CHAPTER I

INTRODUCTION

1.1 Multicomponent reactions

Multicomponent reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product whereby basically all or most of the atoms contribute to the newly formed product.[1] In an MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product. The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products. The result is clearly dependent on the reaction conditions: solvent, temperature, catalyst, concentration, the kind of starting materials and functional groups. Such considerations are of particular importance in connection with the design and discovery of novel MCRs.[2]

There are many different types of MCR reaction. Some of examples are the following.

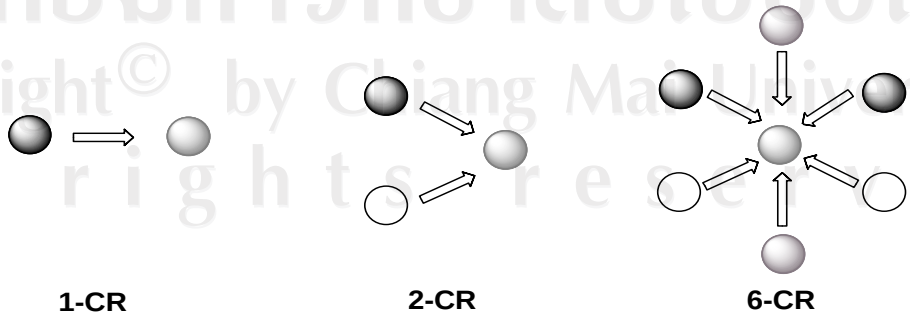
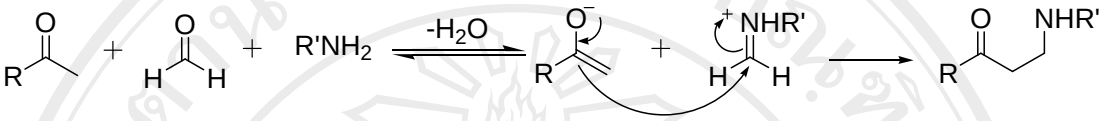


Figure 1 A divergent 1-component reaction, and convergent 2- and 6-component reactions.

1.1.1 Multicomponent Reaction with Carbonyl Compounds

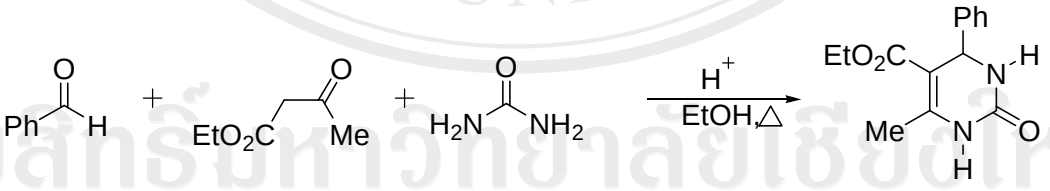
Some of the first multicomponent reactions to be reported function through derivatization of carbonyl compounds into more reactive intermediates, which can react further with a nucleophile. One sample is Mannich reaction:



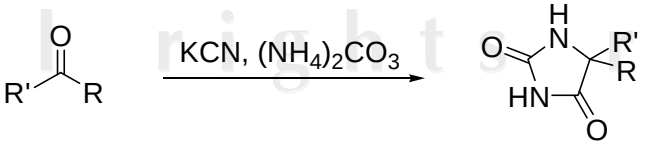
Mannich reaction:

The Mannich reaction via a multicomponent reaction only proceeds if one carbonyl compound reacts faster with the amine to give an imine, and the other carbonyl compound plays the role of a nucleophile. In cases where both carbonyl compounds can react as the nucleophile or lead to imines with the same reaction rate, preforming the intermediate is an alternative, giving rise to a standard multistep synthesis.

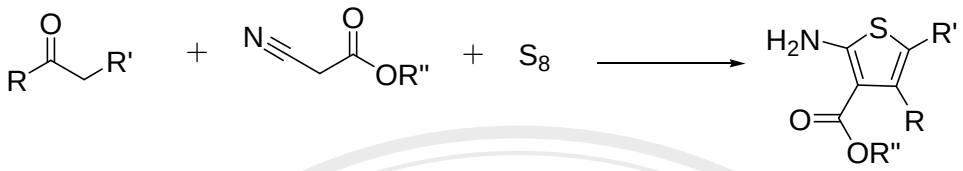
Carbonyl compounds played a crucial role in the early discovery of multicomponent reactions, as displayed by a number of name reactions:



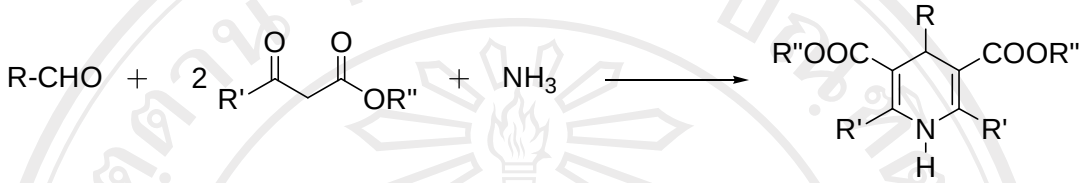
Biginelli reaction



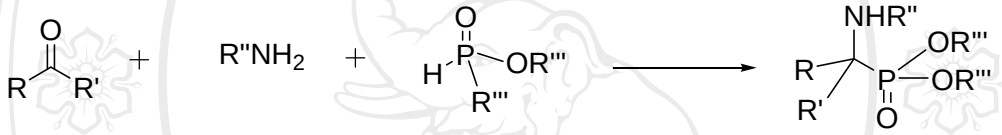
Bucherer-Bergs Reaction



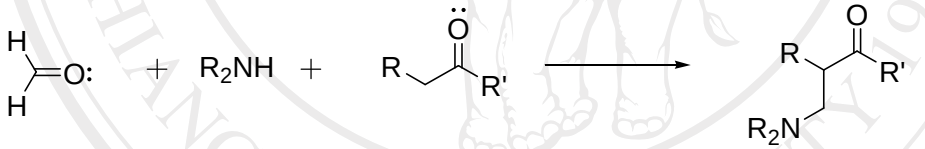
Gewald Reaction



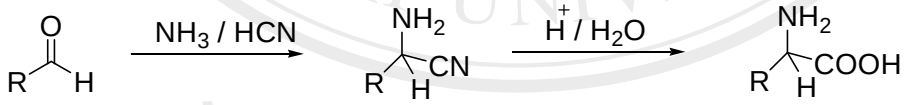
Hantzsch Dihydropyridine (Pyridine) Synthesis



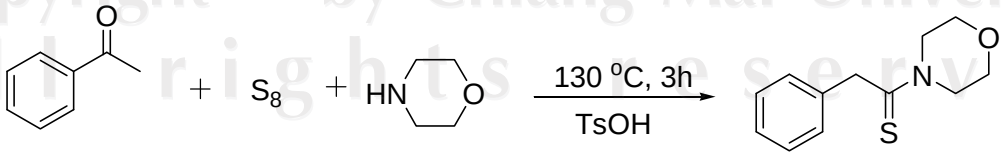
Kabachnik-Fields Reaction



Mannich Reaction



Strecker Synthesis



Kindler Thioamide Synthesis

1.1.2 Isocyanide-Based Multicomponent Reactions

Isocyanides play a dual role as both a nucleophlie and electrophile, allowing interesting multicomponent reactions to be carried out. One of the first multicomponent reactions to use isocyanides was the Passerini reaction. The mechanism (Figure 2) shows how the isocyanide displays ambident reactivity. The driving force is the oxidation of C^{II} to C^{IV}, leading to more stable compounds.

Passerini reaction

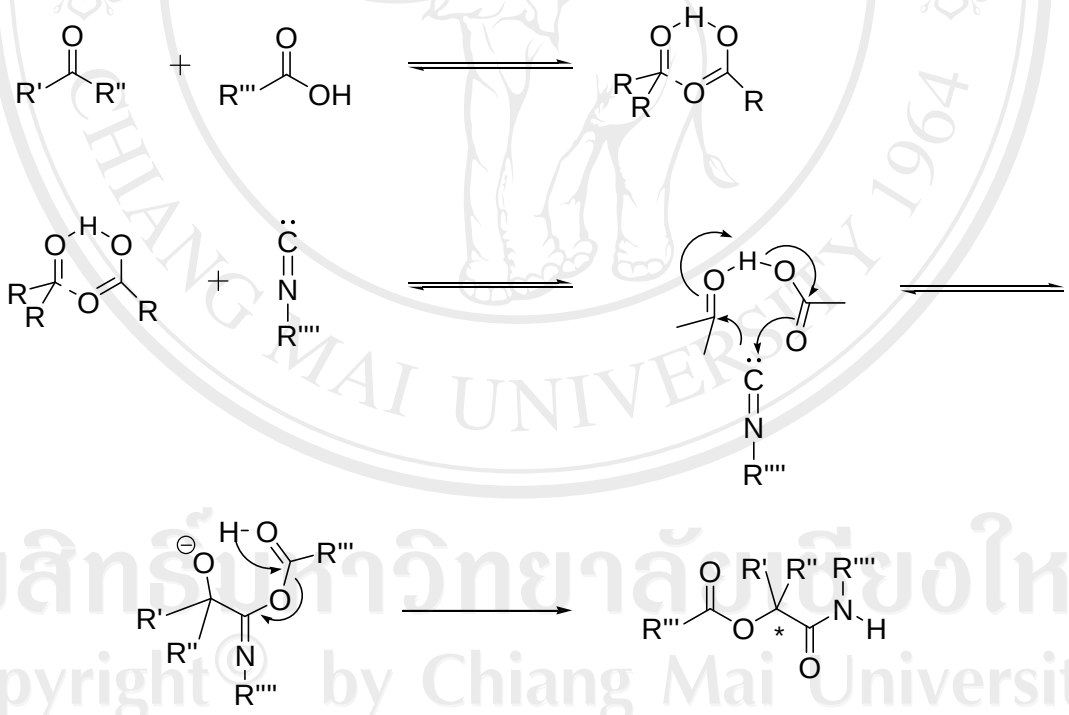
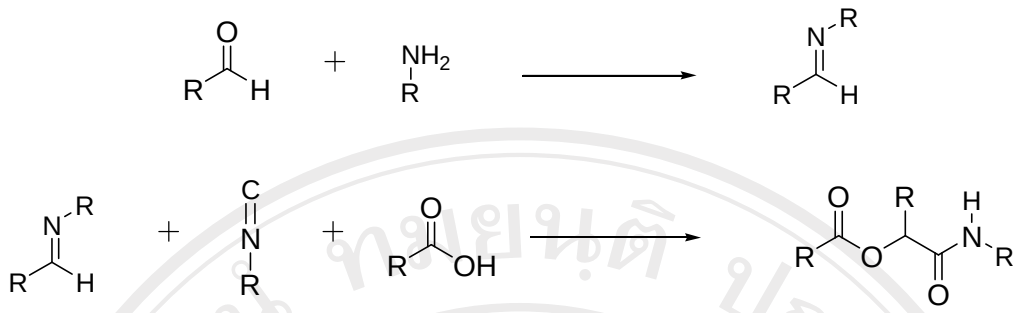


Figure 2 The mechanism of Passerini reaction.

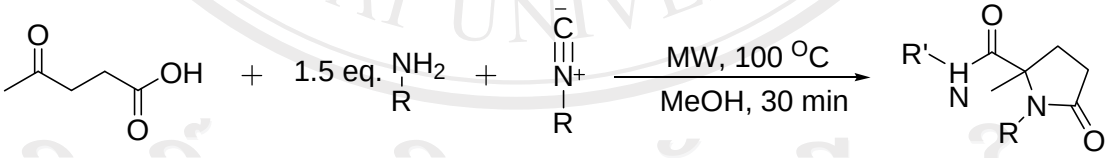
This interesting isocyanide chemistry has been rediscovered, leading to an overwhelming number of useful transformations. One of these is the Ugi Reaction:



Ugi Reaction

Both the Passerini and Ugi Reactions lead to interesting peptidomometic compounds, which are potentially bioactive. The products of these reactions can constitute interesting lead compounds for further development into more active compounds. Both reactions offer an inexpensive and rapid way to generate compound libraries. Since a wide variety of isocyanides are commercially available, an equivalently diverse spectrum of products may be obtained.

Variations in the starting compounds may also lead to totally new scaffolds, such as in the following reaction, in which levulinic acid simultaneously plays the role of a carboxylic acid and a carbonyl compound: [3]



Some very interesting MCRs have even been discovered by preparing a library from 10 different starting materials. By analyzing the products of each combination (three-, four-, and up to ten-component reactions), one is able to select those reactions that show a single main product. HPLC and MS are useful analytical methods, because the purity and mass of the new compounds help to decide rapidly whether a reaction might be interesting to be investigated further. The search and discovery for new MCR's is therefore of considerable current interest.

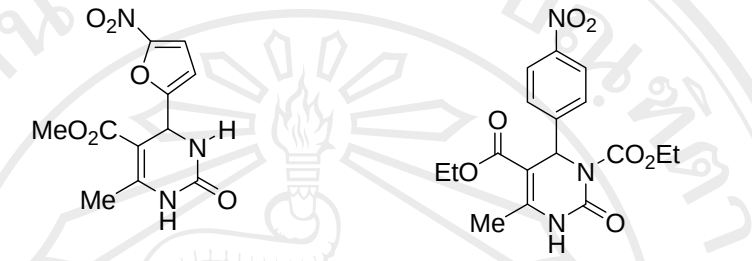
1.2 Dihydropyrimidine Synthesis

3,4-Dihydropyrimidin-2(1*H*)-ones (DHPM) and their sulfur analogs have been reported to possess remarkable pharmacological properties (Figure 3). Some of them have antiviral, antitumor, antibacterial, anti-inflammatory, and antipertensive activities.[4-8] Some are calcium channel modulators[9] and α_{1a} adrenoceptor-selective antagonists.[10] The structurally rather simple DHPM monastrol specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drugs.[11] The batzelladine alkaloids A and B inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy.[12] P. Biginelli (1893)[4a] was the first to synthesize functionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) by the one-pot three-component condensation reaction of an aromatic aldehyde**,** urea, and ethyl acetoacetate in the presence of catalytic HCl in refluxing ethanol.

From the late 19th century through the mid 1970s few papers were published concerning this reaction. However, from the mid-1970s to the present, the utility of this reaction has grown rapidly, especially because some DHPMs possess significant therapeutic and pharmacological properties.[13] These synthetic interests have included both methodological improvements of the original Biginelli reaction conditions and total syntheses of natural products.[13b,14]

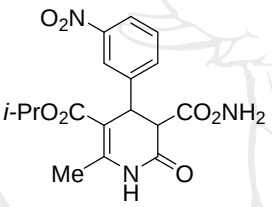
As a result new synthetic methods for the efficient preparation of these heterocyclic compounds are of great importance. Very recently, several modified and improved procedures for the one-pot synthesis of dihydropyrimidinones have been reported, but many of reported methods have drawbacks such as long reaction time, harsh reaction condition, the use of stoichiometric reagents or of toxic and

inflammable solvents, difficult work-ups or low yields of products, and incompatibility with other functional groups in the molecules. Consequently, there is a need to develop new methods which employ less hazardous reagents and solvents, or even better, ones that can be carried out under solvent-free conditions.

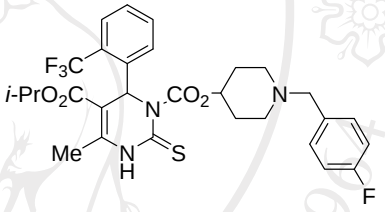


ICI 17025 nitractin

Calcium channel blocker



SQ 32926



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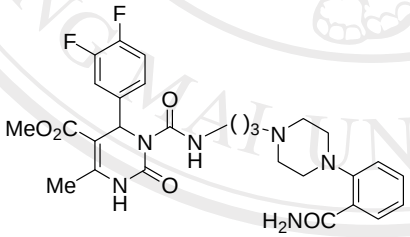
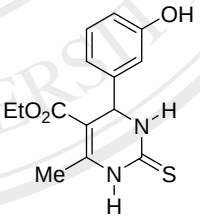
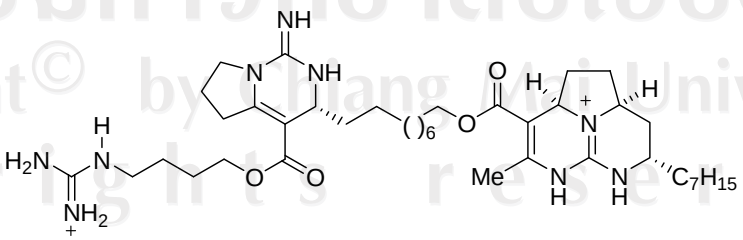


α_{1a}-adrenergic antagonists



monastrol



Batzelladine B

Figure 3 Examples of biologically active DHPMs.

1.3 Microwave-assisted organic synthesis

Traditionally, organic reactions are heated using an external heat source (such as an oil bath), and therefore heat is transferred by conductance. This is a comparatively slow and inefficient method for transferring energy into the system because it depends on the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture. By contrast, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with the polar molecules (for example, solvents, reagents and catalysts) that are present in the reaction mixture.[15]

Microwaves are part of electromagnetic radiation. James Clark Mazwell predicted the existence of electromagnetic waves in 1864. The existence of microwaves was demonstrated for the first time by Hertz in 1888. Microwaves occupy the frequency range between infrared and radiofrequencies. The frequency range of microwave irradiation is 0.3 to 300 GHz; corresponding to wavelengths of 1 cm to 1 m. Wavelengths in this range are also used for RADAR and telecommunication purposes. Therefore microwave ovens use a standard frequency according to ISM bands (Industrial Scientific and Medical frequencies) to avoid interferences with telecommunications. All domestic microwave ovens and dedicated microwave reactors for chemical synthesis operate at a frequency of 2.45 GHz, corresponding to a wavelength of 12.25 cm.[16] There are two types of reactions used for microwave-assisted organic synthesis: multimode reactors and monomode reactors. Domestic microwave ovens as multimode reactors are the most common instruments used in organic synthesis since they are comparatively inexpensive and readily available.[17] The first report on the use of a microwave oven for rapid organic

synthesis was published by Gedye and coworkers in 1986.[18] They tried hydrolysis and esterification reactions in sealed Teflon vessels, heated by a domestic microwave oven.

The short reaction times provided by Microwave-assisted organic syntheis (MAOS) make it ideal for rapid reaction scouting and optimization. Most reagents, catalysts and substrates have been shown to survive temperature extremes for shot periods of time. Similar to traditional chemistry, the success of reactions is as dependent on factors such as solvent and reagent selection as it is upon temperature and time.

1.3.1 Advantages of microwave synthesis[19]

It is becoming evident that microwave approaches often providing faster reactions and improved yields can probably be developed for most chemical transformations that require heat. Higher reaction temperatures can be obtained by combining rapid microwave heating with sealed-vessel technology. In many instances significantly reduced reaction times, higher yields and cleaner reaction profiles will be experienced, allowing foe more rapid reaction optimization and library synthesis. Moreover, solvents with lower boiling points can be used under pressure and be heated at temperature considerably higher than their boiling point. Microwave heating allows direct ‘in core’ heating of the reaction mixture, which results in a faster and more even heating mixture. In addition, specific microwave effects that cannot be reproduced by conventional heating can be exploited-for example, the selective heating of strongly microwave-absorbing catalysts. Microwave heating is more energy efficient than classical oil-bath heating because of direct molecular heating

and inverted temperature gradients. With the modern technology, it is now possible to perform an on-line control of temperature and pressure profiles is possible, which leads to more reproducible reaction conditions. As a result, microwave heating can easily be adapted to automated sequential or parallel synthesis. With the availability of commercial microwave equipment intended for organic synthesis and the development of the solvent-free techniques, microwave assisted organic chemistry has experienced exponential growth since the mid-1990s.

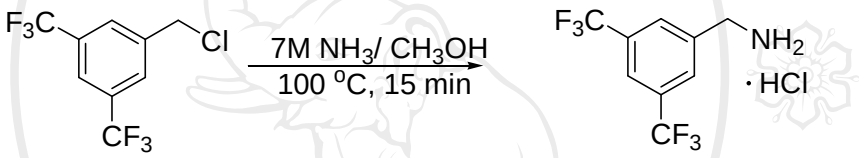
1.3.2 Scope of microwave-assisted organic synthesis [20]

There are very few limitations to the types of chemistries that can be done using microwave heating. To date, the most common types of reactions that have been performed have been in the area of solution-phase synthesis, although the technique has been used in solid-phase synthesis and is rapidly gaining popularity with solid-supported reagents and scavengers and other areas of chemistry, including polymer [21] and solid state chemistry.[22]

1.3.2.1 Solution-phase synthesis

Although the majority of reactions performed in traditional organic chemistry utilizes solvent, in microwave-assisted chemistry the use of solvents has only been recent. This is because most early MAOS was carried out exclusively in domestic microwave ovens, which lack temperature and pressure control and the heating of organic solvents in open vessels often led to violent explosions induced by sparking or electric arcs inside the cavity. The advent of purpose built commercial microwave reactors, incorporating magnetic stirring, temperature and pressure regulation and the ability to process sealed reaction vials in explosion proof cavities, has opened up the entire realm of organic reactions to MAOS. The ability to run high-

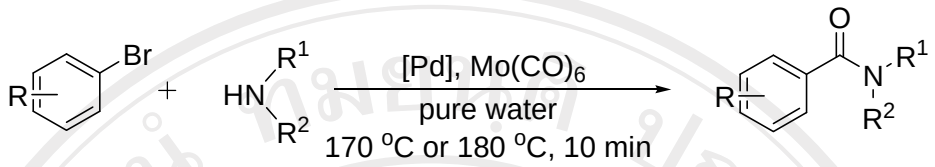
temperature reactions with volatile substrates and low-boiling solvents has allowed access to reactions that were not previously possible by conventional heating techniques. The use of low-boiling points solvents has the added advantage of simplifying workup. This is exemplified by the atom-economical synthesis of hydrogen halide salts of primary amines by microwave irradiation of halides, mesylates and tosylates in 7 M ammonia (NH_3) in methanol (MeOH) at 130 ºC for 0.5-2.5 h.[23]



This procedure avoids the production of significant amounts of secondary amines side products and requires only evaporation of the solvent to afford products in yields generally greater than 90%, which is ideal for parallel synthesis. The fact that hydrogen halide salts of the primary amine products are obtained directly allows even very volatile primary amines to be accessed in good yields.

The use of water as a solvent in organic reactions is becoming increasingly popular in MAOS. Water, when heated well above its boiling point in sealed vessels, become less polar and thus pseudo-organic in nature so that substrates become more soluble.[24] The high heat capacity of water allows for precies control of the reaction temperature. Its lack of flammability makes it safe with pressurized exothermic reactions. Numerous examples of reactions using water as solvent have been reported.[25,26] Most recently aryl bromides were converted to the corresponding secondary and

tertiary benzamides in water, using molybdenum hexacarbonyl [$Mo(CO)_6$] [27,28] as the source of carbon monoxide after only 10 min of microwave heating.[29]



1.3.2.2 Solid-phase synthesis

Microwave heating has been employed to accelerate the reaction rate on insoluble polymers. Polystyrene, Rink amide, Merrifield and Wang resins are examples of a few resins that have been widely used as insoluble polymers in microwave solid-phase synthesis. MAOS speeds up these conventionally sluggish reactions. The polymer backbones are, in general, stable at the high temperature used with MAOS for the short periods of time required for most of these reactions. Portal et al.[30] have recently utilized a resin-bound analytical construct to quantify the reactivity of a range of monomers in the Ugi reaction. The effect of variations in concentration on monomer reactivity and product profiles were also rapidly determined using this approach, opening up the way for studying, in a single pot, multiple reactions with a broad range of monomers under identical and self-consistent reaction conditions. For a comprehensive overview of applications of MAOS in solid-phase synthesis, the reader can refer to reviews [31, 32, 33] and references therein.

1.3.2.3 Solid-supported reagent in solution-phase synthesis

Solid-supported reagents are becoming increasingly popular in solution-phase chemistry, because workup and isolation of products simply involves filtration of the resin and evaporation of the solvent. Desai et al.[34] recently described a rapid

and easy route to formamides by microwave-assisted *N*- formylation of primary and secondary amines using an insoluble polymer-supported reagent as a formylating agent. Microwave irradiation furnished the corresponding formamides in high yields, with reduced reaction time and solvent volume compared with classical approach.

The example of solid-supported reagent in solution-phase microwave synthesis is shown in Figure 4.

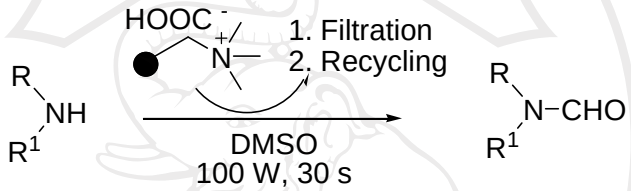


Figure 4 Example of solid-supported reagent in solution-phase microwave synthesis

1.3.2.4 Solvent-free synthesis

In the past, MAOS has been carried out under dry or solvent-free conditions, mainly to avoid the hazards of using and flammable organic solvents in domestic microwave ovens. Although the solvent-free technique claims to be environmentally friendly, as it avoids the use of solvents, this is debatable because solvents are often used to pre-absorb the substrates onto, and wash the products off, the solid supports. For neat solids, it is very difficult to obtain a good temperature control at the surface of the solids and local hot spots might be encountered. This can sometimes give rise to unexpected results and inevitably lead to problems regarding reaction predictability, reproducibility lead to problems regarding reactions requiring

high temperature; however, the presence of microwave-absorbing solids can be advantageous. The example of solvent-free microwave reaction is shown in Figure 5.

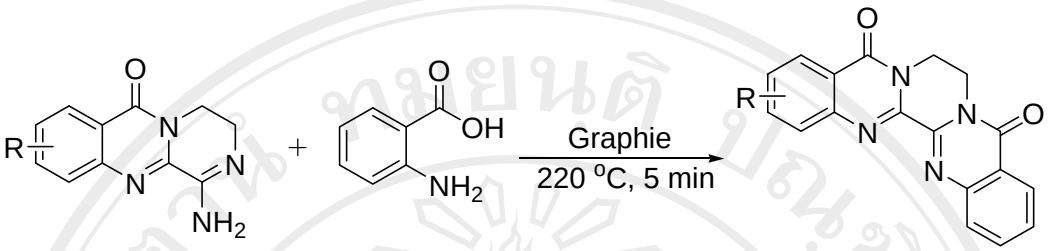
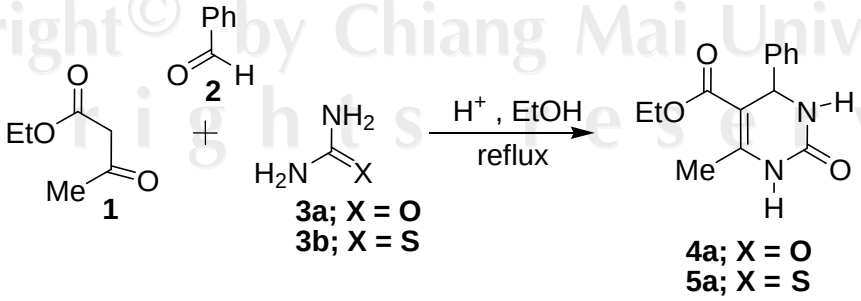


Figure 5 Example of solvent-free microwave reaction

1.4 Literature review

In 1893, the Italian chemist Pietro Biginelli (University of Florence) for the first time reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate **1**, benzaldehyde **2**, and urea **3a**.[4a] The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling the reaction mixture was identified as 3,4-dihydropyrimidin-2(1*H*)-one 4 (Scheme 1). This reaction is nowadays referred to as the "Biginelli reaction", "Biginelli condensation" or as the "Biginelli dihydropyrimidine synthesis".

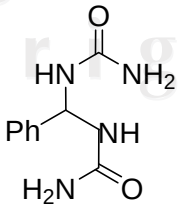


Scheme 1 The original Biginelli dihydropyrimidine condensation

While the early examples of this cyclocondensation process typically involved a β-ketoester, aromatic aldehyde and urea, the scope of this heterocycle synthesis has now been extended considerably by variation of all three building blocks, allowing access to a large number of multifunctionalized pyrimidine derivatives. For this particular heterocyclic scaffold the acronym DHPM has been adopted in the literature and is also used throughout this chapter. Owing to the importance of multicomponent reactions in combinatorial chemistry there has been renewed interest in the Biginelli reaction, and the number of publications and patents describing the synthesis of novel DHPM analogues is constantly growing.

1.4.1 Mechanistic studies

Since the 1930s several mechanism pathways have been proposed for the Biginelli reaction.[13a-b, 35, 36, 37] In 1933 Folkers and Johnson reported that one of three intermediates **6-8**, was likely present in this reaction.[35] These included bisureide **6** which was formed by a condensation reaction between the aryl aldehyde and the urea followed by subsequent attack of the resultant imine with another equivalent of urea. Also, 3-ureido ethyl acrylate **7** arose from a condensation reaction between the β-ketoester and urea. Finally, the reaction of the β-ketoester and the aldehyde delivered the aldol adduct **8**.



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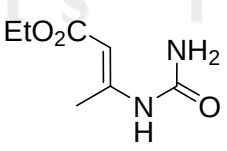

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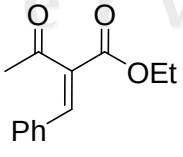

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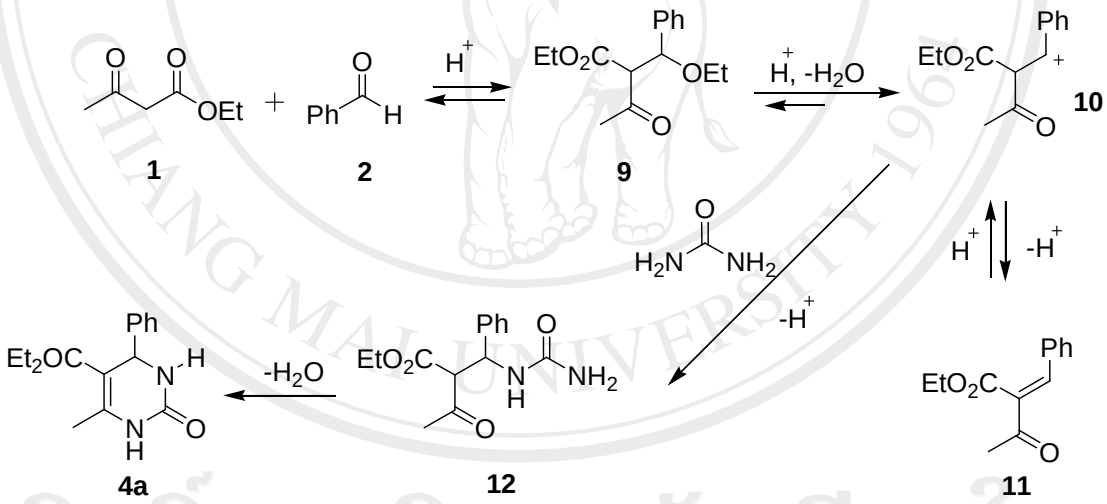
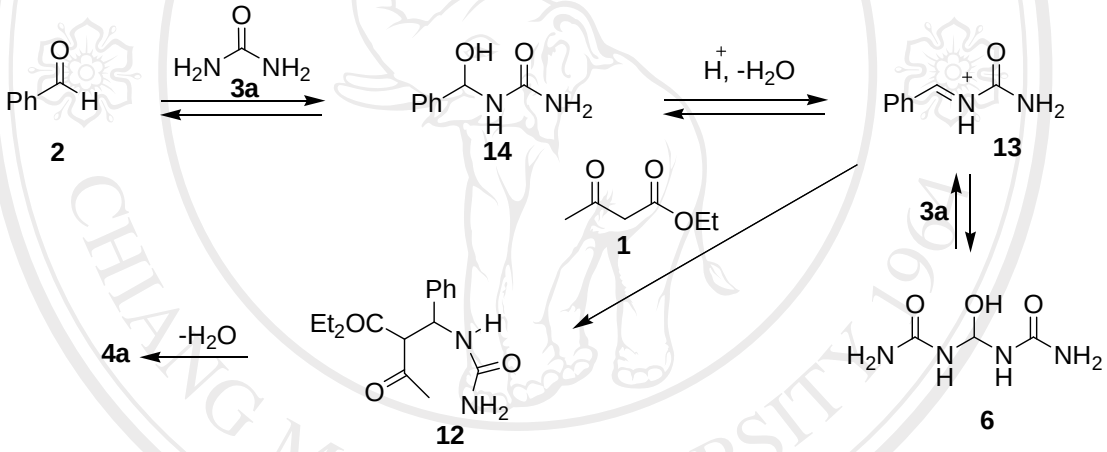
Forty years after the initial proposes, Sweet and Fissekis[36] proposed a more detailed pathway involving a carbenium ion species. According to these authors the first step involved an aldol condensation between ethyl acetoacetate **(1)** and benzaldehyde **(2)** to deliver the aldol adduct **9**. Subsequence dehydration of **9** furnished the key carbenium ion **10** which was in equilibrium with enone **11**. Nucleophilic attack of **10** by urea then delivered ureide **12**. Intramolecular cyclization produced a hemiaminal which underwent dehydration to afford dihydropyrimidinone **4a**. These authors demonstrated that the carbenium species was viable through synthesis. After enone **11** was synthesized, it was allowed to react with *N*-methyl urea to deliver the mono-*N*-methylated derivative of DHPM **4a** (Scheme 2).



Scheme 2 The mechanism of the Biginelli reaction proposed by Sweet and Fissekis.

The mechanism was then reexamined 25 years later in 1997 by Oliver Kappe and co-workers,[37] by using ^{1}H and ^{13}C spectroscopy to support the argument that the key intermediate in the Biginelli reaction was the iminium species **13**. In the event, **2** reacted with **3a** to from an intermediate "hemiaminal" **14** which subsequently dehydrated to deliver **13**. Iminum cation **13** then reacted with **1** to give **12**, which

underwent facile cyclodehydration to give **4a**. Kappe also noted that in the absence of **1**, bisureide **6** was afforded as a consequence of nucleophilic attack of **13** by urea (**3a**). This discovery confirmed the conclusion of Folkers and Johnson in 1933.[35] As far as the proposal from 25 years earlier by Sweet and Fissekis,[36] Kappe saw no evidence by ^{1}H and ^{13}C spectroscopy that a carbenium ion was a required species in the Biginelli reaction. When benzaldehyde **(2)** and ethyl acetoacetate (**1)** were mixed under standard Biginelli conditions the requisite aldol product **9**, which was necessary for the formation of carbenium ion **13**, was not detected (Scheme 3).



Scheme 3 The mechanism of the Biginelli reaction proposed by Kappe.

1.4.2 Reaction conditions

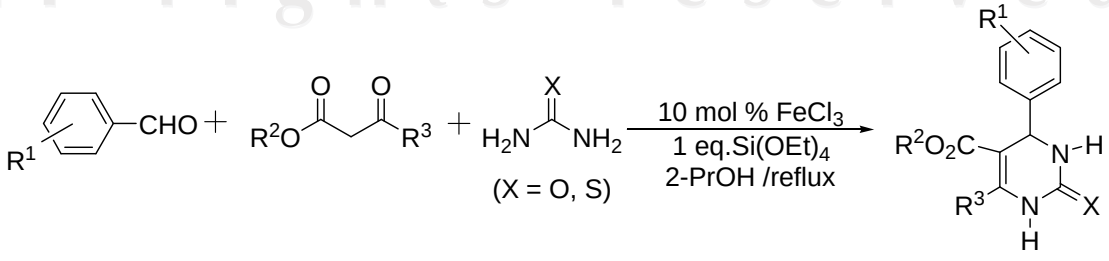
There is a great variety of suitable reaction conditions for Biginelli condensations. For the condensation of ethyl acetoacetate with benzaldehyde and urea, at least 100 different experimental conditions are now known.[38] Traditionally, Biginelli condensations are carried out in a solvent such as ethanol or methanol, but more recently aprotic solvents such as tetrahydrofuran,[39,40,41,42] dioxane[43] or acetonitrile [44-48] have also been used successfully. In some cases, it is necessary to use

acetic acid as a solvent.[49-51] Biginelli reactions in water and ionic liquids are also known. A recent trend is to perform the condensation without any solvent with the components either adsorbed on an inorganic support or in the presence of a suitable catalyst.[52]

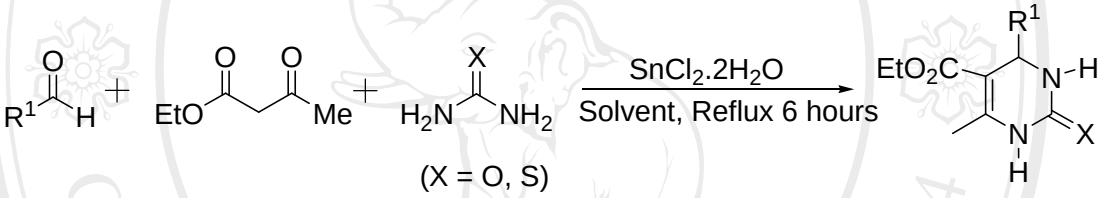
The Biginelli condensation is strongly dependent on the amount of acidic catalyst present in the reaction medium.[35] Traditionally, strong Brønsted acids such as hydrochloric or sulfuric acid have been employed,[13a] but nowadays the use of lewis acids such as BF_3OEt_2 and CuCl,[39] $LaCl_3$,[53,54] $FeCl_3$,[55-61] $NiCl_2$,[58,62] $Yb(OTf)_3$,[52, 63,64] $La(OTf)_3$,[65] $InCl_3$,[66] $InBr_3$,[67] $In(OTf)_3$,[68] LiBr,[42,46] $CoCl_2$,[54] $BiCl_3$,[44] $LiClO_4$,[69] $Mn(OAc)_3$,[70] $ZrCl_4$,[71] $Cu(OTf)_2$,[45] $CuCl_2$,[72] $Bi(OTf)_3$,[73] $CeCl_3$,[56] VCl_3,[75] $Zn(OTf)_2$,[76,77] $Sm(NO_3)_3$,[78] $SmCl_3$ [79] is prevalent.

A representative group of Lewis acids listed above was carried out with the traditional Biginelli conditions. The yields are greatly improved for aromatic aldehydes bearing an electron-donating or electron-withdrawing substituent.

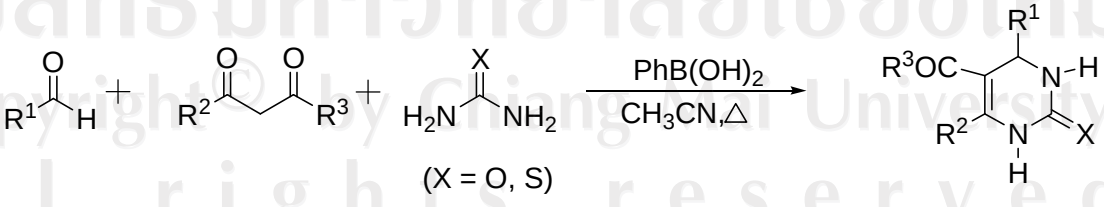
Recently, Cepanee and co-worker reported an efficient method for the Biginelli reaction of aldehydes, acetoacetate esters and urea employing tetraethyl orthosilicate in the presence of ferric chloride. These improved reaction conditions allow the preparation of a wide variety of substituted dihydropyrimidinones (including sterically encumbered ones) in high yields and purity under under mild reaction conditions: [80]



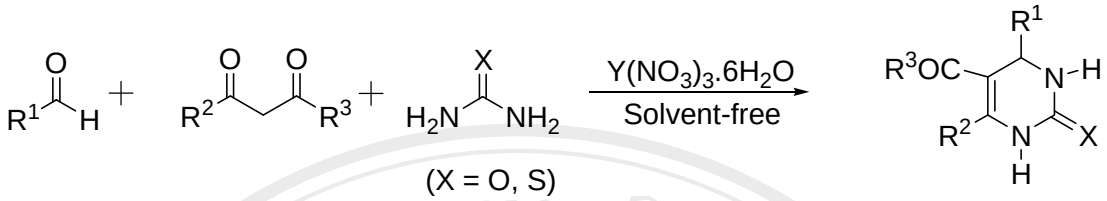
Russowsky and co-workers[81] have described the ability of $SnCl_2.2H_2O$ as catalyst to promote the Biginelli three-component condensation reaction from a diversity of aromatic aldehydes, ethyl acetoacetate and urea or thiourea. The reaction was carried out in acetonitrile or ethanol as solvents in neutral media and represents an improvement of the classical Biginelli protocol and an advantage in comparison with $FeCl_3.6H_2O$, $NiCl_2.6H_2O$ and $CoCl_2.6H_2O$ which were used with HCl as co-catalyst. The synthesis of 3,4-dihydropyrimidinones was achieved in good to excellent yields:



Debache and co-workers[82] have demonstrated the synthesis of 3,4-dihydropyrimidinone derivatives. The reaction was achieved in good to excellent yields using phenylboronic acid as catalyst to promote the Biginelli three-component condensation of a diversity of aromatic aldehydes, ethyl acetoacetate and urea or thiourea:

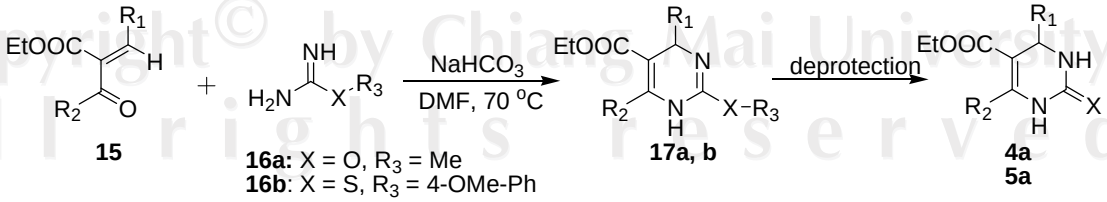


It was found that yttrium (III) nitrate hexahydrate can be used as a catalyst for one-pot synthesis of large size dihydropyrimidinones. This catalyst has been shown to have a high activity and high yield: [83]



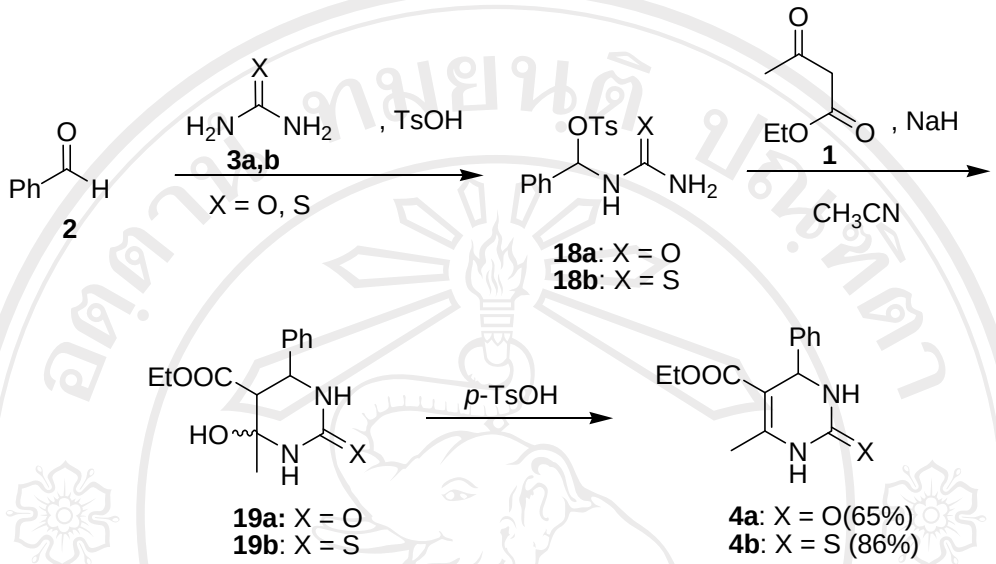
In addition, material such as an silica/H_2SO_4[84] or silica aerogel-ion oxide nanocomposites[85] have been reported as efficient supported catalysts for the Biginelli reaction. Other reported reaction mediators include amidosulfonoc acid,[86-88] CBr_4,[89] NH_4Cl,[90] *N*-butyl-*N,N*-dimethyl-α-phenylethylammonium bromide,[91] p-toluenesulfonic acid,[92-94] tartaric acid,[13a] polyphosphate ester,[40,95,96] TMSCl/NaI,[47] TMSCl/DMF,[48] TMSOTf,[97] boric acid,[98] KH_2PO_4,[99] $KHSO_4$,[100] $CdSO_4$,[101] triphenylphosphonium perchlorate,[102] and iodine.[35]

In addition to modification of the catalyst, several variants of the Biginelli reaction have emerged as viable alternative methods. These methods require pre-formation of intermediates that are normally formed in the one-pot Biginelli reaction. Atwal and coworkers reported the reaction between aldol adducts **15** with urea **16a** or thiourea **16b** in the presence of sodium bicarbonate in dimethylformamide at 70 ^oC to give 1,4-dihydropyrimidines **17**.[103] DHPM **4a** and **5a** was then produced by deprotection of **17**.

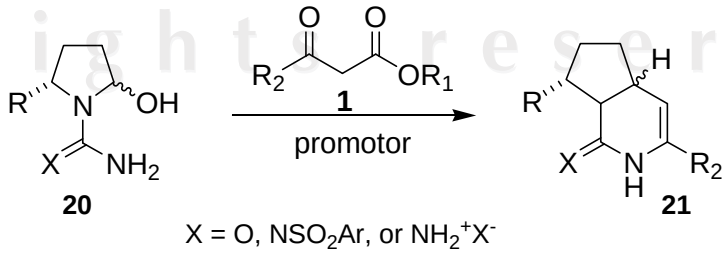


Furthermore, Shutalev and coworkers reported a two-step modification.[104] Urea **3a** or thiourea **3b** was condensed with **2** in the presence of *p*-toluenesulfonic acid to deliver α-tosylderivative **18**. The enolate of **1** was then allowed to react with

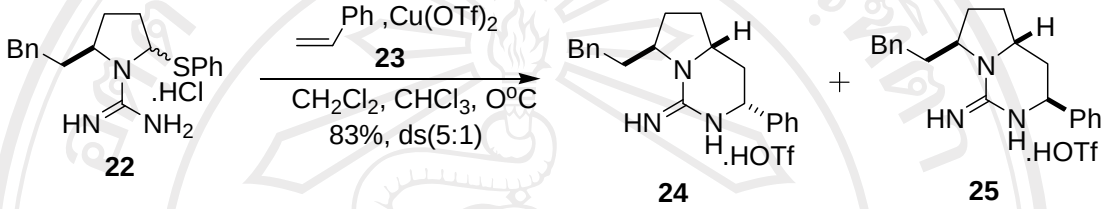
18 to give a substitution product which then cyclized to give "hemiaminal" **19**. Dehydration of the hemiaminal with *p*-toluenesulfonic acid delivered **4a** and **5a**.



Moreover, Overman and Rabinowiz developed an intramolecular variant of the Biginelli reaction.[14a] This tethered Biginelli reaction has been important in the synthesis of a variety of natural products. This modification involved guanidine hemiaminal **20** reacting with 1,3-dicarbonyl **1** in the presence of a promoter such as morpholinium acetate or piperidinium acetate to deliver DHPM **21** with stereochemical control. For instance, ureas (X = O) and *N*- arylsulfonylguanidines (X = NSO_2Ar) afforded the *cis*-stereochemistry, while the unprotected guanidine (X = NH_2^+) furnished the *trans*-geometry around the pyrrolidine ring.

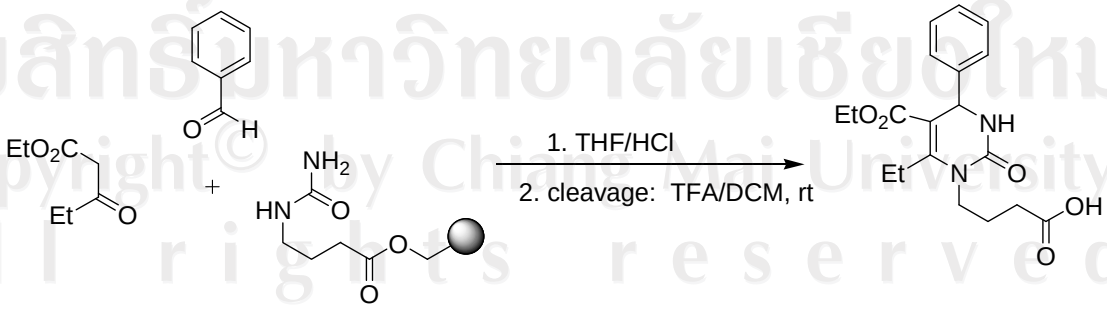


Overman has extended his tethered Biginelli reaction to include alkenes and dienes instead of β-keto eaters to deliver **24** diastereoselectively over **25** in the presence of $Cu(OTf)_2$.[14e]



Apart from these conventional solution-phase methods, it is also possible to employ polymer-supported reagents to aid in the purification and work-up protocol. Polymer-assisted solution-phase chemistry using polymer-supported Lewis acid (Yb-(III)-reagent supported on Amberlyst 15) in combination with polymer-supported urea scavenging resins (Amberlyst 15 and Ambersept 900 OH) permits a rapid parallel Biginelli synthesis with a simple and efficient purification strategy.[105]

Solid-phase protocol allows an even higher degree of throughput and automation.



For example, a γ-aminobutyric acid-derived urea was attached to Wang resin using standard procedures. The resulting polymer-bound urea was then condensed with an excess of a *β*-ketoester and aromatic aldehydes in the presence of a catalytic amount

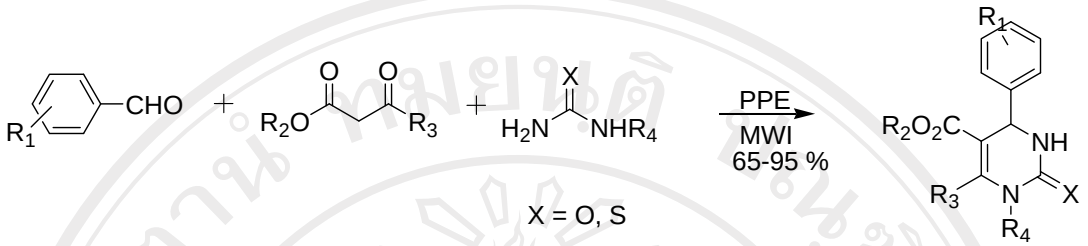
of hydrochloric acid to afford the corresponding immobilized DHPMs. Subsequent cleavage of the product from the polystyrene resin with trifluoroacetic acid provided DHPMs in high yields and excellent purities.[41]

Aliphatic aldehydes typically provide only moderate yields in the Biginelli reaction unless special reaction conditions are employed, such as Lewis-acid catalysts or solvent-free methods, or the aldehydes are used in a protected form. The C4-unsubstituted DHPM can be prepared in a similar manner employing suitable formaldehyde synthons. Of particular interest are reactions where the aldehyde components is derived from a carbohydrate. In such transformations, DHPMs having a sugar-like moiety in position 4 (C-nucleoside analogues) are obtained. Also of interest is the use of masked amino acids as building blocks. In a few cases, bisaldehydes have been used as synthons in Biginelli reactions.

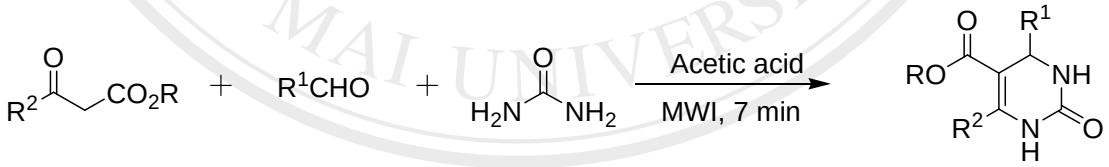
Thioureas follow the same general rules as ureas, although longer reaction times are required to achieve good conversion. Yields are typically lower when compared to the corresponding urea derivatives. In some instances it is also possible to react protected ureas or thioureas (isoureas), or guanidines under weak basic conditions with the aldehyde and CH-acidic carbonyl component (or with a precondensed Knoevonagel-type enone) to yield the corresponding protected DHPMs. This latter method, using precondensed enones as building blocks has been frequently referred to as the "Atwal modification" of the Biginelli reaction. [106-108]

Over the last several years, Kappe research group has also explored the use of microwaves to increase the reaction rate and efficiency of the Biginelli reaction. In one example, polyphosephate ester (PPE) was used as the promoter under microwave

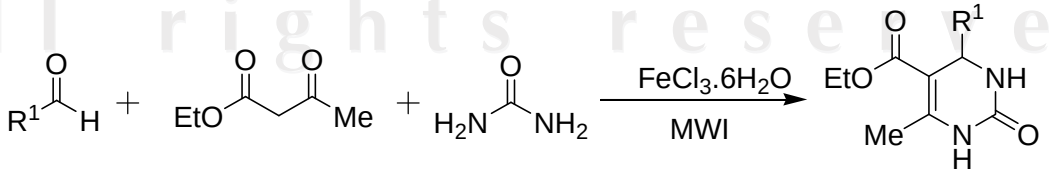
conditions to deliver a variety of DHPMs in yields ranging from 65-95% with reaction times typically below 2 min.[95]



Sujatha and co-workers[109] have synthesized a series of 4-(substituted)-3,4-dihydropyrimidinone derivatives by heating 1,3-dicarbonyl compounds, urea, and aromatic aldehydes in acetic acid under microwave irradiation conditions. The cardiovascular effects of 3,4-dihydropyrimidinones were studied on isolated perfused frog heart at different dose levels and compared with the activity of dioxin. The interaction of 3,4-dihydropyrimidinones with β-blocker and calcium channel blocker was also investigated. Compound (R = Et, R^1 = 4-HOC_6H_5, R^2 = CH_3) emerged as the most interesting compound in this series with potential cardiotonic activity.



Recently, it was found that ferric chloride hexahydrate could be used under solvent-free condition and microwave irradiation condition. Ferric chloride hexahydrate increased the catalytic activity.[110]



One major drawback of the original method, apart from the long reaction times involving reflux temperatures (2-12 h, 80 °C), is that, when using more complex building blocks, the product yield is frequently only moderate (20-60%). Implementing sealed-vessel microwave irradiation at 120 °C in the Biginelli protocol provides significant rate-enhancements and higher product yields (30-90%), and the reaction is complete in 10-20 minutes.[111]

1.5 Aims of this research

1.5.1 To study Biginelli reaction using CsF-Celite under solvent free condition.

1.5.2 To study the effect of substituent on the aromatic aldehydes.

1.5.3 To study Biginelli reaction using conventional method and microwave method.