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A Review on Solvent-Free Microwave Assisted Condensation Reactions

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Abstract

From preceding three decades, solvent-free microwave assisted reactions are being concerned. This technique eliminates waste, avoid the use of toxic solvents and serve a flexible platform for chemical reactions. In this review, our aim is to corroborate recent data available on solvent-free microwave assisted condensation reactions.

Key words: Aldol condensation, Knoevenagel condensation, Biginelli condensation, Mannich condensation, Kabachnik-Fields Reaction.

Introduction

In the recent years, organic chemistry directed towards green chemistry has attained great interest, which leads to new environmental friendly procedures to save resources and energy. Solvent-free microwave assisted techniques create new opportunities to perform reactions that are not feasible via conventional methods [1, 2]. Gedye *et al.* first used microwave irradiation techniques to carry out chemical reaction [3]. Now-a-days, solvent-free microwave assisted reactions are gaining importance because of their advantages over the conventional method in terms of minimum waste, shorter reaction time and higher yield (Figure 1) [1, 2].

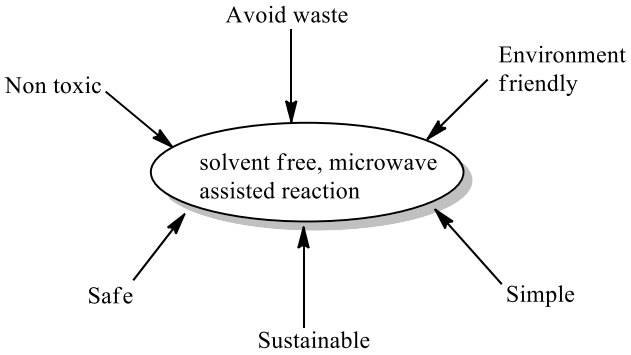

Figure 1. Advantages of solvent-free microwave assisted reactions.

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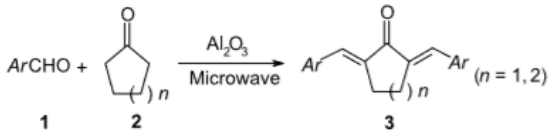
There are three categories of solvent-free microwave assisted reactions namely, reactions using solid-liquid phase transfer catalysis (PTC), reactions using neat reactants and reactions using solid mineral supports. Reactions of neat reactants require at least one liquid molecule as starting material [4].

In such case, two different mechanisms are possible, either the liquid gets adsorbed onto the solid surface or the solid gets partially soluble in liquid phase [4, 5]. The second category is reaction using phase transfer catalyst in the absence of solvent [6]. The third category is a reaction between supported reagents on solid mineral supports in "dry media" by impregnation of compounds on silica, alumina or clay [7]. Solvent-free microwave irradiation technique is a more efficient method compared to a conventional method to carry out condensation reactions [8].

Condensation reactions are the reaction of two or more molecules with the elimination of water or other small molecules. The conventional method for the formation of the condensed product is often slow and inefficient. But solvent-free microwave irradiation reactions consume lesser time and results in higher yields [8]. Elegant reviews by Tanaka [9], Bougrin [10], Nóra [11], Madhvi [12] summarized various microwave assisted reactions. In this review, we have summarized important solvent-free, microwave assisted condensation reactions. Here, we have discussed Aldol condensation, Knoevenagel condensation, Biginelli condensation, Mannich reaction and Kabachnik-Fields reaction.

Aldol-condensation reactions

An aldol condensation is a condensation reaction in which aldehyde or ketone reacts with a carbonyl compound to give β-hydroxyaldehyde or β-hydroxyketone, followed by dehydration to give a conjugated enone [13]. Abbas *et al.* reported Aldol-condensation reaction via solvent-free microwave irradiation technique. The reaction of aromatic aldehydes 1 and ketones 2 in the presence of acidic alumina under microwave irradiation resulted in aldol condensed product 3 in good yield. Use of acidic alumina as a catalyst resulted in good yield within 2.5-8 min whereas in conventional methods use ofcatalyst $FeCl_3.6H_2O$ needs 6-10 hours. Authors used basic, acidic and neutral alumina to study the effect of a catalyst on reaction yield (Table 1). Among the three different catalysts acidic alumina resulted in high yield compared to the basic and neutral alumina. This reaction eliminates the use of toxic solvents. Short reaction time and non-aqueous workup are the major advantages of this method (Scheme 1) [14].

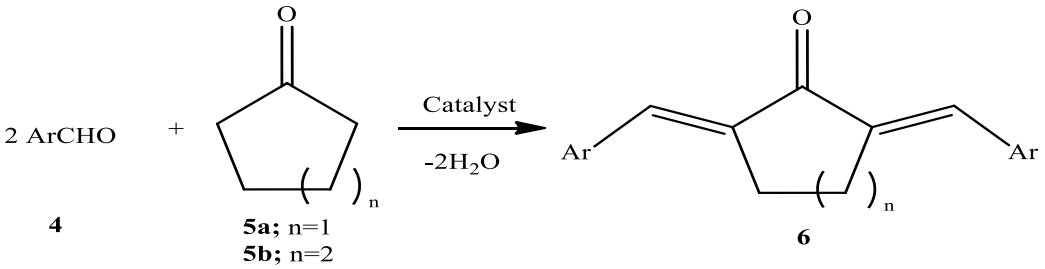


Scheme 1. Aldol condensation reaction using Al_2O_3.

Table 1. Aldol condensation reaction using different alumina

Entry	Types of alumina	Time/min	Yield/%
1	Acidic alumina	4	98
2	Basic alumina	10	-
3	Neutral alumina	10	10

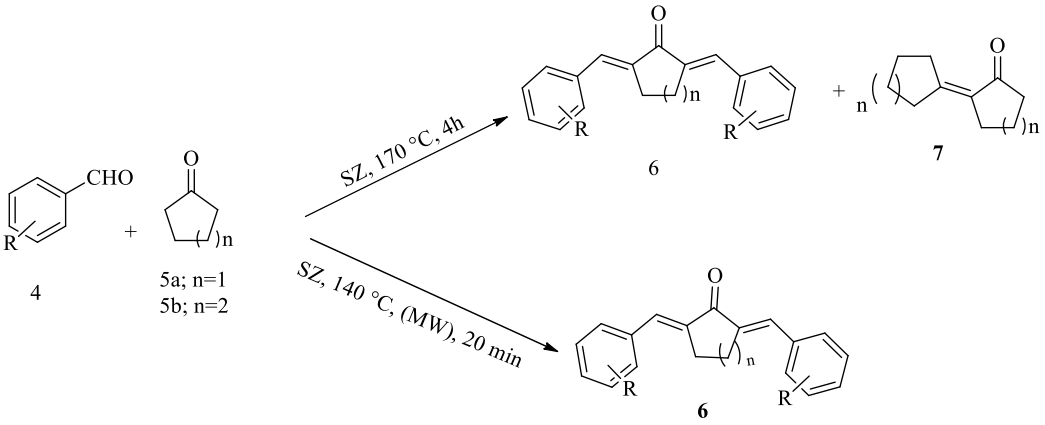
Kira e*t al.* reported synthesis of substituted cycloalkanones via solvent-free microwave irradiation reaction. Treatment of aromatic aldehydes 4 and cycloalkanones 5 in the presence of pre-activated sulphated-zirconia (SZ) catalyst is to get cycloalkanones 6 in good yield (Scheme 2). After the completion of reaction, the reaction mixture was poured into the methanol to dissolve the product and the undissolved catalyst was filtered and reused [15].



Ar = Benzaldehyde, 4-OMe-benzaldehyde, 4-NO2-benzaldehyde, 2-OMe-benzaldehyde
2-Cl-benzadehyde, 2,4-diOMe-benzaldehyde, 3-NO2-benzaldehyde

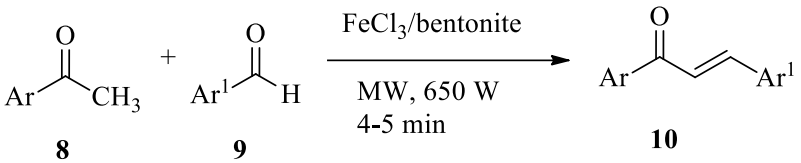
Scheme 2. SZ catalysed Aldol condensation reaction

The GC-MS analysis revealed that the same reaction by thermal heating resulted self-condensed product 7 in higher proportions whereas reaction under microwave irradiation resulted selectively cross-condensed product 6 as the major product. Microwave irradiation activates the aldehydic group and promotes cross condensation reaction rather than self-condensation reaction (Scheme 3) [15].



Scheme 3. SZ catalyzed Aldol condensation reaction under thermal and microwave irradiation

Muthuvel *et al.* synthesised $FeCl_3$/bentonite catalyzed chalcones under solvent-free, microwave irradiation technique in good yield in the range of 80-88%. An equimolar mixture of ketones 8 and aldehydes 9 reacted in the presence of new solid acid catalyst $FeCl_3$/bentonite at 650W for 4-5 min to give aldol condensed product 10 (Scheme 4).

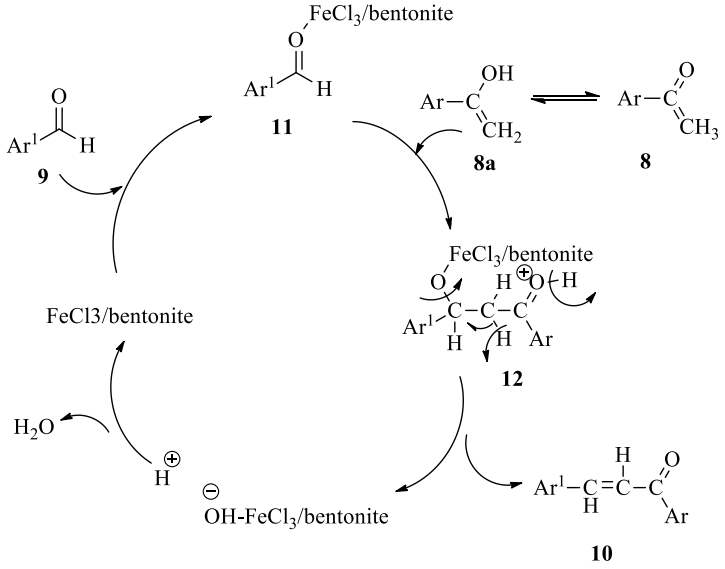


Ar = Ph, 4-$N(CH_3)_2$Ph, 4-NH_2Ph, 4-F-Ph, 2,4$Cl_2C_6H_4$, 4-(OH)-Ph, 1-Naph, 2-Naph, Biph

Ar^1 = Ph, 4-ClPh, 1-Naph, 4-OCH_3Ph, 1-Pyrene,

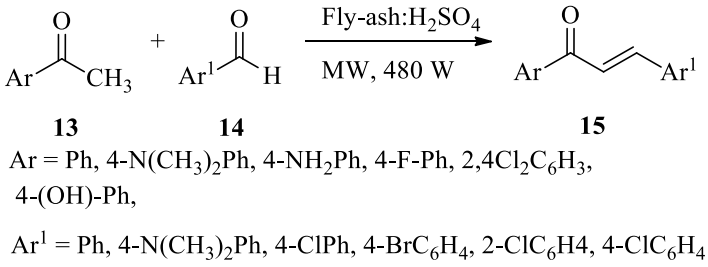
Scheme 4. $FeCl_3$/bentonite catalysed aldol condensation reaction.

The catalyst showed similar activity even after fifth run. The mechanistic pathway for the synthesis of compound 9 is shown in Scheme 5. Initially**,** the catalyst $FeCl_3$/bentonite attacks the aldehydic carbonyl group to give an intermediate which was further attacked by enol group of ketone to give another intermediate. In the final step, the catalyst initiates dehydration reaction of condensed product to give chalcone. The authors also studied the effect of amount of catalyst on the reaction yield. The percentage yield of product increased from 84-87% with increase in the amount of catalyst from 0.1-0.4 g beyond which no further increase in the yield was observed [16].



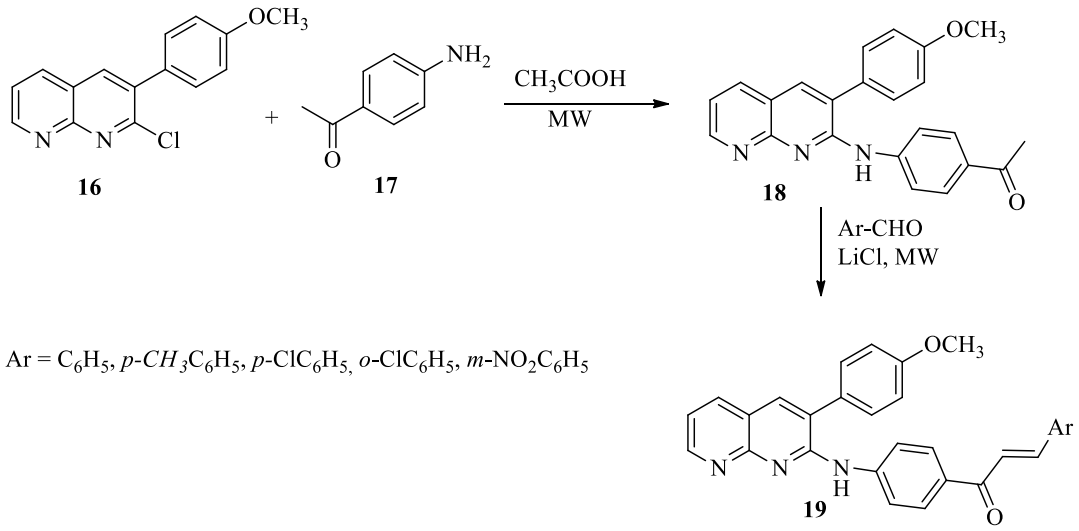
Scheme 5. Mechanistic pathway for the synthesis of chalcone using $FeCl_3$/bentonite catalyst.

Tirunarayanan *et al.* reported fly-ash:H_2SO_4 catalyzed solvent-free synthesis of chalcones via cross aldol-condensation reaction. An equimolar mixture of aryl ketone 13 and aldehyde 14 in the presence of fly-ash:H_2SO_4 subjected to microwave and heated for 5-6 min at 480 W to yield final product 15. After the completion of reaction, the reaction mass was cooled followed by product was separated. The insoluble catalyst was filtered, dried and recycled. This method gave very good yield (more than 90%) (Scheme 6) [17].



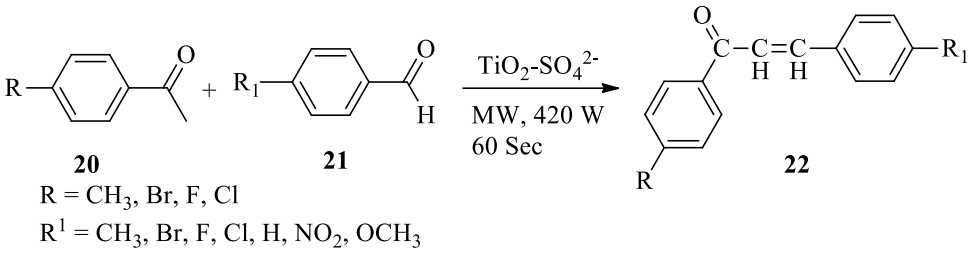
Scheme 6. Fly-ash:H_2SO_4 catalysed aldol-condensation reactions.

Mogilaiah *et al.* reported solvent-free LiCl catalysed Claisen–Schmidt Condensation (crossed aldol-condensation) reaction using microwave irradiation technique. The reaction of compound 16 with ketone 17 in the presence of glacial acetic acid resulted in compound 18. The reaction mixture was subjected to microwave irradiation for 4 min at 450 W. The compound 18 reacted with different aromatic aldehydes using lithium chloride as catalyst to get condensed product 19. The reaction was carried out under microwave irradiation at 300 W for 4min. This method resulted in good yields in the range of 80-86% (Scheme 7) [18].



Scheme 7. Lithium chloride catalysed aldol condensation reaction.

Krishna Kumar *et al.* reported solvent-free, microwave irradiation method for the synthesis of chalcone derivatives 22. An equimolar mixture of substituted ketone 20 and aromatic aldehyde 21 reacted in the presence of TiO_2-SO_4^{2-} under microwave irradiation at 420 W for 60 sec to yield chalcone derivative 22 (Scheme 8). Authors also studied the effect of different concentration of sulfate on reaction yield. Initially, the reaction was carried out using TiO_2 (without SO_4^{2-}), resulted in 97% of yield. The same reaction was carried out using 3, 5 and 7% wt of sulfate concentration which resulted in good yield of 98.1, 99 and 98.5% respectively. Among these concentrations, 5% wt of sulfate concentration resulted in maximum yield and this is considered as optimum reaction condition (Table 2) [19].



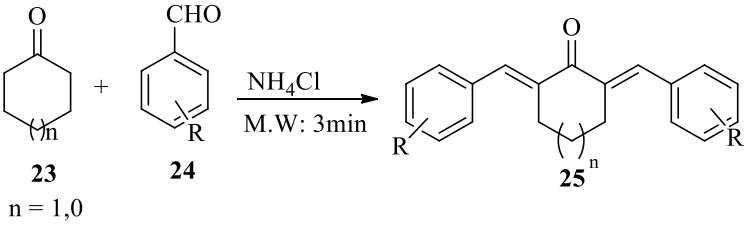
Scheme 8. TiO_2-SO_4^{2-} catalysed aldol condensation reaction.

Table 2. Effect of catalysts on reaction yield.

Entry	Catalyst	Time (s)	Yield[a] (%)
1	Prepared TiO_2	120	97.0
2	3 wt.% of TiO_2-SO_4^{2-}	60	98.1
3	5 wt.% of TiO_2-SO_4^{2-}	60	>99
4	7 wt.% of TiO_2-SO_4^{2-}	60	98.5

[a] Yields with respect to ketone

Pal *et al.* reported synthesis of chalconesvia cross aldol condensation reaction using solvent-free microwave irradiation technique. The reaction of various aromatic aldehydes 24 with cyclohexanone or cyclopentanone 23 in presence of solid ammonium chloride under microwave irradiation at 480 W for 3 min afforded chalcone derivatives 25. This technique resulted good yields in the range of 70-96%. In conventional method, the reaction mixture was refluxed for 6 hrs and the yield obtained was in the range of 40-59% (Scheme 9) [20].

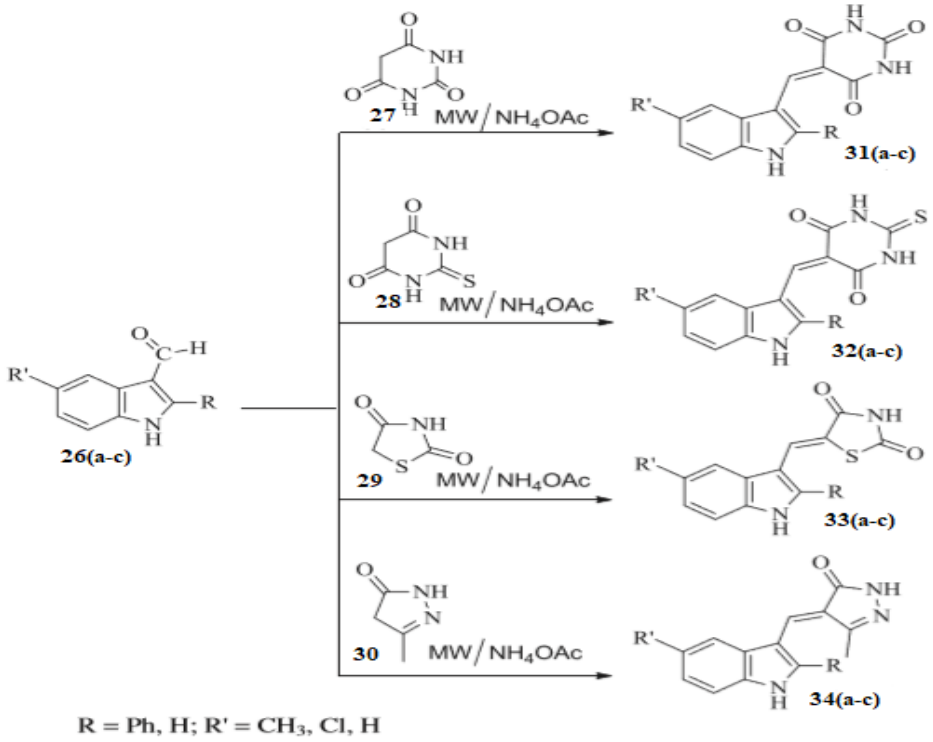


Scheme 9. Ammonium chloride catalyzed aldol condensation reactions.

Knoevenagel Condensation Reactions

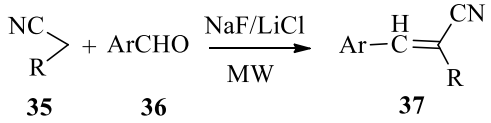
The knoevenagel condensation reaction is a modified aldol condensation reaction. It is a nucleophilic addition of active methylene group to a carbonyl group with the elimination of water molecule [21].

Biradar *et al.* reported ammonium acetate catalyzed Knoevenagel condensation reaction via solvent-free microwave assisted reaction. Substituted indole 3-carbaldehyde 26(a-c) were treated withbarbiturates (27 and 28), thiazolidine 2,4-dione 30 and pyrazole derivatives 30 in presence of ammonium acetate to yield condensed product 31(a-c), 31(a-c) and 33(a-c) respectively. The reaction mixture was irradiated to microwave for 5-10 min (Scheme 10). This method is rapid, environmental friendly and resulted in excellent yield with high purity whereas conventional heating method is time-consuming (2-4 hrs) and resulted in moderate yield [22].



Scheme 10. Ammonium acetate catalyzedknoevenagel condensation reaction.

Mogilaiah and co-workers reported NaF and lithium chloride catalyzedknoevenagel condensation reaction of an aromatic aldehydeand active methylene compound under microwave irradiation for 0.5-2min. A mixture of aromatic aldehyde 36, active methylene 35 compound and NaF and LiCl subjected to microwave irradiation in solvent-free condition to afford arylidene compound 37 in good yields (92-99%) (Scheme 11) [23].

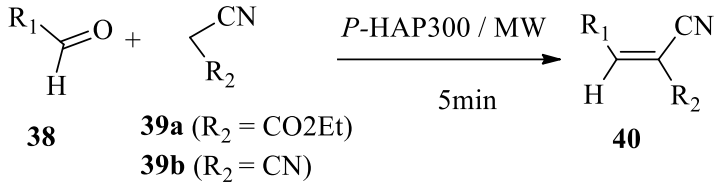


35 36 37

Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$
4-OHC_6H_5, 3,4-$(OCH_3)_2C_6H_3$, 3,4-(O-CH_2-O)$_2C_6H_3$
R = CN, $CONH_2$, $COONH_2$, $COOC_2H_5$

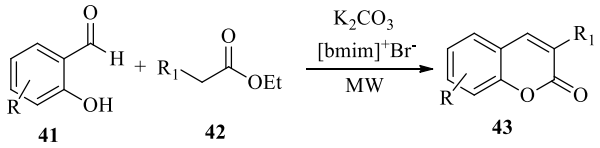
Scheme 11. NaF/LiCl catalyzedKnoevenagel condensation reaction.

Mallouk *et al.* reported efficient and rapid solvent free, microwave assisted knoevenagel condensation reaction catalyzed by porous calcium hydroxyapatite. A mixture of melanonitrile 39, aromatic aldehyde 38 and p-HAP300were added to dichloromethane. The solvent was evaporated under reduced pressure at 28 °C. The residue was then subjected to microwave irradiation (1250 W) at 62-101°C for 2 min to afford condensed product 40. The catalyst is reproduced by simple filtration method and reused upto 10 times without any change in its activity (Scheme 12) [24].



Scheme 12. Porous calcium hydroxyapatite catalyzedKnoevenagel condensation reaction.

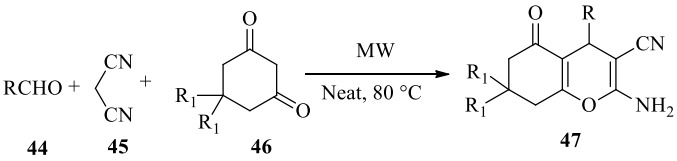
Valizadeh and co-workers described the microwave-assisted synthesis of substituted coumarin derivatives using potassium carbonate as a catalyst. The reaction of substituted salicylaldehyde 41 and acidic methylene compound 42 in 1-n-Butyl-3methylimidazolium Bromide Ionic Liquid afforded coumarin derivatives 43 in good to excellent yields (75-91%). The reaction mixture was irradiated to microwave for 1-2 min (Scheme 13) [25].



R = H, 7-OH, 7-Et_2N, COMe, CN, CO_2Me
R_1 = CO_2Et, COMe, CN, CO_2Me

Scheme 13. K_2CO_3 catalyzed the condensation reaction.

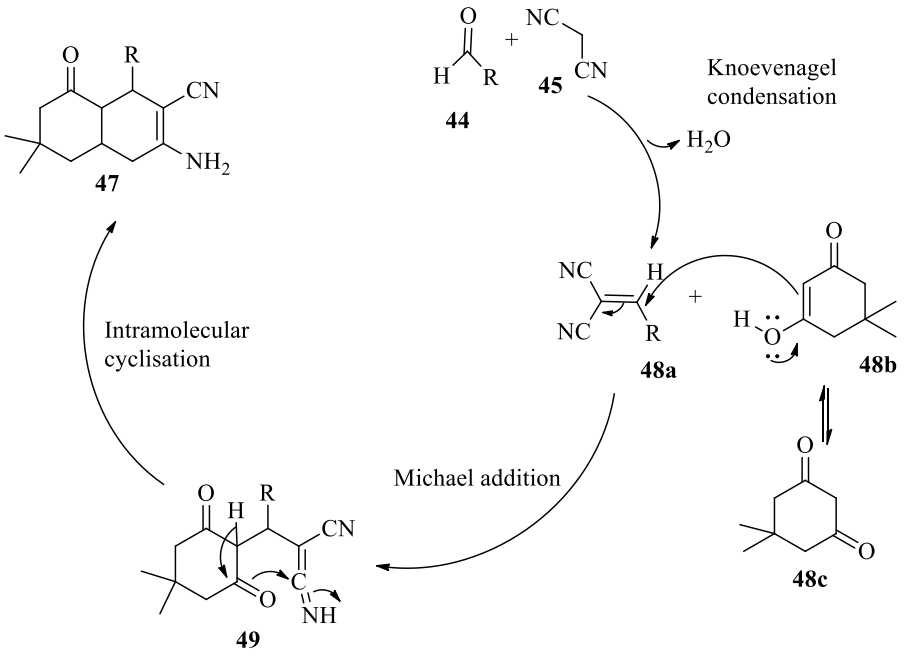
Sougata *et al.* synthesized tetrahydrobenzo [b] pyrans 47 via catalyst and solvent-free knoevenagel condensation reaction. Microwave irradiation of aromatic aldehydes 44, malononitrile 45 and cyclic diketones 46 led to the formation of condensed product 47 in good yield (74-88%) via three-component reaction. The reaction was carried out in the absence of solvent and catalyst at 80 °C (Scheme 14) [26].



R = aryl, alkyl, heteroaryl, cinnamyl
R_1 = H, Me

Scheme 14. Solvent and catalyst-freeKnoevenagel condensation reaction.

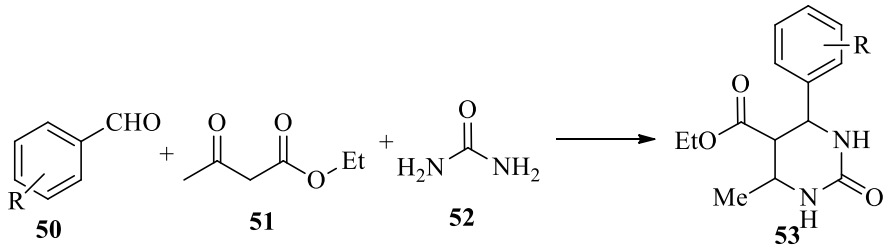
The possible mechanistic pathway for the synthesis of compound 47 is shown in Scheme 15. Initially, the aldehydes and malononitrile undergo knoevenagel condensation reaction to yield cyano olefin 48a which immediately underwent Michael addition with an enolic compound to afford compound 49. This intermediate undergoes intramolecular cyclisation to give final product 47 (Scheme 15) [26].



Scheme 15. Mechanism fort the synthesis of compound 47.

Biginelli reactions

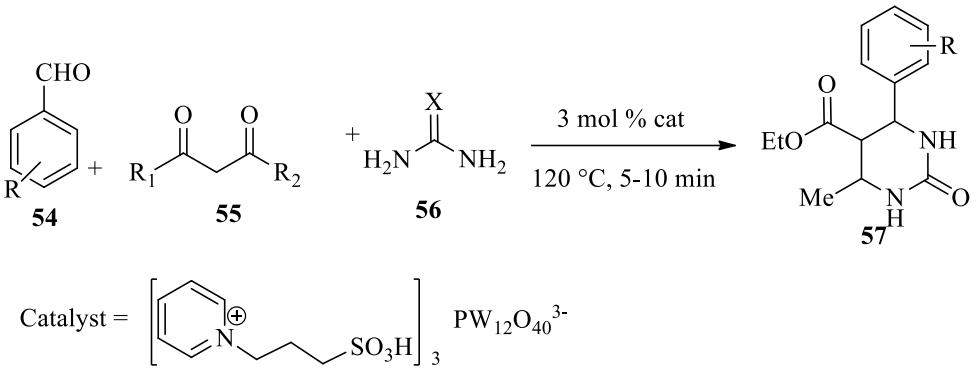
Biginelli reaction is a one-pot multicomponent condensation reaction of an aldehyde, a β-keto ester and urea to give dihydropyrimidinones [27]. Choudhary and co-workers synthesized dihydropyrimidinones via microwave assisted Biginelli reaction. The muti-component condensation reaction of aromatic aldehydes 50, thiourea 52 and ethylacetoacetate 51 in presence of Si-MCM-41 supported $FeCl_3$ catalyst led to the formation of dihydropyrimidinones. The reaction mixture was exposed to microwave irradiation for 3-5 min, which resulted in good yields in the range of 70-94%. Authors concluded that $FeCl_3$ could be a promising catalyst for Biginelli condensation reaction (Scheme 16) [28].



Scheme 16. $FeCl_3$ catalyzed Biginelli reaction.

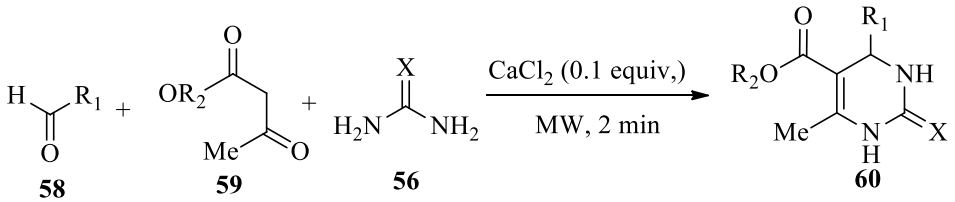
Fu *et al.* reported the synthesis of Dihydropyrimidinones 57 via microwave irradiation technique. The solvent-free reaction of aldehydes 54, 1,3-dicarbonyl compound 55 and thiourea or urea 56 under microwave irradiation (700 W) resulted in the final product in good yields (83-96%). The reaction was carried out at 120 °C for 5-10 min using heteropolyanion based ionic liquid

as a catalyst. In the absence of a catalyst, only 8% of yield is observed. The catalyst exhibited excellent efficiency even after 5 cycles (Scheme 17) [29].



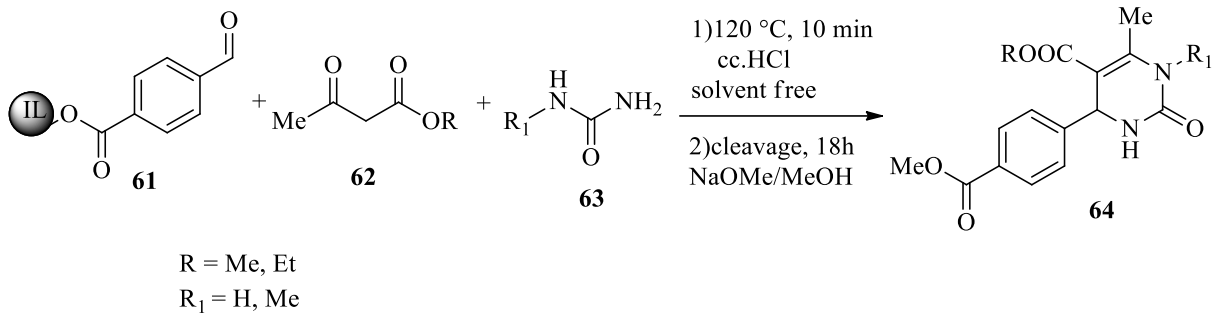
Scheme 17. Ionic liquid catalyzed Biginelli reaction.

Mishra and co-workers reported solvent-free Biginelli reactions using fused calcium chloride as a catalyst. Authors reacted aldehydes 58, methyl acetoacetate 59 and thiourea 56 under solvent-free, microwave irradiation techniques to get the final product in good yields (70-96%). The reaction mixture was irradiated for 2 min. at 120 °C. This method is advantageous over conventional heating, which requires longer time and resulted in lower yields (Scheme 18) [30].



Scheme 18. Calcium chloride catalyzed Biginelli reaction.

Legeay *et al.* synthesized 3,4-dihydropyrimidin-2(1H)-ones using IL supported aldehyde as a starting material. The IL supported aldehydes 61 was treated with 1,3-dicarbonyl compound 62 and thiourea derivatives 63 by introducing reaction mixture to microwave irradiation at 120 °C for 10 min under solvent-free condition. In this reaction HCl is used as a catalyst.Finally, the IL moiety cleaved using sodium methoxide to get final product 64 in good yields (80-86%) **(**Scheme 19) [31].

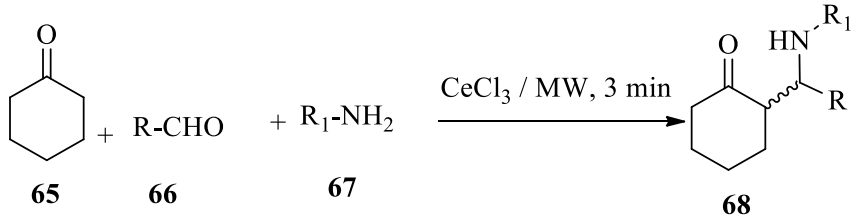


Scheme 19. HCl catalyzed Biginelli reaction.

Mannich reaction

The mannich reaction is a condensation reaction of a non-enilisable and enolizable carbonyl compound with a primary or secondary amine to afford β-amino carbonyl compound [32].

Sankappa Rai *et al.* synthesized aminoketones 68 via three-component reaction of aromatic aldehyde 66, cyclic ketones 65 and amines 67 under microwave irradiation resulted in aminoketones in good yields (83-95%). The reaction was carried out in the presence of $CeCl_3$ catalyst. The advantages of this method included, the reaction was solvent-free and resulted in very good yield in less time (Scheme 20) [33].

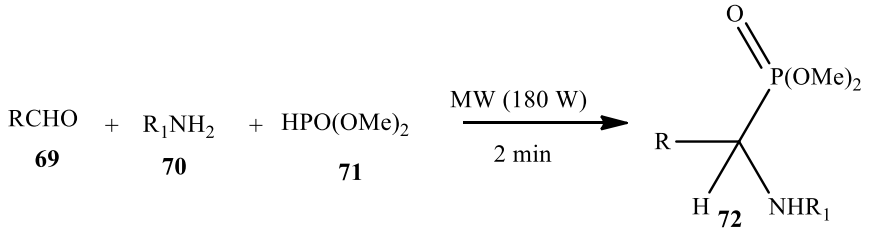


Scheme 20. $CeCl_3$ catalyzedthe Mannich reaction.

Kabachnik-Fields reaction

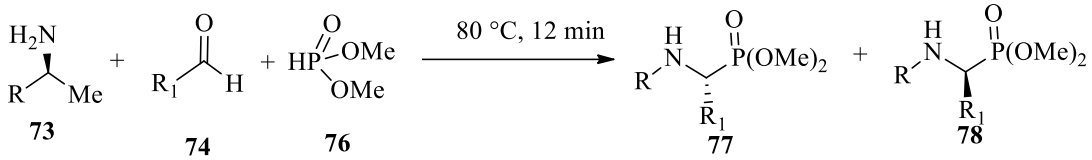
Kabachnik-Fields reaction is multicomponent condensation reaction of a primary or secondary amine, an oxo compound and a >P(O)H reagent to give α-aminophosphonates [34].

Xue-Jun *et al.* described the synthesis of α-amino phosphonates via microwave assisted Kabachnik-Fields reaction. The three-component condensation reaction of aldehydes 69, amines 70 and dimethyl phosphites 71 resulted in amino phosphonates 72 in good yields (40-98%). This reaction was performed under the solvent-free condition for 2 min (Scheme 21) [35].



Scheme 21. Solvent-free and catalyst-free Kabachnik-Fields reaction.

Microwave assisted, solvent-free Kabachnik-Fields reaction was reported by Ordónez *et al.* The three-component condensation reaction of aldehydes 74, chiral amines 73 and dimethyl phosphite 76 resulted in α–aminophosphonates 77 and 78 in good yields (66-86%). The reaction mixture was introduced to microwave irradiation without solvent and catalyst (Scheme 22) [36].



Scheme 22. Solvent-free microwave assisted Kabachnik-Fields reaction.

Conclusion

Solvent-free microwave irradiation technique opens up various opportunities to synthesize new molecules which are pharmacologically active. Nowadays, chemists are more focused towards combination of solvent-free microwave assisted technique with other synthetic strategies such as solid-phase synthesis and one-pot multicomponent reactions. This review contains a glance of important solvent-free microwave assisted condensation reactions.

Acknowledgement

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