carboxylic acids [45]. One remarkable modification was the use of unsaturated ketones instead of the dicarbonyl compound [46]. Thus, a [3+3] annulation–oxidation sequence between α,β-unsaturated ketones and benzamidine hydrochloride was performed using green and recyclable choline hydroxide as both a catalyst and a reaction medium. Strong bases, such as NaOH, KOH and CsOH, catalyzed the reaction better than weak inorganic bases, to give substituted pyrimidine **50** in excellent yields. However, the optimal reaction conditions required the use of choline hydroxide as a catalyst, as well as reaction medium at 60 °C (Scheme 13) [46].
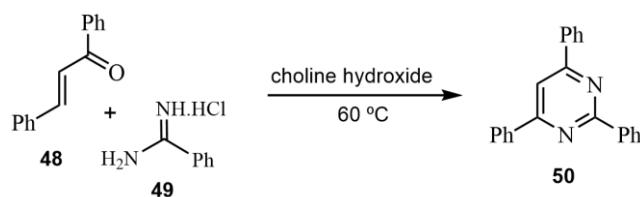


**Scheme 13.** Synthesis of pyrimidines **50** from unsaturated ketones **48** and amidine **49**.

Another variation was carried out by Hu et al., who reported [47] a [3+3] cycloaddition of polysubstituted 5-aminopyrimidines **52** from α-azidovinyl ketones **51** and amidines **39** in the presence of a base ($K_2CO_3$) in anhydrous DMF (Scheme 14).



$R^1$ = Ph, 4-(Me, Cl, $NO_2$, MeO)$C_6H_4$, 2-thienyl
$R^2$ = 4-(Br, F, MeO)$C_6H_4$
$R^3$ = H, Me, Ph
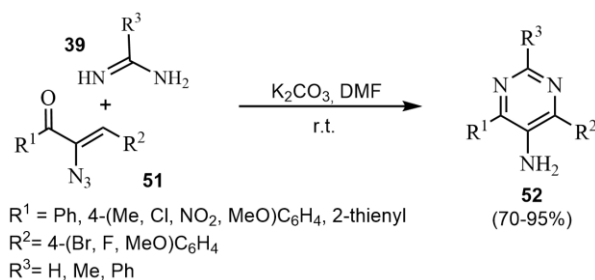
**Scheme 14.** Synthesis of 5-aminopyrimidines **52** from α-azidovinyl ketones **51** and amidines **39**.

Amidines were also condensed via [3+3] annulation with 2,2,2-trichloroethyliden-acetophenones **53**, easily available from chloral and acetophenones, providing novel 2,6-diaryl-6-hydroxy-4-trichloromethyl-1,4,5,6-tetrahydropyrimidines **54** in good yields.

On the other hand, new intermediate 2,4-diaryl-6-trichloromethyl-1,6-dihydropyrimidines **55** were formed by dehydration and found able to undergo base-induced chloroform elimination to give 2,4-diarylpyrimidines **56** (Scheme 15) [48].
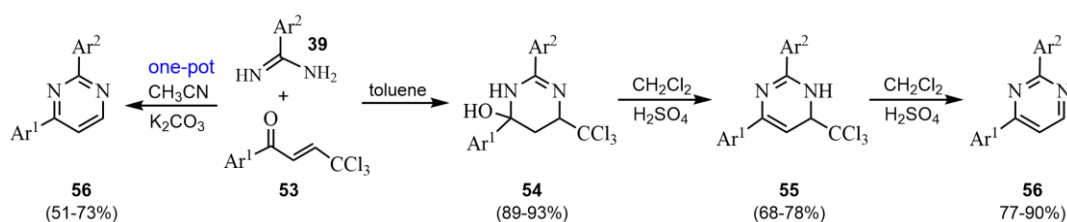
**Scheme 15.** Synthesis of 2,4-diarylpyrimidines **56** from 2,2,2-trichloroethyliden-acetophenones **53** and amidines **39**.

A bromoenone was used to afford trifluoromethylated pyrimidines **59** through the treatment of fluorinated 2-bromoenones **57** with aryl- and alkylamidines **34** [49]. The formation of a pyrimidine core proceeded via an aza-Michael addition–intramolecular cyclization–dehydrohalogenation/dehydration sequence. The influence of the trifluoromethyl group was demonstrated to be necessary to achieve selectively the target heterocycles in high yields (up to 99%) under mild conditions. With other substituents, imidazoles were obtained (Scheme 16).
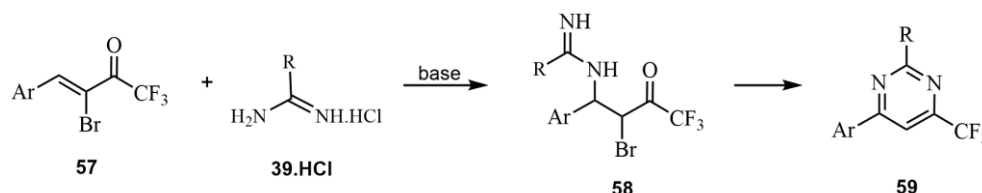


**Scheme 16.** Synthesis of trifluoromethylated pyrimidines **59** from bromoenones **57** and aryl- and alkylamidines **39**.

Another modification was described by Chu et al. [50], starting from a variety of saturated carbonyl compounds: ketones, aldehydes and esters **60**. The condensation was promoted by $FeSO_4$ and 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), selectively favoring β-functionalization. A mechanism initiated by TEMPO reduction via complexed Fe(II) with ketones was proposed. The total sequence included the formation of intermediate enamine and finished with a β-TEMPO elimination, followed by cyclization. The Fe(II) catalytic complex, formed in situ, could be recycled. More than forty pyrimidinic derivatives were obtained (some of them with condensated rings), sixteen of which were of type **61** (Scheme 17) [50].
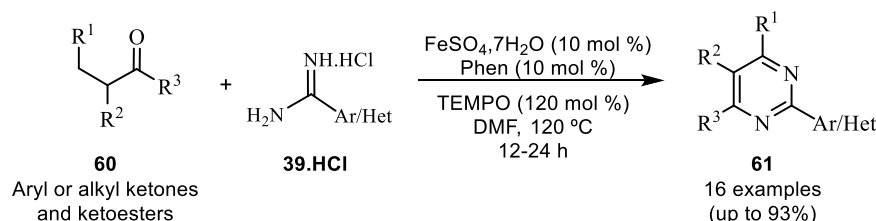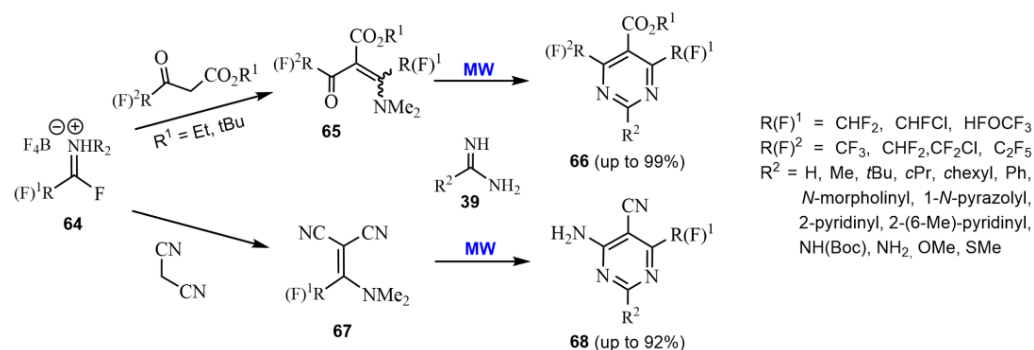


**Scheme 17.** Iron-catalyzed synthesis of pyrimidines **61** from carbonyl derivatives **60** and amidines **39**.

Subsequently, a condensation with a special type of unsaturated ketone, a substituted chromone, was carried out by Yu et al. [51]. The strategy was based on a transition metal-free synthesis of 3-trifluoromethyl chromones via tandem C-H bond trifluoromethylation and chromone annulation reactions of *o*-hydroxyphenyl enaminones. The addition of $K_2S_2O_8$ made the use of any transition metal catalyst or additive unnecessary. The 3-trifluoromethyl chromone products were successfully used for the synthesis of 3-trifluoromethyl pyrimidines through reactions with guanidine/amidine substrates (Scheme 18).
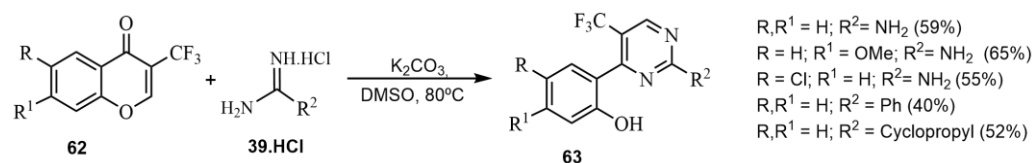
**Scheme 18.** Synthesis of $F_3C$-functionalized pyrimidines **63** from chromones **62**.

[3+3] cycloadditions have also been carried out from fluorinated building blocks. Thus, an efficient microwave-assisted cyclization reaction was developed to provide faster and efficient access to new fluoroalkyl pyrimidines **66** and **68** from fluorinated acetoacetates, malononitrile, various amidines and fluoroalkyl amino reagents (Scheme 19) [52].



**Scheme 19.** Synthesis of fluoroalkyl pyrimidines **66** and **68** under MW irradiation.

Very recently, in 2022, Xiang and Yang reported [53] a photoredox-catalyzed amination of *o*-hydroxyarylenaminones with tert-butyl [(perfluoropyridin-4-yl)oxy]carbamate, a versatile amidyl radical precursor. This method allows 3-aminochromones to be obtained under mild conditions, with an additional application in the synthesis of a series of amino pyrimidines (Scheme 20) [53].
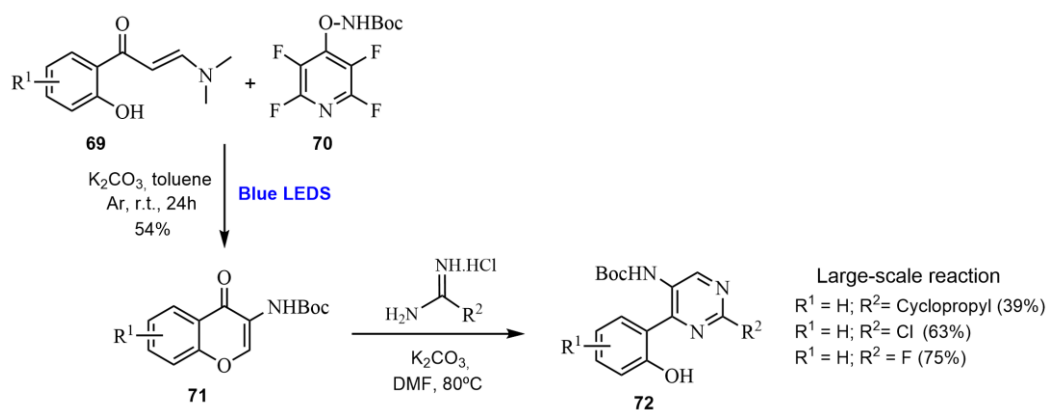


**Scheme 20.** Synthesis of 3-aminochromones **71** and amino pyrimidines **72**.

Not many examples of bis-pyrimidines are found in the literature. With the aim of obtaining new biological active pyrimidine derivatives **75**, **76** and **77**, Dabholkar and Ansari [54] proposed this synthesis starting from bis-α,β-unsaturated esters **74** and carbamide C, thiocarbamide (T) and guanidine (G) as efficient substrates under ultrasound (US) irradiation in aqueous media (Scheme 21).
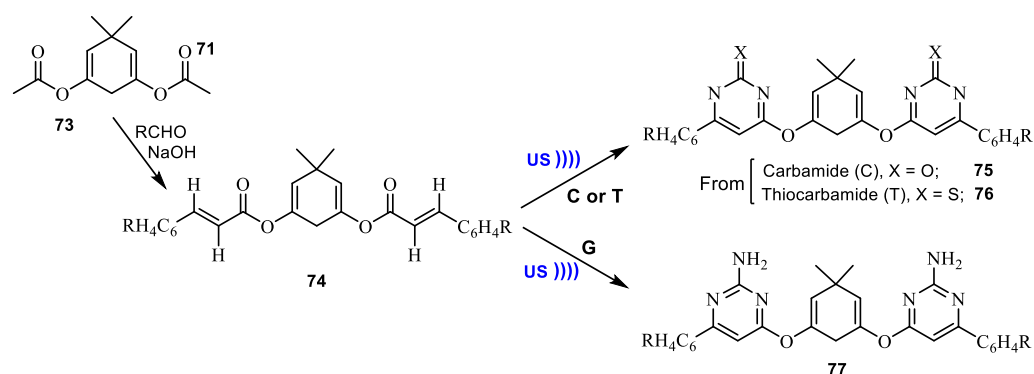
**Scheme 21.** Synthesis of bis-pyrimidines **75**, **76** and **77** under US irradiation.

The effectiveness of the cyclization reactions involving alkynes and nitrogen compounds for the synthesis of pyrimidines, using a variety of promoters and catalysts, has been demonstrated. More specifically, the Cu(II)-catalyzed cycloaddition reaction of alkynes is considered a powerful tool for the construction of pyrimidines using nitrogen-containing molecules, such as amidines, guanidines and sulfonyl azides [27]. Müller and colleagues [55] planned a versatile copper-catalyzed synthesis of 2,6-disubstituted pyrimidones **79** from terminal alkynes **7**, $CO_2$ and amidine hydrochloride **34** in DMF. Although the total reaction involved three components, the formation of a pyrimidine ring can be considered a [3+3] cycloaddition strategy. After an initial carboxylation/methylation of terminal alkynes to produce the methyl arylpropiolates **78**, a Michael addition cyclocondensation led to pyrimidones **79** with moderate-to-good yields (Scheme 22) [55].
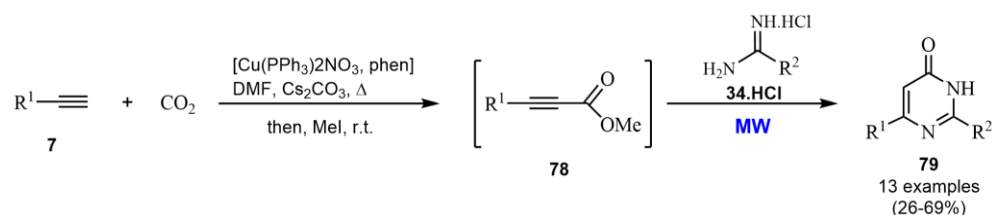


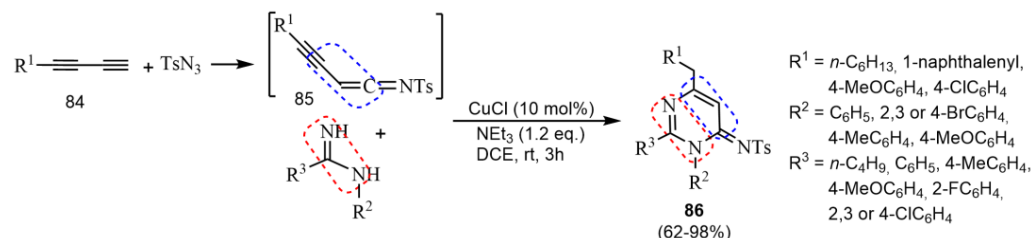**Scheme 22.** Copper-catalyzed synthesis of 2,6-disubstituted pyrimidones **79** with MW.

Lin et al. [56] described the use of Cu(II) triflate (20 mol%) as an efficient catalyst to synthesize 2,4-disubstituted or 2,4,6-trisubstituted pyrimidines **83** from propargyl alcohols and amidine. The synthesis started with a Cu(II) activation of propargyl alcohol **80**, followed by a [3+3] addition combined with ring closure in a 6-*endo-dig* mode. The authors proposed the initial formation of the propargyl cation **81**, which triggers the attack on amidine to complete the pyrimidine skeleton, as a key step of the reaction mechanism. A subsequent aromatization by oxidation was the last step leading to pyrimidines **83** (Scheme 23) [56].
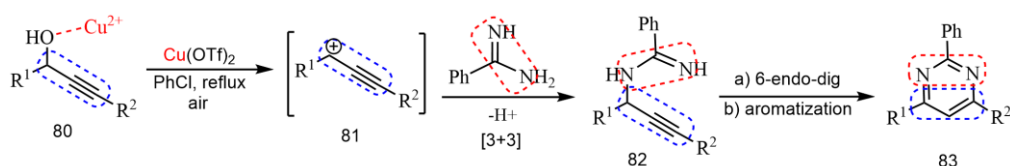


**Scheme 23.** Mechanistic proposal for Cu(II)-catalyzed tandem synthesis of pyrimidines **83**.

A series of 4-iminopyrimidines **86** using the strategy of [3+3]-A cycloaddition was synthesized from intermediate β-alkynyl-*N*-sulfonyl ketenimines **85** with a copper catalyst. The sequence started with the reaction of butadiynes **84** and sulfonylazides and continued with the addition of hydrazides or imidamides (Scheme 24) [57]. The best reaction conditions to first form ketenimine **85** with subsequent cycloaddition were with CuCl (10 mol%)

as a catalyst with NEt$_3$ in DCE at room temperature. Although three components are involved in this reaction, in two sequential steps, the atoms of the starting azide are not integrated in the pyrimidine core in the cycloaddition (Scheme 24) [57].



**Scheme 24.** Copper-catalyzed synthesis of 4-iminopyrimidines **86**.

Sharma et al. [58] took advantage of the Selectfluor's ability to regioselectively functionalize a variety of methylthio-substituted β-enaminones **87**, which were transformed into α-fluoro-β-enaminones in acetonitrile. The resulting crude reaction was condensed with guanidinium nitrate under basic conditions. The corresponding 6-aryl- or 6-alkylamines-2-amino-5-fluoropyrimidines **88** were obtained in good overall yields (Scheme 25) [58].
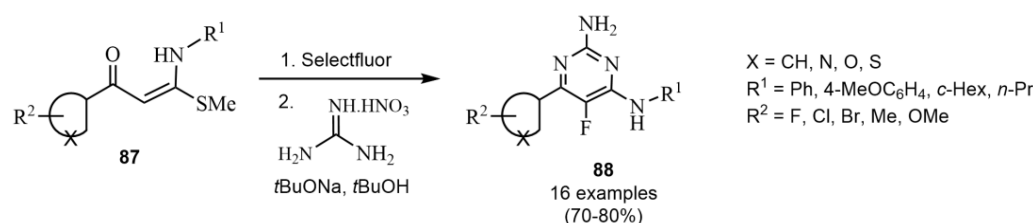


**Scheme 25.** Sequential synthesis of 4-amino-5-fluoropyrimidines **88**.

Sulfur derivatives are frequently compounds of interest in biomedical applications. With the aim of obtaining sulfur-functionalized pyrimidines, a practical microwave-assisted protocol for the synthesis of 2,6-disubstituted pyrimidinones **91** was developed. It was based on a domino Michael addition/cyclocondensation reaction between substituted thioureas/guanidines and acetylencarboxylates (Scheme 26). Following this strategy, the subsequent synthesis of not easily accessible *N*-DABO (dihydro-alkoxyl-benzyl-oxopyrimidine) derivatives was reported [59].
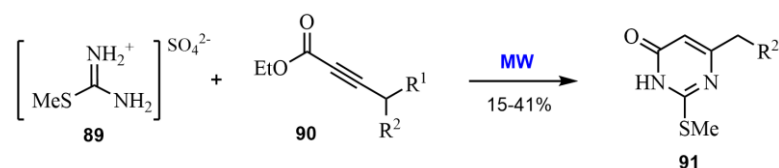


**Scheme 26.** Microwave-assisted tandem Michael addition–cyclocondensation to form sulfur-functionalized pyrimidines **91**.

A direct and single-step procedure towards substituted pyrimidine and pyridine derivatives via Lewis-acid-promoted [3+3] annulation between 3-ethoxycyclobutanones and enamines or amidines is presented. These 3-ethoxycyclobutanones act as 1,3-dicarbonyl surrogates. Choosing the right reaction conditions, diverse substituted pyrimidine **95** and pyridine derivatives **94** were obtained in good-to-high yields with a wide substrate scope (Scheme 27) [60].
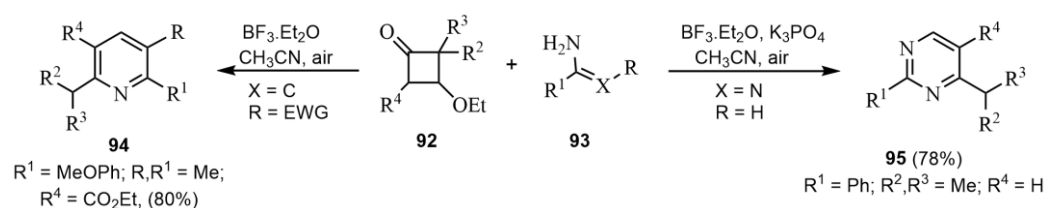
**Scheme 27.** Synthesis of pyrimidines **94** and **95** from 3-ethoxycyclobutanones **92**.

A new [3+3] strategy was carried out by El-Sayed et al. [61], preparing pyrimidine derivatives via an epoxy ketone. Pyrimidinic compounds **98** and **99** were synthesized starting from unsaturated carbonyl compound **96**, which, with hydrogen peroxide, yielded epoxy ketone **97**. After a reaction with urea or thiourea by epoxide opening, the corresponding derivatives **98** were formed. Compound **99** was prepared by the treatment of epoxy ketone with thiosemicarbazide. The anticancer activity of these derivatives was studied against the MCF-7 human breast cancer cell line (Scheme 28) [61].
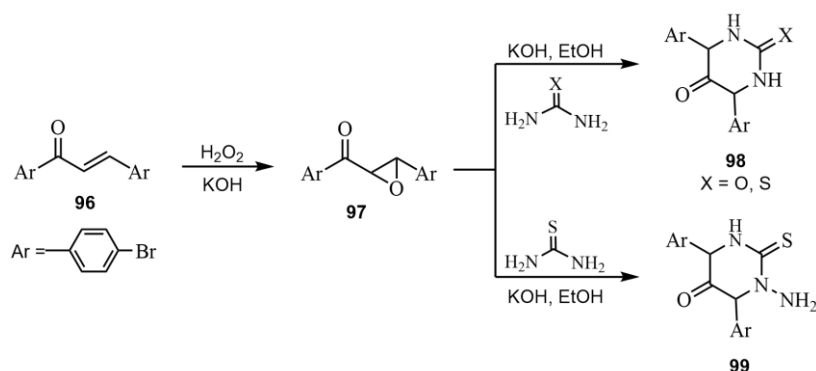


**Scheme 28.** Synthesis of oxo and thio pyrimidine derivatives **98** and **99** via epoxyde **97**.

Modified nucleobases and nucleic acids have found many biological and pharmaceutical applications. Burgula et al. [62] have reported a [3+3] green procedure for the single-step preparation of a series of uracil and cytosine nucleobases **100** and **101**. Uracil analogs **100** were synthesized through the treatment of the respective β-ketoesters or β-aldehydoesters **102** with urea, whereas the cytosine derivatives **101** were obtained from benzoylacetonitriles **103** or *N,N*-diethylamide precursors (Scheme 29). A Lewis acid catalyst (BF$_3$:Et$_2$O) and MW irradiation improved the reaction, with higher yields and lower reaction times. The crystal structures of 5-isopropyl-6-methyluracil and 6-phenyluracil were also determined.
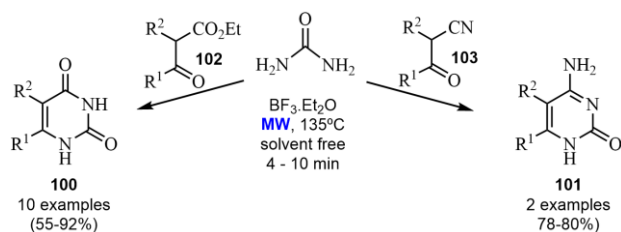


**Scheme 29.** Green synthesis of uracil and cytosine analogs (**100** and **101**).

A good synthetic design was reported by Tejedor and García-Tellado [63] to obtain pyrimidine derivatives **105** with an oxy-functionalized acetate chain at the ring. Amidines **32** with electrophilic diynes **104** interacted in two consecutive aza-Michael additions, followed by a second domino process involving sequential [H]-shift and a [3,3]-sigmatropic rearrangement, giving pyrimidine derivatives **105** (Scheme 30).
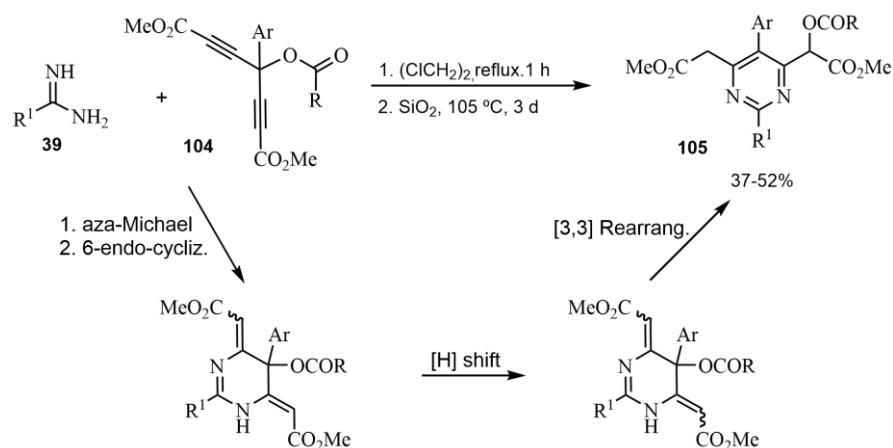
**Scheme 30.** Synthesis of functionalized pyrimidines from electrophilic diynes **104** and amidines **39**.

Hosamani et al. reported the MW-assisted synthesis of 3-(2-(4-fluorobenzyl)-4-(substituted phenyl) pyrimidin-6-yl)-2*H*-chromen-2-ones **108** [64]. The reactions proceeded through a [3+3] cyclic condensation of substituted chalconated coumarins **106** with 2-(4-fluorophenyl) acetamidine hydrochloride **107** in DMF. Improved yields and shortened reaction times, when using MW irradiation compared to conventional heating, were observed (Scheme 31). Although we do not focus on the biological activities of the compounds in this review, this work is of interest because it evaluates the role of the substituents in the pharmacological activities and it evaluates the obtained products against cancer lines.
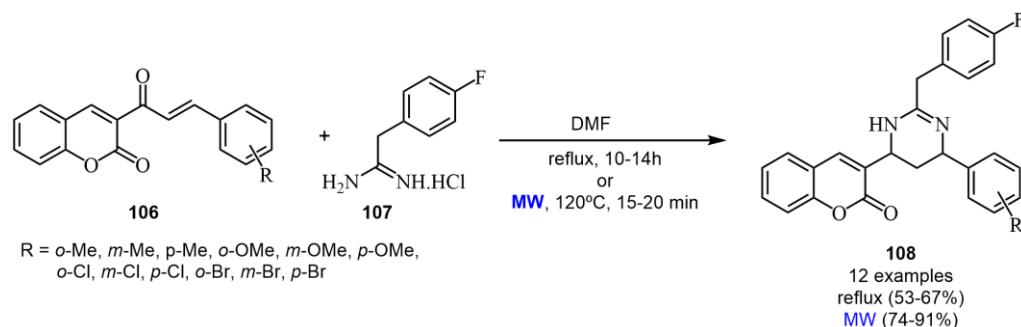
**Scheme 31.** MW-assisted synthesis of fluorinated coumarin–pyrimidine hybrid molecules **108**.

Very recently, in 2022, the effective and accessible synthesis of (*E*,*E*)-4,6-bis(styryl)-pyrimidines was carried out with TFA as a catalyst and water as a solvent. The pyrimidine ring formation was achieved from acetylacetone and urea by [3+3] cycloaddition. A subsequent aldol condensation with differently substituted aromatic aldehyde gave the desired (*E*,*E*)-4,6-bis(styryl)-pyrimidines **110** in moderate-to-good yields (Scheme 32) [65].
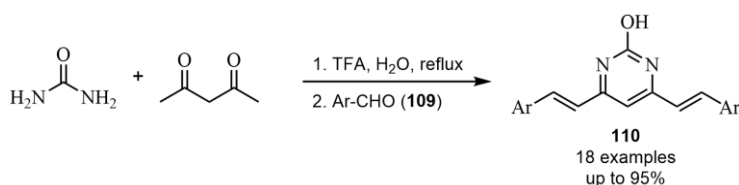
**Scheme 32.** Synthesis of (*E*,*E*)-4,6-bis(styryl)-pyrimidines **110**.

### 2.2. Three-Component Cycloadditions

There is a plethora of three-component condensations leading to pyrimidine and related products. We start by describing an example of a [4+1+1] reaction and continue with [3+2+1] reactions.

### 2.2.1. [4+1+1] Cycloadditions

Yuan et al. [66] developed a base-promoted formal [4+1+1] annulation of aryl alde-hyde **109**, *N*-benzyl arylamidines **111** and DMSO to access to a series of 2,4,6-triaryl pyrim-idines **112** in moderate-to-good yields, with molecular O2 as the sole eco-friendly oxidant (Scheme 33). It is to be noted that DMSO served as a methine source, which was pro-moted by a base rather than either a Lewis acid or electrophile. A detailed mechanism was proposed.
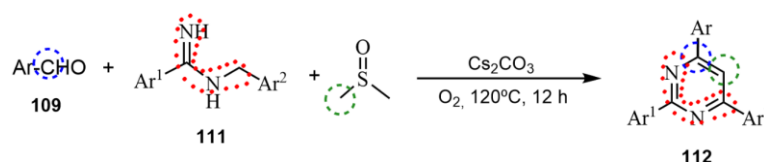


**Scheme 33.** Base-promoted synthesis of 2,4,6-triaryl pyrimidines **112** from aryl aldehyde **109,** *N*-benzyl arylamidines **111** and DMSO.

### 2.2.2. [3+2+1] Cycloadditions

One of the classical multicomponent strategies for synthesizing dihydropyrimidines is the Biginelli three-component condensation (type [3+2+1]-A, Figure 1) of an aldehyde, an α-keto ester and a urea or thiourea that gives a 3,4-dihydropyrimidin-2(1*H*)-(thi)one [18]. Due to the vast information and literature on this type of multicomponent reaction (MCR), we will soon provide a further review of this reaction. Now, we detail other strategies, although a number of them may be considered by other authors as modifications of the Biginelli reaction.

Thus, in the following, we look at other possibilities with the [3+2+1] combination that differ from the classical Biginelli reaction. In pyrimidine synthesis, the in situ oxy-dation of alcohols to provide the formyl component in MCRs is a good option. Thus, a comparative study of nickel-catalyzed syntheses of pyrimidines via the dehydrogenative multicomponent coupling of alcohols and amidines using two types of nickel complex catalysts has been reported [67]. Catalyst **I** dehydrogenates alcohols via a two-electron hydride transfer pathway, while in the presence of **II**, the dehydrogenation of alcohols proceeds via a one-electron hydrogen atom transfer (Scheme 34).
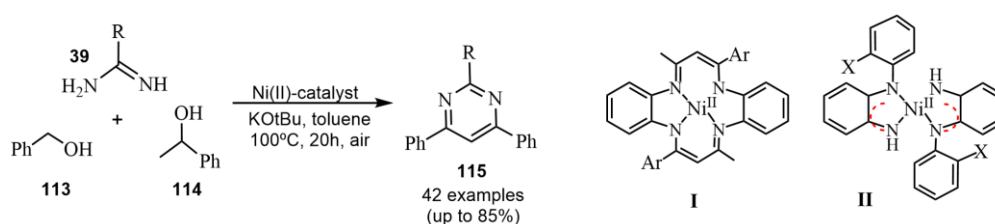


**Scheme 34.** Nickel-catalyzed syntheses of pyrimidines **115** from alcohols and amidines.

With the aim of obtaining 2-(*N*-alkylamino)pyrimidines, heterocycles widely found in various pharmaceutically drugs, a new ruthenium-catalyzed synthesis was reported in a [3+2+1] fashion [68]. The method consisted of a new cooperative ruthenium-complex-catalyzed, multicomponent tandem synthesis of 2-(N-alkylamino)pyrimidines directly from guanidine salt and alcohols. The reactions proceeded through the dehydrogenation of alcohols, followed by C–C coupling and sequential C–N coupling with guanidine and primary alcohol, with the elimination of three equivalents of hydrogen gas. Several Ru catalysts were tested, Ru catalyst I (2 mol %) being that which provided the best results (Scheme 35). The viability of this method was demonstrated through the preparative-scale synthesis of a few products. Mechanistic studies and DFT calculations were subsequently performed (Scheme 35) [68].
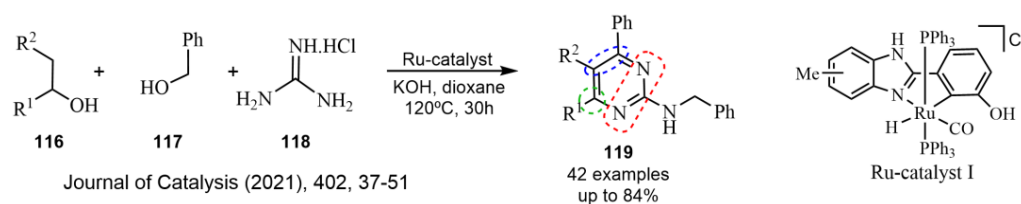
**Scheme 35.** Synthesis of 2-(N-alkylamino)pyrimidines **119** directly from guanidine salt and alcohols.

A series of [3+2+1] three-component annulations of amidines **39**, ketones and *N,N*-dimethylaminoethanol **120** to obtain pyrimidine derivatives **121** was reported. This productive and eco-friendly method showed the oxidation of *N,N*-dimethylaminoethanol through $C(sp^3)-H$ activation to provide one carbon donor to be the principal action. It is worth mentioning, in this strategy, the good tolerance to many important functional groups in air, with improvements to the existing methods of 4-aliphatic pyrimidine formation (Scheme 36) [69].
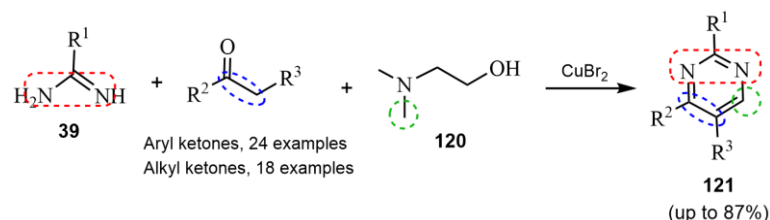


**Scheme 36.** Copper-mediated synthesis of 4-aliphatic pyrimidines **121** from ketones, amino alcohol **120** and amidines **39**.

2.2.3. [2+2+2] Cycloadditions

A copper acetate-catalyzed tandem Blaise/Pinner-type reaction with nitriles and a Reformatsky reagent was performed to obtain pyrimidinones **125**. Nitrile **122** reacted with Reformatsky reagent **123** to form a Blaise intermediary **124**, and then, a second nitrile **122** was added to complete the targeted ring (Scheme 37) [70].
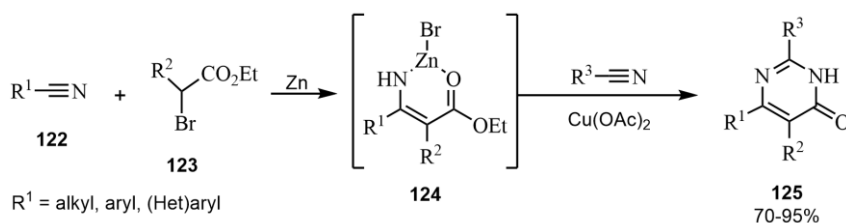


**Scheme 37.** Zinc-mediated synthesis of pyrimidinones **125** from nitriles **122** and ethyl bromoacetates **123**.

The multicomponent condensation [2+2+2] (*C-C+N-C+N-C*) of oxygenated arylacetic acids with electron-donating trimethoxybenzene provided *o*-diaryl pyrimidines in acetonitrile at 60 °C. On the other hand, electron-withdrawing nitroarylaldehydes followed the annulation route (*C-C-C-C+C+N*) to give 1-aryl isoquinolinones. The uses of various metal triflates and reaction conditions were investigated in these one-pot reactions, highlighting bismuth triflate Bi(OTf)$_3$, which acted in mild conditions in open vessels (Scheme 38). The reaction mechanisms were proposed [71].
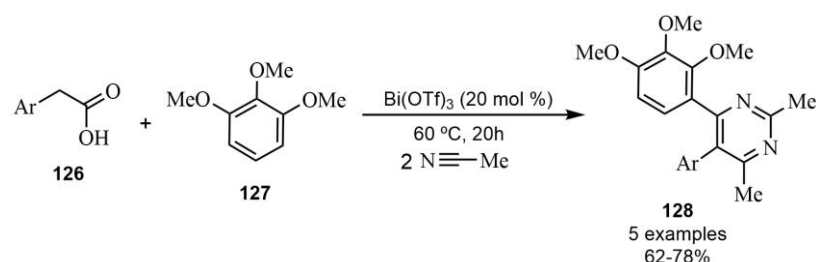
**Scheme 38.** Bismuth-mediated synthesis of pyrimidinones **128** from arylacetic acids **126** with trimethoxybenzene **127**.

Gold complexes have been used to catalyze different cycloadditions to give pyrimidines. Karad and Liu reported the intermolecular [2+2+2] cycloaddition of ynamides **129** ($R^2$ = Ms, Ts) with nitriles to give 4-aminopyrimidines **130** [72]. The reaction conditions were studied in detail, indicating that the use of $Ph_3PAuNTf_2$ (5 mol%) in DCE at 75 °C was the best option to obtain the products in good yields (Scheme 39).



R$^1$ = alkyl, aryl, (Het)aryl
R$^2$ = Ms, Ts
R$^1$ = alkyl, aryl, (Het)aryl, vinyl
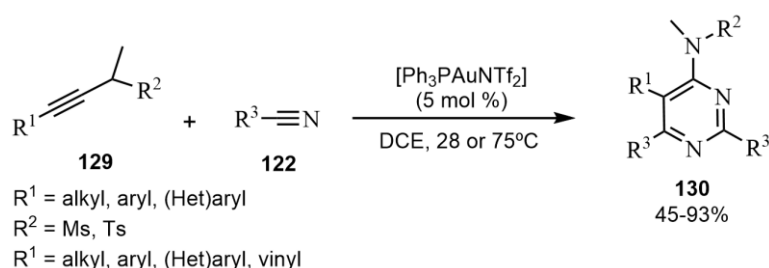
**Scheme 39.** Gold-complex-mediated synthesis of 4-aminopyrimidines **130** by [2+2+2] cycloaddition of alkynes **129** with nitriles **122**.

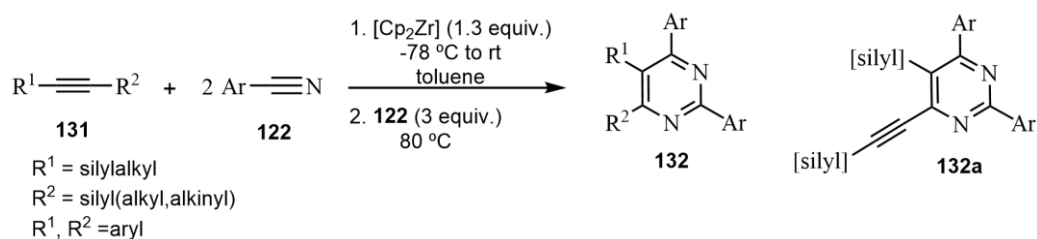A zirconium-mediated reaction of silyl-butadiynes with two molecules of aryl nitriles was described, which provided rapid access to polysubstituted pyrimidines **132** in a regioselective manner and in a one-pot fashion. On the other hand, employing aliphatic nitriles resulted in the coupling of only one nitrile, leading to the formation of enynyl ketones after hydrolysis. The reaction was extended to a zirconocene–monoyne complex, which underwent similar reactions with nitriles to form highly substituted pyrimidines (Scheme 40) [73].



R$^1$ = silylalkyl
R$^2$ = silyl(alkyl,alkinyl)
R$^1$, R$^2$ =aryl

**Scheme 40.** Zirconium-mediated synthesis of polysubstituted pyrimidines **132** with silyl-butadiynes or other alkynes **131** and with two molecules of aryl nitriles **122**.

In a similar strategy [2+2+2], Low et al. reported the synthesis and reactivity of Zr complexes $Zr(IV)L(THF)_3$, which display a two-electron-reduced anthracene moiety. Mechanistic studies suggest that selectivity to form pyrimidines **133** originates from the preferred formation of an azazirconacyclopentadiene intermediate, which reacts preferentially with nitriles over alkynes (Scheme 41) [74]. Previously, Sato et al. reported a similar synthesis catalyzed by $NbCl_5$ [75].
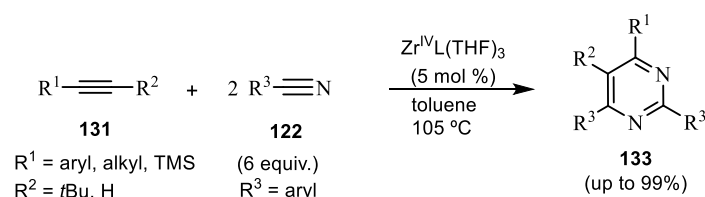
**Scheme 41.** Zirconium-mediated synthesis of polysubstituted pyrimidines **133** with alkynes **131** and two molecules of nitriles **122**.

In the following synthesis of diversely functionalized pyrimidines with a [2+2+2] strategy, the cyclization of ketones with nitriles was carried out under basic conditions with a copper catalyst. The reaction proceeded via a pathway involving the nitriles acting as electrophiles, with consecutive C–C bonds and two C–N bond formations. The method shows a broad substrate scope and a good tolerance for many important functional groups (Scheme 42) [76].
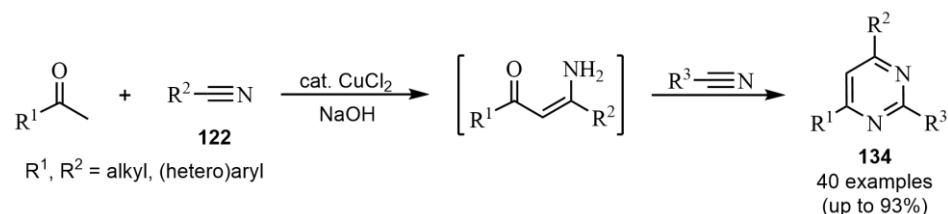


**Scheme 42.** Copper-catalyzed synthesis of pyrimidines **134** from ketones and nitriles **122**.

Babaoglu et al. described a sequential three-component, one-pot reaction sequence for the formation of 2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates following a [2+2+2] strategy (Scheme 43) [77].
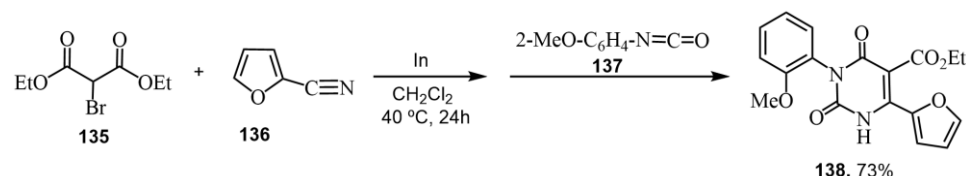


**Scheme 43.** Indium-mediated Blaise-type synthesis of pyrimidines **138** via the reaction of bromomalonates **135** with nitriles **136** and isocyanates **137**.

Jadah and Singh planned an oxidative annulation promoted by $K_2S_2O_8$, involving anilines, aryl ketones and DMSO as a methine (=CH-) equivalent. In the process, a sulfenium ion was formed. This methodology was applied to the synthesis of 4-arylpyrimidines **139** from aryl ketones, via the activation of acetophenone–formamide conjugates **141**. The proposed mechanism is depicted in Scheme 44 [78].
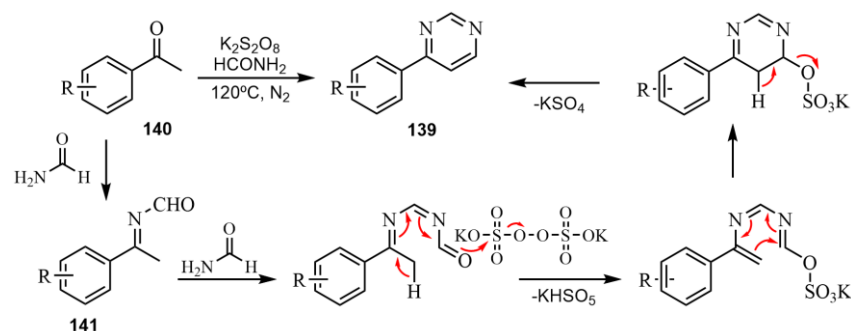


**Scheme 44.** Synthesis of pyrimidines **139** and proposed mechanism from aryl ketones **140**.

### 2.3. Four-Component Cycloadditions

A regioselective, iridium-catalyzed [3+1+1+1] synthesis of alkyl or aryl pyrimidines **142** from amidines and up to three (different) alcohols was carried out. The reaction proceeded via a sequence of condensation and dehydrogenation steps, which gave rise to selective C–C and C–N bond formations. PN5P–Ir–pincer complexes (cat. [Ir]) efficiently catalyzed the regioselective process. A total of thirty-eight different pyrimidines were synthesized in isolated yields of up to 93% (Scheme 45). The authors pointed out that the combination of this novel protocol with established methods for converting alcohols to amidines could allow the selective assembly of pyrimidines from four alcohol building blocks and two equivalents of ammonia [79]. Later, a similar approximation using an Mn complex stabilized by a PN5P–pincer ligand (cat. [Mn]) as a catalyst gave pyrimidines from amidines and up to three (different) alcohols. The consecutive four-component reaction combines the concept of borrowing hydrogen or hydrogen auto transfer with dehydrogenation–condensation to permit selective C–N and C–C bond formation, as in the previous work (Scheme 45) [80].
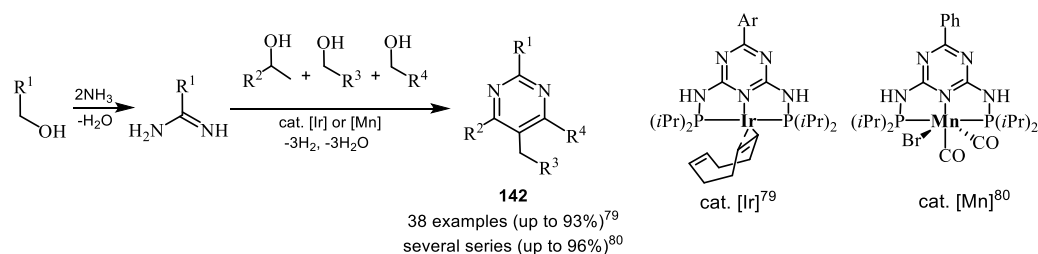


**Scheme 45.** Iridium- or manganese-mediated four-component synthesis of pyrimidines **142** from amidines and alcohols.

Using β-cyclodextrin (β-CD) as a catalyst, pyrimidine derivatives were synthesized from a variety of substituted phenyl and heterocyclic aldehydes in aqueous medium. The advantage of this [3+1+1+1] method is that β-CD is a recyclable, inexpensive, economically viable, non-toxic and readily available material. Thus, the reaction of a series of aromatic aldehydes with ammonium acetate and 1,3-diketones afforded a series of pyrimidine derivatives **143**. The method worked well with both electron-withdrawing and electron-releasing substituents in the aromatic groups, giving pyrimidines **143** in good-to-excellent yields (Scheme 46 [81].
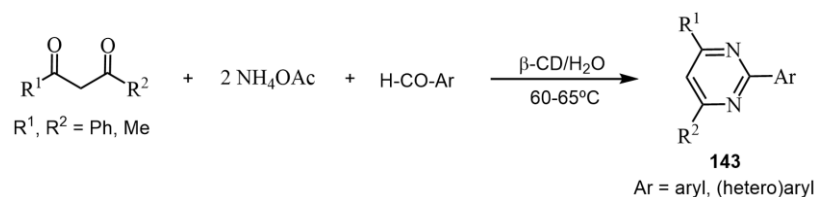


**Scheme 46.** β-cyclodextrin (β-CD)-catalyzed synthesis of pyrimidine derivatives **143** from a variety of substituted phenyl and heterocyclic aldehydes in aqueous medium.

2,4,6-Triarylpyrimidines **144** were synthesized via a simple, one-pot, four-component [2+2+1+1] annulation among aryl methyl ketones, benzaldehydes, aromatic nitriles and hydroxylamine under microwave irradiation and solvent-free conditions in good-to-excellent yields (Scheme 47) [82].
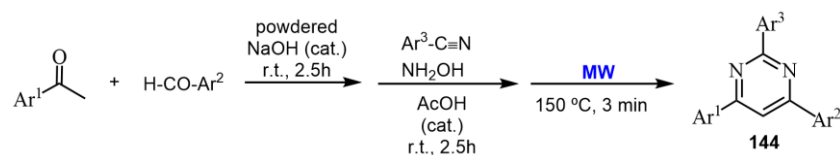
**Scheme 47.** Synthesis of 2,4,6-triarylpyrimidines **144** by [2+2+1+1] annulation from aryl methyl ketones, benzaldehydes, aromatic nitriles and hydroxylamine under MW irradiation.

Guo et al. [83] designed an effective four-component reaction methodology for the synthesis of pyrimidine carboxamides **145** from three different starting compounds: amidines, styrene and *N,N*-dimethylformamide (DMF). Regarding this Pd-catalyzed oxidative process, the versatility of DMF as a dual synthon ought to be mentioned, providing both a one-carbon atom and amide synthons. These roles were proven by isotope labeling experiments, which showed the usefulness of this reaction from easily available starting materials (Scheme 48) [83].
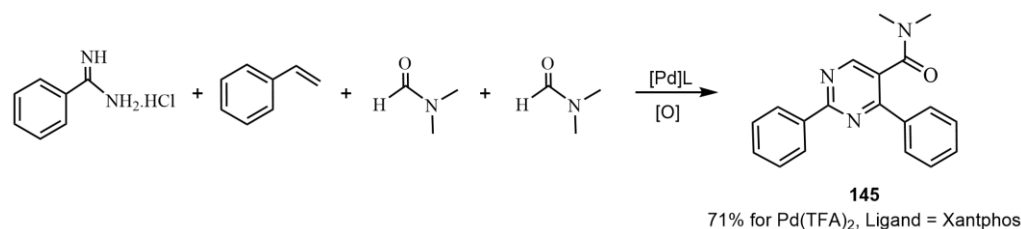


**Scheme 48.** Pd-catalyzed synthesis of pyrimidine carboxamides **145** from amidines, styrene and *N,N*-dimethylformamide (DMF).

### 2.4. Pseudo Five-Component Cycloadditions
[2+1+1+1+1] Cycloadditions

Ding et al. reported a [*C-C+C+N+C+N*] multicomponent cyclocondensation between methyl aryl ketone, two equivalents of aromatic aldehyde and two of ammonium acetate to give pyrimidines **146**. That is to say, five components were involved in the ring formation, but with only three different molecules. Thus, the authors called it a pseudo five-component reaction. The process was catalyzed by triflic acid (Scheme 49) [84].
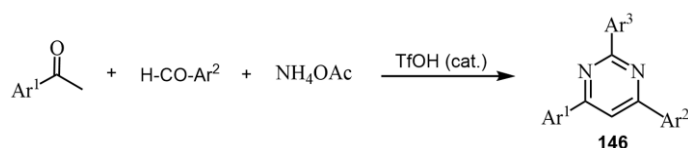


**Scheme 49.** Synthesis of pyrimidines **146** via the multicomponent cyclocondensation between methyl aryl ketone, two equivalents of aromatic aldehyde and two of ammonium acetate.

### 2.5. Miscellaneous

In this section, we have highlighted several reactions due to their peculiarity. For example, a multifunctionalized pyrimidine **149** was synthesized from 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine (**147**) through the treatment with Ph$_3$P. An intermediate spirocycle **148** was obtained with a 66% yield, and its degradation with BnEt$_3$NCl (0.5 equiv.) afforded 4,5,6-trichloropyrimidine-2-carbonitrile (**149**) in an 81% yield. Rational mechanisms to explain the intermediate and product formation were proposed (Scheme 50) [85].
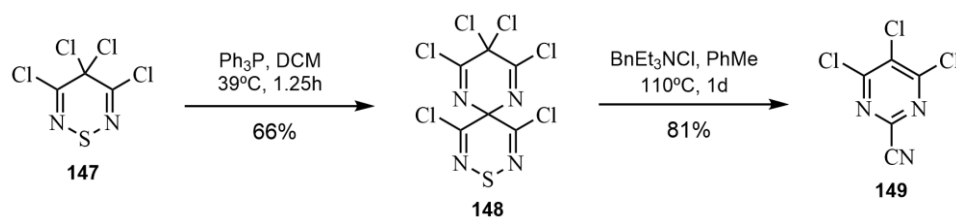
**Scheme 50.** Ph$_3$P-mediated pyrimidine **149** synthesis from 3,4,4,5-tetrachloro-4H-1,2,6-thiadiazine (**147**).

A straightforward synthesis of pyrimidines **153** or **154** via Au(III) or Au(I)/Lewis-acid-catalyzed cascade reactions of propargyl alcohols **150** with 3-amino-benzo[d]isoxazoles **151** has very recently been carried out. The propargyl amine intermediates **152** were readily generated in situ via oxophilic activation by Au(III) or a Lewis acid. After the intermediate cyclization/1,2-H or group migration/aromatization, the desired products were delivered. The selective migratory aptitude was dependent on the steric and electronic properties of the propargylic groups used (Scheme 51) [86].
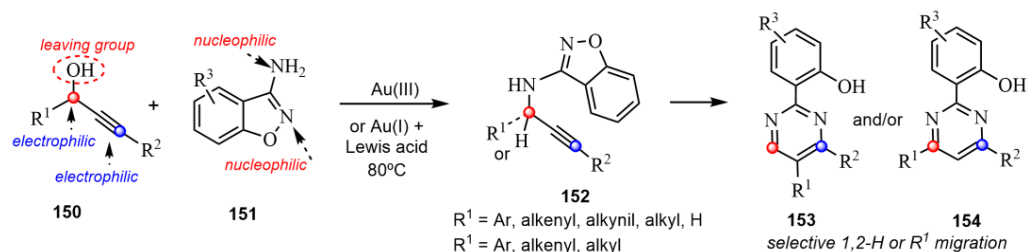


**Scheme 51.** Gold-mediated pyrimidine **153** and **154** synthesis from propargyl alcohols **150** with 3-amino-benzo[d]isoxazoles **151**.

Dofe et al. reported a convenient and facile methodology for the synthesis of a new series of pyrazole and pyrimidine derivatives **156** from chromenones **155** and thiourea under ultrasound irradiation. With regard to pyrimidine derivatives, they have been synthesized in better yields and shorter reaction times compared with the conventional method (Scheme 52) [87].
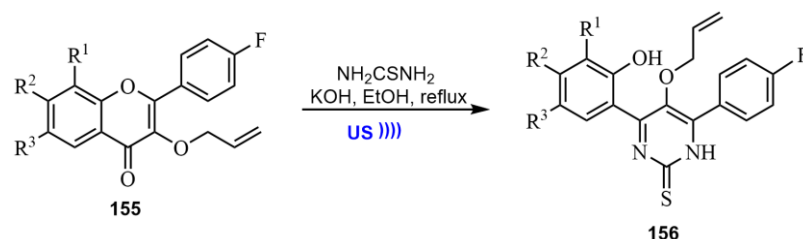


**Scheme 52.** Synthesis of pyrimidines **156** from chromones **155** and thiourea under ultrasound irradiation.

Pyrimidine N-oxides **158** were prepared from β-keto enamides **157** and hydroxylamine hydrochloride by a reaction in r.t. for 5–19 days or at 70–75 °C for 4.5–6.5 h under MW irradiation. The required β-keto enamides **157** were prepared by the MCR of nitriles, trichloroacetic acid and lithiated methoxyallene. N-oxides **158** were obtained in moderate-to-excellent chemical yields (28–61% and 71–96%), together a pyridine side product (2%). The acetylation of the methyl group of the pyrimidine N-oxides **158** was achieved with Ac$_2$O at 130 °C through Boekelheide rearrangement to provide the acetylated **159** (Scheme 53) [88].
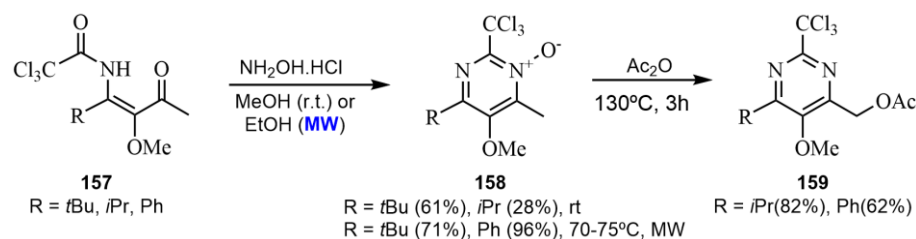
**Scheme 53.** Synthesis of pyrimidine *N*-oxides **158** from β-keto enamides **157** and hydroxylamine hydrochloride under MW irradiation.

### 3. Conclusions

The MCR is a valuable synthetic approach to obtain new pyrimidine derivatives and related compounds, not only by using the Biginelli reaction. Catalysis is of great value in this type of reaction, and a large number of new catalysts have been developed. New perspectives for known catalysts have also been discovered. In addition, the use of various technologies, such as microwave and ultrasound irradiation, also helps to improve reaction conditions and yields. In general, in the period of time considered in this review, increasingly more importance has been given to eco-friendly reactions.

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**Data Availability Statement:** Not applicable here.

**Conflicts of Interest:** The authors declare no conflict of interest.

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