

RECENT SYNTHETIC DEVELOPMENTS IN KNOEVENAGEL CONDENSATION: A GREENER PERSPECTIVE

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ABSTRACT

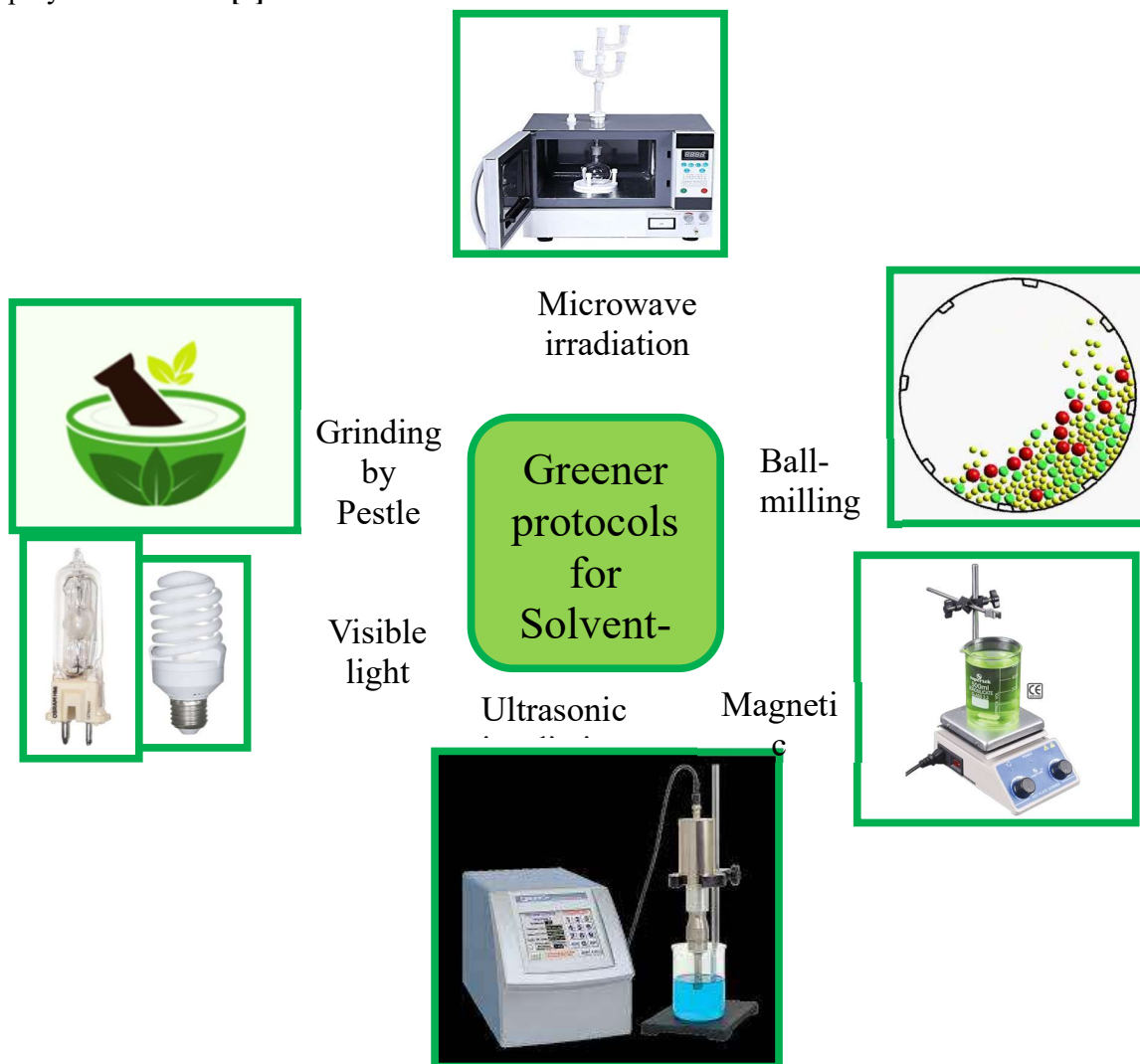
Knoevenagel condensation reaction is a basic reaction of organic chemistry for its significant detgency in the formation of electrophilic alkenes. It has numerous applications in the ingenious synthesis of different heterocyclic systems and widely used in the total synthesis of a wide verity of biologically active natural products such as coumarins derivatives. Many traditional Knoevenagel reactions make use of huge amount of toxic and volatile organic solvents *viz* not in line with green chemistry. In this review we discuss recent synthetic developments in solvent-free or greener Knoevenagel condensation reactions by the use of mechanochemical grinding over traditional conventions involving various solvents. Considering the enormous utility of Knoevenagel condensation reaction, number of greener protocols have been reported under solvent-free conditions like Microwave and ultrasonic irradiation, visible light irradiation, mechanochemical grinding, ionic liquids or green solvent like water, solid support and various heterogeneous base catalysts used whereby an excellent end was obtained. Certainly this review would put forward a great insight to research community to accelerate further research for the development of wide range of electrophilic alkenes, dienophiles for Diels-Alder reaction and various intermediates (coumarins) which are useful in cosmetics perfumes and biologically active compounds.

Keywords: Knoevenagel condensation, grindstone, microwave and mechanochemical

Introduction:

In 1894 Emil Knoevenagel described the original "classic" Knoevenagel condensation reaction of aliphatic formaldehyde with diethylmalonate using diethyl amine as a catalyst for the formation of C-C bond [1]. Between 1896 and 1898 Knoevenagel reported the condensation of aromatic aldehydes or ketones either with malonates or β -keto esters in the presence of primary or secondary amines, their salts and ammonia [2] provided various intermediate for natural product synthesis. Overall E. Knoevenagel regarded as a pioneer for C-C bond formation as well as he was the first who reported amino catalysts [3]. Over the years (1902 and 1940) Doebner and Verley reported significant modification of the classical Knoevenagel condensation by using an organic di-acid (malonic acid) instead of diethyl malonates under piperidine catalyst used by Doebner [4, 5] and β -alanine used as a co-catalyst in Verley modification gave α , β -unsaturated compound [6]. In literature survey we found that Knoevenagel condensation reaction is also catalyzed by many other bases/acids, $ZnCl_2$ [7], ZnO , MgO , ZnO , Al_2O_3 , Na_2CO_3 , $Ni-SiO_2$, $AlPO_4$, $BiCl_3$, CdI_2 , $KF-Al_2O_3$, natural phosphate and synthetic phosphate [8] etc under homogeneous conditions which gave higher yield of the products but not in line with green chemistry, because these protocols required high

temperature, excess solvents for reaction media extraction and purification and thus dispose of huge amount of organic waste for large scale synthesis furthermore there were possibility of formation of undesirable side product resulting from self condensation, bis-addition and polymerisation etc[9].



In this decade number of review article published on Knoevenagel condensation reaction, Very recently J. N. Appaturiet al published a review article focusing on heterogeneous catalysts for Knoevenagel condensation[10] and another review article published by Beurden and group entitled the historical path of Knoevenagel condensation. In 2019, Rupainwar et al wrote a review on importance and applications of Knoevenagel condensation reaction by highlighting the synthesis of 4H-chromenes[11].Vekariya et al reported a review for the synthesis of coumarins derivatives through Knoevenagel condensation. In 2020, M.M. Heraviet al highlighted the application of Knoevenagel reaction on the total synthesis of biologically active natural products[12].

Research continue for synthetic developments in green Knoevenagel condensation reaction with various solvent-free techniques such as microwave and ultrasound irradiation, ball-milling, grinding by pestle and mortar, solvent-free novel new heterogeneous catalysts(ionic

liquids, zeolites, metal-organic framework, hydrotalcites, heteropolyacids, carbon based materials and functionalized mesoporous silica) and photochemical condensation with fruit extract as catalysts. In this review, we discuss some aforementioned green protocols for Knoevenagel condensation reaction, each method was found to have its own merits. Keeping in mind the use of expansive catalysts, some reactions have also been shown which are solvent and catalyst free [13].

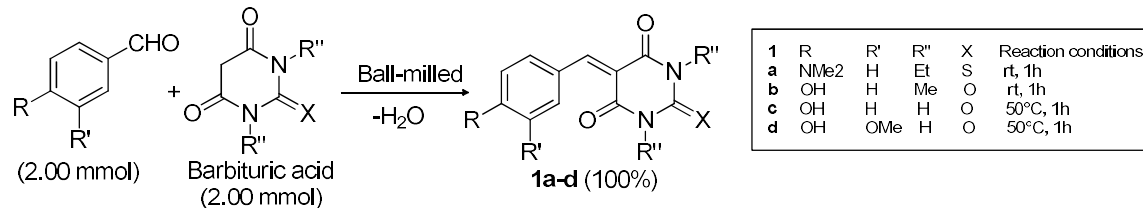
Recent development in Knoevenagel condensation under solvent free conditions:

Mechanochemical method

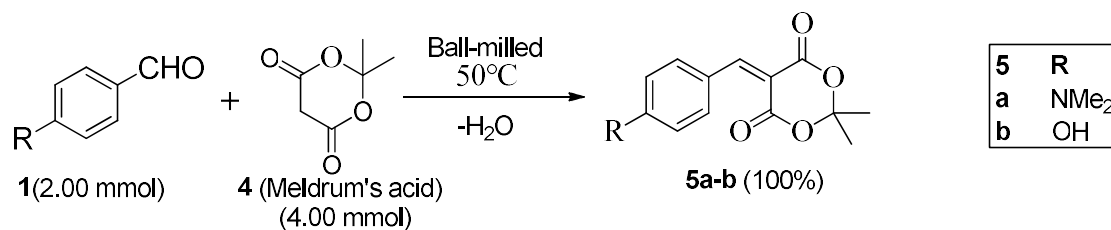
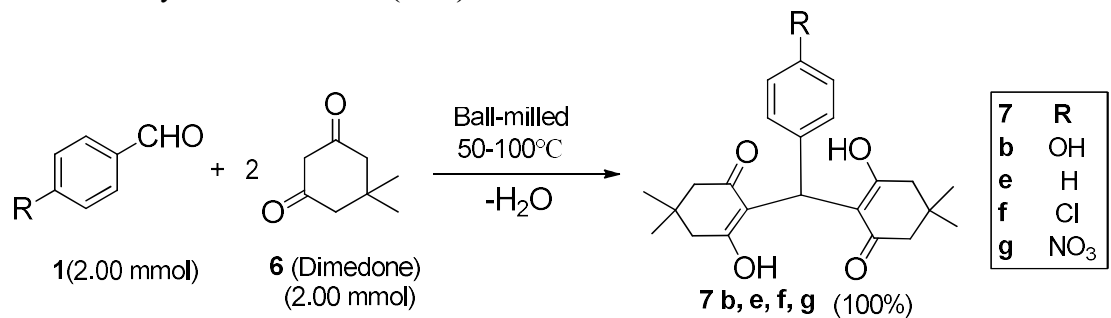
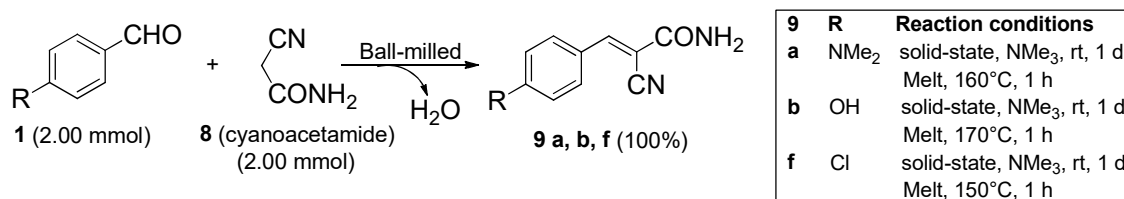
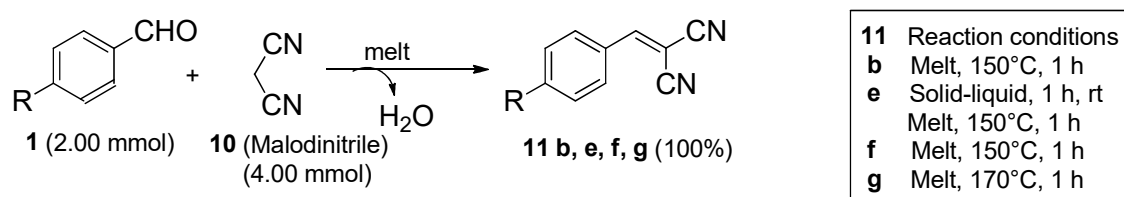
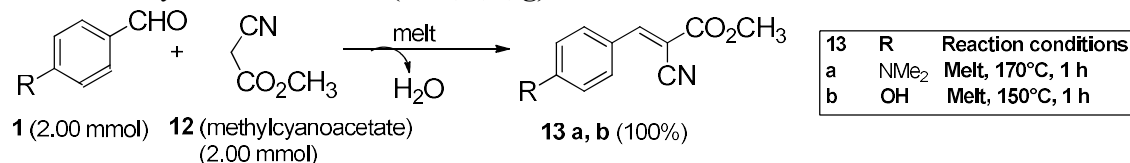
In Mechanochemistry, we discuss the type of reaction that accomplished by mechanical energy such as quiet/complex grinding of two reactant using pestle and mortar (discussed later) and ball milling [14]. Firstly discuss ball milling, it is a process used to grind/blend/crush crystalline substrate into extremely fine particles or nanostructure size by supplied kinetic energy during grinding, resulting size of particles depend upon many factors like, no of balls used, diameter of the balls, rotation speed, nature of material to be used, material used for the balls and surface of the rotating cylinder which rotates its own axis etc. Due to reduction of particle size there would be generation of fresh surfaces which provided large surface for reacting [15]. There are many classifications of ball mills as horizontal, planetary, high energy or shakerball mills but for laboratory scale syntheses shaker and planetary mills are used. Solvent-free mechanochemical organic syntheses gained increasingly popularity for its greener approach. Here we discuss some reported solvent-free Knoevenagel condensation using ball mills which gave excellent yield of the product in short reaction time and avoided/reduced the use of solvent for extraction or purification, moreover only catalytic amount of non toxic and recyclable catalyst required not stoichiometric amount required and no need of physical efforts [16].

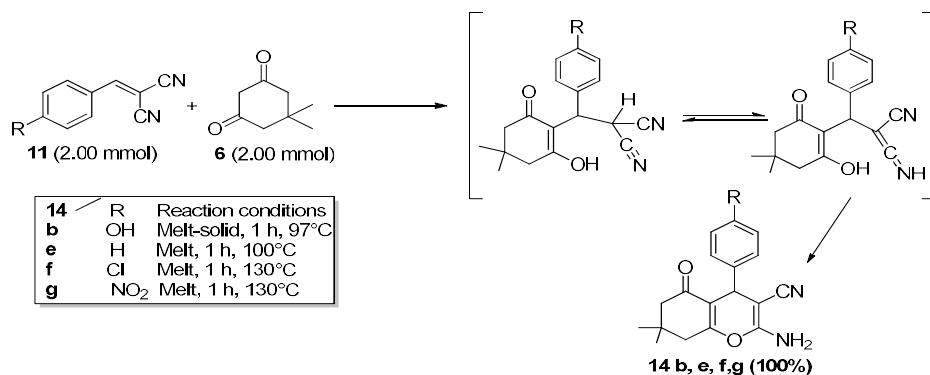
Ball milling

In 2003, Kaupp group provided various Knoevenagel condensations of solid or liquid aromatic aldehydes with active methylene compounds (four barbituric acids, Meldrum's acid, dimedone, cyanoacetamide, malodinitrile and methyl cyanoacetate) in stoichiometric mixture of the solids or of stoichiometric melts [17]. The product does not require purifying workup and the quantitative yield of the product was obtained in 23 reported cases. The new vibrational ball-milling technique provided various common electron-poor alkenes very easily which are valuable building blocks for Michael additions. Also the Michael adducts can be quantitatively obtained in stoichiometric melts in the absence of any auxiliaries or microwave irradiation and this is demonstrated with stable and cyclizing/rearranging Michael adducts using dimedone. The quantitative yields are most easily obtained if the crystallize directly from the melt at the reaction temperature.



Scheme 1. syntheses of alkene (3a-d)

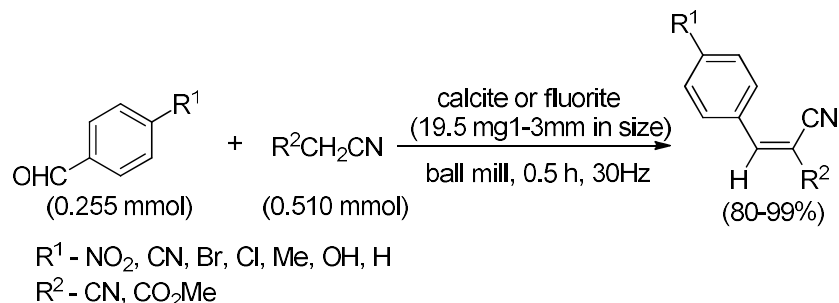
Scheme 2. Syntheses of alkene (**5a-b**)Scheme 3. Syntheses of alkene (**7 b, e, f, g**)Scheme 4. Syntheses of alkene (**9 a, b, f**)Scheme 5. Syntheses of alkene (**11 b, e, f, g**)Scheme 6. Syntheses of alkene (**13 a, b**)



Scheme 7. Quantitative Michael addition reactions of alkenes (**11**) with dimedone (**6**)

Kaupp's group observed that the mechanochemical reactions of the aromatic aldehydes **1b**, **1e**, **1f** and **1g** [Scheme 5] did not proceed with malononitrile at rt [17]. Suzuki et al used calcite or fluorite as mild catalyst for the Knoevenagel condensation of aromatic aldehydes with malononitrile and methylcyanoacetate under dry and neutral conditions i.e. ball-milling conditions gives the respective arylidenemalononitrile and (E)- α -cyanocinnamic ester in good to excellent yield [Scheme 8] [18].

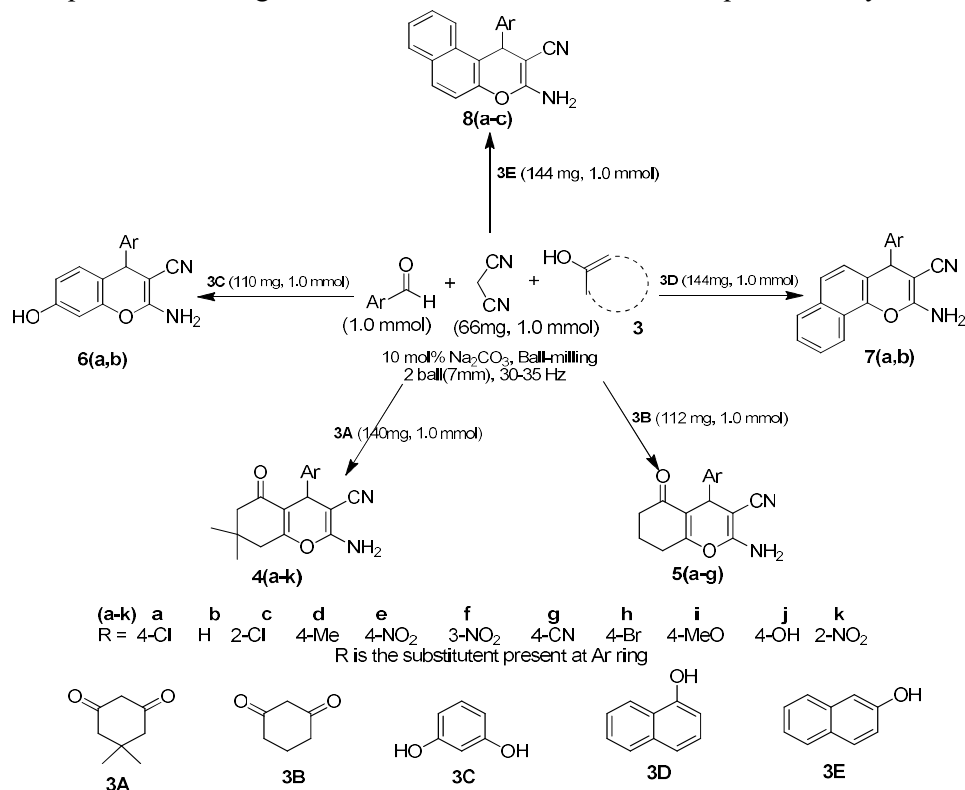
- Aromatic aldehydes substituted by electron withdrawing groups led to higher yield where as aromatic aldehydes substituted by electron-donating groups led to lower yield.
- The naked carbonate or fluoride anion act as a strong base used to deprotonate the active methylene compounds.
- To resolve the oxidative loss of aldehydes small amount of hydroquinone as antioxidant was added.
- Under same reaction conditions, aromatic ketones and acetophenone gives 23% expected product but benzophenone failed to react.



Scheme 8. Syntheses of electrophilic alkenes

In 2012 M. R. Naimi-Jamala et al used solvent-free ball-milling method for the syntheses of 2-amino-4-aryl-3-cyano-4H-chromene derivatives from three component, reaction of benzaldehyde derivatives with malononitrile and 1,3-diketones (dimedone **A** and 1,3-cyclohexanedione **B**) or reactive phenols (resorcinol **C**, α -naphthol **D** and β -naphthol **E**) at room temperature gave excellent yield of the product in the presence of catalyst Na₂CO₃ (10 mol%) (Scheme 9) [19]. Benzaldehyde derivative substituted by electron withdrawing group accelerate the reaction, completed in 10 minutes milling but benzaldehyde with electron donating group required up to 40 min for completion. This method found to be more superior, it was shown by comparative study of this protocol with some reported methods for the

preparation of **4e**(Table 1) but the given reaction conditions was not good for compound **8**required 1h heating of the reaction mixture at 125°C for quantitative yield.

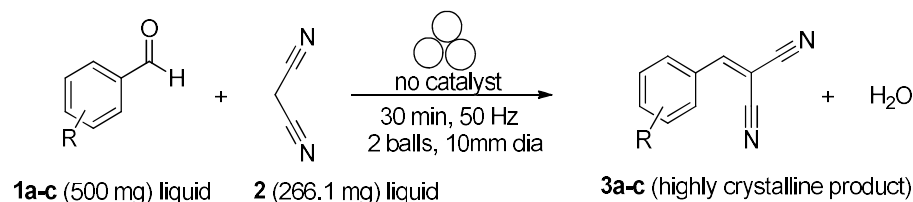


Scheme 9. Synthesis of alkenes

Table 1 Comparison of some reported method for the preparation of **4e**.

Catalyst	Temp	Time	Catalyst loading	Yield (%)
Na ₂ CO ₃ [19]	Rt	10 min	10 mol%	100
NMe ₄ OH[38]	Rt	0.5-2 h	10 mol%	80
ZnO-beta Zeolite[39]	Reflux	50 min	100mg	87
DABCO[40]	Stirring	2 h	10 mol%	94
S-Proline[41]	Rt	0.5 h	5 mol%	82

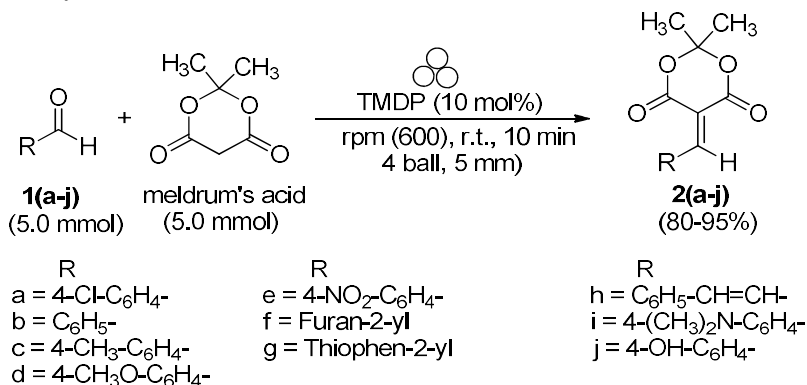
In 2018, S. Haferkamp showed that it is possible to perform Knoevenagel condensations using liquid substrates in a mechanochemical reaction[20]. Three different fluorinated benzaldehydes (p-, m-, and o-fluorobenzaldehyde) and malononitrile undergo mechanochemical Knoevenagel condensation under solvent and catalyst-free conditions and reactions led to a complete turnover(**Scheme 10**).



R=F in -p, -m or -o position

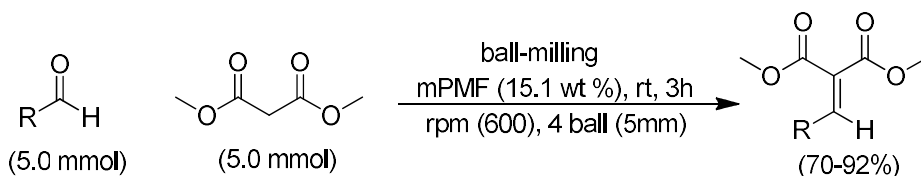
Scheme 10. Syntheses of p-, m- and o-fluorobenzylidenemalononitrile

A clean and ecological protocol has been developed for Knoevenagel condensation using 4,4'-trimethylenedipiperidine (TMDP) as a new organocatalyst under mild and solvent-free conditions [21]. At room temperature various aryl and heteroaryl aldehydes were reacted with Meldrum's acid in the presence of catalytic amounts of TMDP using planetary ball milling, arylidene analogues of Meldrum's acid were obtained in good to excellent yield under optimal reaction conditions (Scheme 11). Aldehydes containing electron-withdrawing groups afforded a slightly higher yield of products than electron-donating groups at the same position. Attractive features of utilizing TMDP catalyst over piperidine or pyridine are- After completion of reaction it is easy to separate, less volatile, non-toxic, safe to handle by less experienced chemist, act both as a nucleophile towards the aldehydes and as a base towards active methylene.



Scheme 11. Syntheses of arylidene analogues of Meldrum's acid

In 2021 N. G. Khaligh group synthesized arylidene and alkylidene malonates by the use of planetary ball-mill for solvent-free Knoevenagel condensation of substituted aromatic aldehydes or heteroaromatic aldehydes with dimethylmalonates catalyzed by nitrogen-rich porous organic polymer (POP) viz mesoporous poly-melamine-formaldehyde (mPMF) at room temperature [22]. After addition of hot ethanol into the milling jar catalyst mPMF easily separated by using vacuum filtration (Buchner funnel) and recovered catalyst gave high yield (88%) of the product after 10th run. This method was found to be more superior than the Sakai et al method [23] because Sakai et al obtained comparatively less yield of the same product by the use of toxic flammable toluene at 60°C for 6h.



R = Para substituted aryl group, substituent may H, CH₃, OCH₃, NO₂, CN, CF₃, F, (CH₃)₂N, 4-Pyridinecarbox aldehyde, C₆H₅-CH=CH-, 2,6-Dichloropyridine-3-carboxaldehyde, 3,4,5-(CH₃O)₃-C₆H₂-, (CH₂)₅CH-

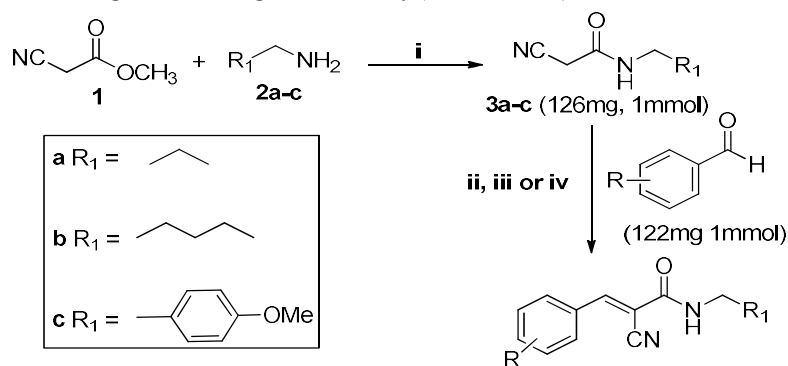
Scheme 12. Synthesis of electrophilic alkenes

Grinding mode synthesis:

Solvent-free Knoevenagel condensation reaction at room temperature under grindstone method gaining more popularity over the traditional methods because these reactions offers extra advantages in terms of novel, high yield, selectivity, simplicity and complete within few

minutes rather than hours[24]. It works on the principle of local heat produced through friction by grinding the crystals of reagent and substrate in mortar[25].

In 2002 Mcluskey et al. developed a comparative study of the Knoevenagel reaction with a range of substituted benzaldehydes (17 examples) and cyanoamides (3 examples) using different practice (i) traditional ethanol reflux (ii) water reflux and (iii) solvent-free conditions[26]. In solvent-free condition these reactions proceeded faster, more cleanly and in higher yield furthermore allowed the use of nitrobenzaldehyde which failed to yield the desired products under traditional and water based approaches **Table 2**. In conclusion, we have shown, in this instance, it is possible to apply the tents of green chemistry to a medicinal setting in the development of solvent-free conventions to the propagation of biologically interesting molecules using Knoevenagel chemistry (**Scheme 13**).



R = H, OH, OMe, Cl, Br, NO₂, COOH, N(CH₃)₂

(i) mix at rt (ii) EtOH reflux for 2 h overnight, piperidine (cat) (iii) water reflux for 2 h overnight, piperidine (cat) (iv) grind gently 5 min, piperidine (cat)

Scheme 13. Synthesis of alkenes

Reagents and conditions:

In this process 51 reactions were discussed of functionalized benzaldehydes and cyanoamides [26]. Some reactions are shown here.

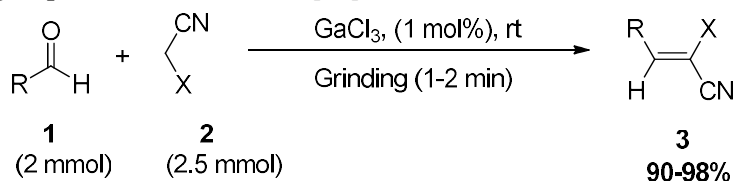
Table 2. Reaction of benzaldehydes/nitro-benzaldehydes with cyanoamides **3a-c**

Entry	Benzaldehyde(d)	R ¹	EtOH reflux (%)	H ₂ O (%)	Solvent-free (%)
1	Benzaldehyde	CH ₂ CH ₃	42	46	68
2	-3-NO ₂		17	46	74
3	-4-NO ₂		0	80	>99
4	Benzaldehyde	(CH ₂) ₄ CH ₃	37	55	>99
5	-3-NO ₂		0	33	96
6	-4-NO ₂		0	27	12
7	Benzaldehyde	p-MeO-PhCH ₂	10	50	96
8	-3-NO ₂		9	37	69
9	-4-NO ₂		0	22	51

Entry 6 shows a notable exception (12% yields in solvent free condition)

In 2011, L. Muralidhar et al developed grind stone method for Knoevenagel condensation between various aldehydes such as araldehydes and heteroaromatic aldehydes as well as active methylene compounds, namely, ethyl cyanoacetate or malononitrile under solvent-free

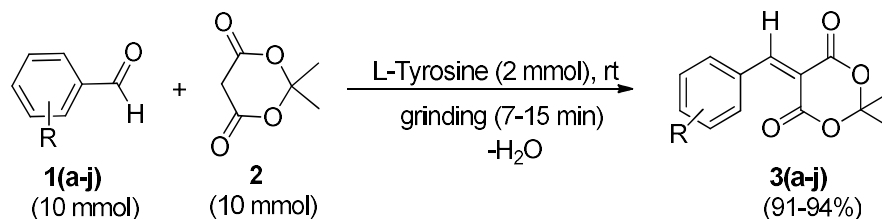
conditions using gallium chloride catalyst **Scheme 14**. At room temperature reaction provided good purity of product in high yield. There is no effect on the yields of the products of aromatic aldehydes with electron-withdrawing groups such as -Cl, -Br, -NO₂, or electron donating groups -CH₃, -OCH₃, -OH [27].



R = Ph, furfuryl, pyridyl
X = CN or COOEt

Scheme 14. Syntheses of electrophilic alkenes

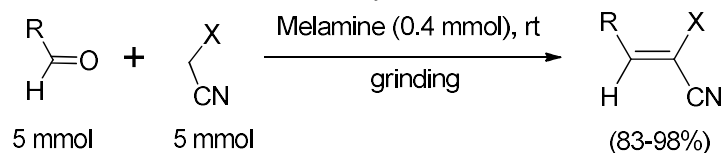
G. Thirupathi et al. used L-Tyrosine as an eco-friendly and efficient catalyst for Knoevenagel condensation of arylaldehydes with Meldrum's acid containing cyclic active methylene group in solvent-free condition under grindstone method to produce substituted -5-benzylidene-2,2-dimethyl-[1,3]dioxane-4,6-diones **3(a-j)** [28]. Electron withdrawing group such as -NO₂, -Cl at para-position of arylaldehydes led to higher yield and shorter time than electron donating group such as -OH, -OCH₃, and N, N-dimethyl at para-position of arylaldehydes (**Scheme 15**).



3(a-j). (a) R = C₆H₅, (b) p-CH₃-C₆H₄, (c) p-OCH₃-C₆H₄, (d) p-(Me₂N)-C₆H₄, (e) p-(OH)-C₆H₄, (f) p-(Cl)-C₆H₄, (g) p-(NO₂)-C₆H₄, (h) o-(NO₂)-C₆H₄, (i) o-(Cl)-C₆H₄, and (j) m-(OH)-C₆H₄.

Scheme 15. Syntheses of substituted -5-benzylidene-2,2-dimethyl-[1,3]dioxane-4,6-diones compound.

In 2012 Yang group developed a rapid, efficient, and eco-friendly protocol for the Knoevenagel condensation of active methylene compounds such as malononitrile or ethyl cyanoacetate with aromatic aldehydes in the presence of melamine with good to excellent yield at room temperature without solvent [29]. Aromatic aldehydes containing electron-withdrawing substituent could react very well with malononitrile in a very short period of time (1-2 min), while the less-active ethylcyanoacetate takes a longer time (15-50 min) for the corresponding aldehydes (**Scheme 16**). It was also found that after five runs melamine still catalyze this reaction without loss of activity.

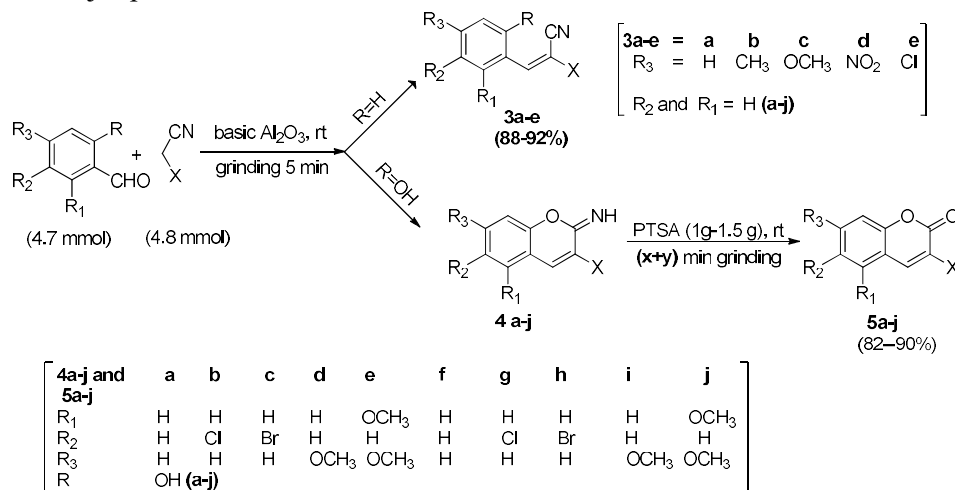


X = CN, COOEt

R = 3-NO₂C₆H₄, 4-NO₂C₆H₄, 2-ClC₆H₄, 4-ClC₆H₄, C₆H₅, 2-Furyl, 4-(CH₃)₂NC₆H₄, 4-CH₃OC₆H₄

Scheme 16. Syntheses of electrophilic alkene

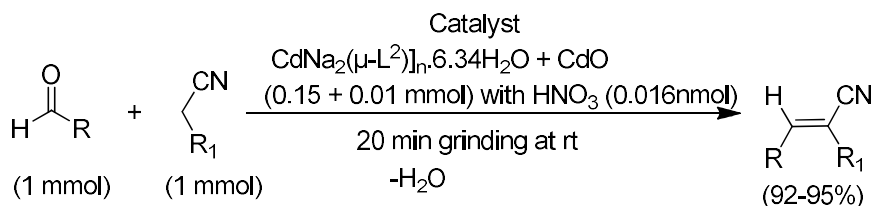
Facial syntheses of 3-cyano and 3-carbethoxycoumarins has also been developed, which involves the grinding of 2-hydroxybenzaldehydes with malononitrile or ethylcyanoacetate respectively over basic alumina followed by making use of solvent-free grinding with *p*-toluenesulphonic acid in the same mortar [30]. It was found that a reaction between 2-hydroxybenzaldehyde and ethylcyanoacetate using basic alumina, -CN functional group will participate in cyclisation not -COOEt group (**Scheme 17**). So it may be the case of trans-selectivity of the Knoevenagel reaction which promotes (*E*)-ethylbenzylidene-cyanoacetate as the major product.



x = 5 min (Grinding time); y = 10-20 min (Time for which reaction mixture kept at room temperature)

Scheme 17. Syntheses of benzylidenemalononitriles and 3-cyano/3-carbethoxycoumarins compounds.

R Jlassi et al reported the comparative study of solvent-free Knoevenagel condensation of aryl and heteroaromatic aldehydes with malononitrile by using catalytic amount of $[\text{CdNa}_2(\mu\text{-L}^2)]_n \cdot 6.34\text{H}_2\text{O} + \text{CdO}$ compounds under grindstone method and microwave assisted [31]. For the given reaction better results were obtained by the solvent-free grindstone method at room temperature than the optimizing conditions of MW irradiation at 70W and 150 moreover this protocol gave desired product from nitrobenzaldehyde at room temperature which was not found by traditional and water based approaches. To improve further yield small amount of additive (0.016 mmol HNO₃) was added.

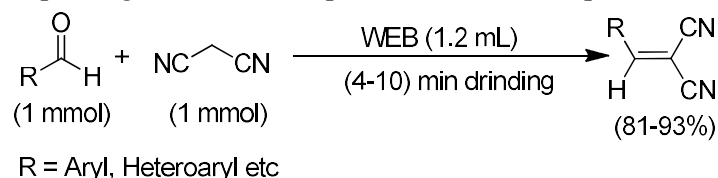


R = C₆H₅, *o*-(OH)C₆H₄ and *p*-(OH)C₆H₄
 R₁ = CN, COOEt

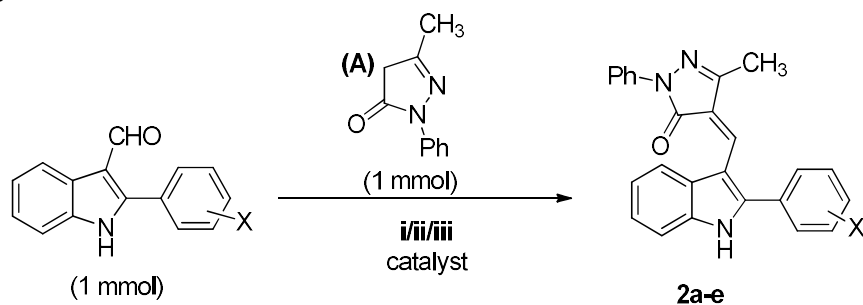
L = 2-(2-(4,4-dimethyl-2,6-dioxocyclohexylidene)hydrazinyl)terephthalate

Scheme 18. Synthesis of electrophilic alkenes

In 2019 K. Kantharaju's group used water extract of banana (WEB) for catalyzing solvent-free Knoevenagel condensation of aromatic/heteroaromatic aldehydes with malononitrile under grindstone method at room temperature in a very short reaction time (6min)[32]. It was the first protocol found for solvent-free Knoevenagel condensation reaction catalyzed by agro-waste stuff ash extract in a china mortar and pestle. Tong et al also reported a simple method for solvent-free Knoevenagel condensation based on grinding, but they used a special glass mortar and pestle which was not possible with china mortar and pestle [33].

**Scheme 19.** Synthesis of electrophilic alkenes

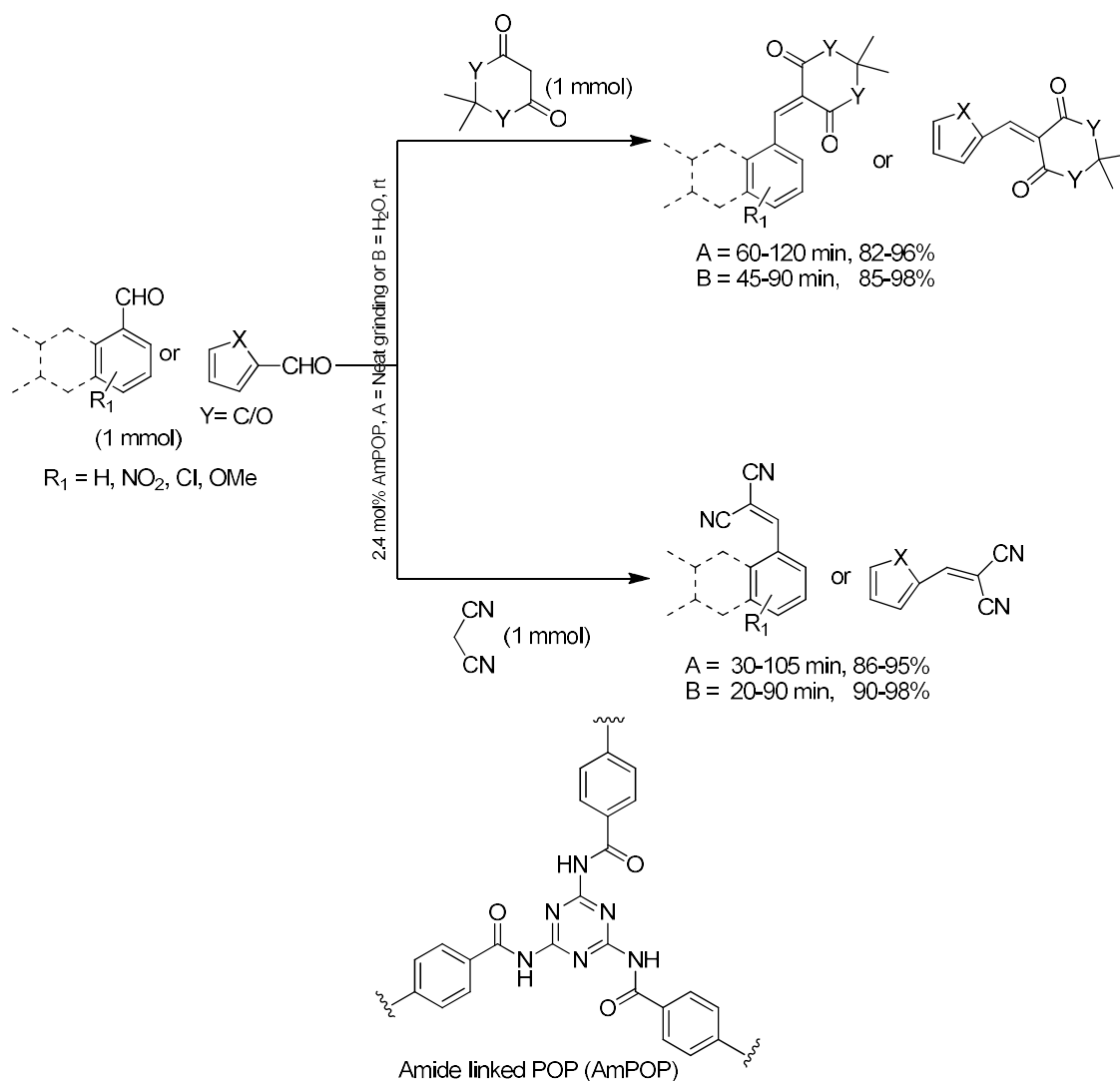
By using solvent-free grindstone method Y. Madan reported Knoevenagel condensation of indole-3-carbaldehydes (**1a–e**) with 3-methyl-1-phenyl-5-pyrazolone (**A**) in the presence of ZnO nanoparticles and compared with traditional refluxing method[34]. Grindstone method for preparation of these products lead to many advantages in terms of high reaction rate, excellent yields, short reaction time, and economic perspective and also attracts the attention towards green synthesis.



2a-e	X	(i) conventional method		(ii) ZnO nps mediated refluxing		(iii) grinding with ZnO nps	
		Yield(%)	time(hrs)	yield(%)	time (min)	Yield(%)	Time (min)
2a	H	80	4.0	90	6.5	91	1.5
2b	4-Cl	82	5.0	92	7.0	92	2.0
2c	4-F	83	4.5	89	7.0	90	1.8
2d	4-Br	86	4.0	90	8.0	92	1.8
2e	4-CH ₃	84	5.0	87	7.5	90	1.6

Scheme 20. Syntheses of (Z)-3-Methyl-1-Phenyl-4-((2-Phenyl-1H-Indol-3-yl) methylene)-1H-pyrazol-5(4H)-ones compound(**2a-e**).

In 2021 Sarma's group reported a nitrogen-rich metal free amorphous porous organic polymer (AmPOP) which catalysed the Knoevenagel condensation of aromatic/heteroaromatic aldehydes with various active methylene compounds both in water and solvent-free grindstone method at room temperature[35]. In both conditions high yield of the product observed. There were only few reports[36, 37] found for Knoevenagel condensation catalysed by metal-free porous organic polymer and pH neutral conditions in water.



Scheme 21. Synthesis of electrophilic alkenes

Conclusion:

From the above discussion it was found that solvent free Knoevenagel condensation reaction is a great reaction of organic chemistry for the synthesis of different electrophilic alkenes without use of any harmful solvents. However it also gave high to excellent yield of the product in a very short reaction time without the loss of catalytic activity of the catalyst used. Here we reported some reactions and procedure of mechanochemical grinding which provided various reactions intermediate for further useful applications in cosmetics, medicines etc.

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