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Review Article

RECENT DEVELOPMENTS IN KNOEVENAGEL CONDENSATION REACTION: A REVIEW

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ABSTRACT

Knoevenagel condensation reaction is a basic reaction of organic chemistry employed for the construction of C-C double bonds from aromatic carbonyl compounds specially aldehydes or ketones with active methylenes materials using different catalysts and also employed for the total synthesis of natural products, fine chemicals, pharmaceutical products, functional polymers and various important drug intermediates. In this article we discuss some recent developments to catalyze the Knoevenagel condensation reaction of different reactant in different catalytic environment, under different reaction conditions and comparative study of activity of some literate reported catalyst for Knoevenagel condensation reaction. Certainly this review will provide a great help to researchers for the new developments in the field of Knoevenagel condensation.

Keywords: Knoevenagel condensation, Aldehydes, Active methylenes, Protocol.

1. INTRODUCTION

In between 1896 and 1898 Emil Albert Knoevenagel reported a basic condensation reaction of aromatic aldehydes or ketones with active methylenes compounds in presence of basic catalyst such as primary and secondary amine, not tertiary amine, for the synthesis of electrophilic alkenes [1-7] and a lot of applications were found in the total synthesis of natural products [8], fine chemicals [9], pharmaceutical products such as antioxidant, antimalarial, antiviral and anticancer agents [10], functional polymers [11] and important drug intermediates (substituted alkenes) [12].

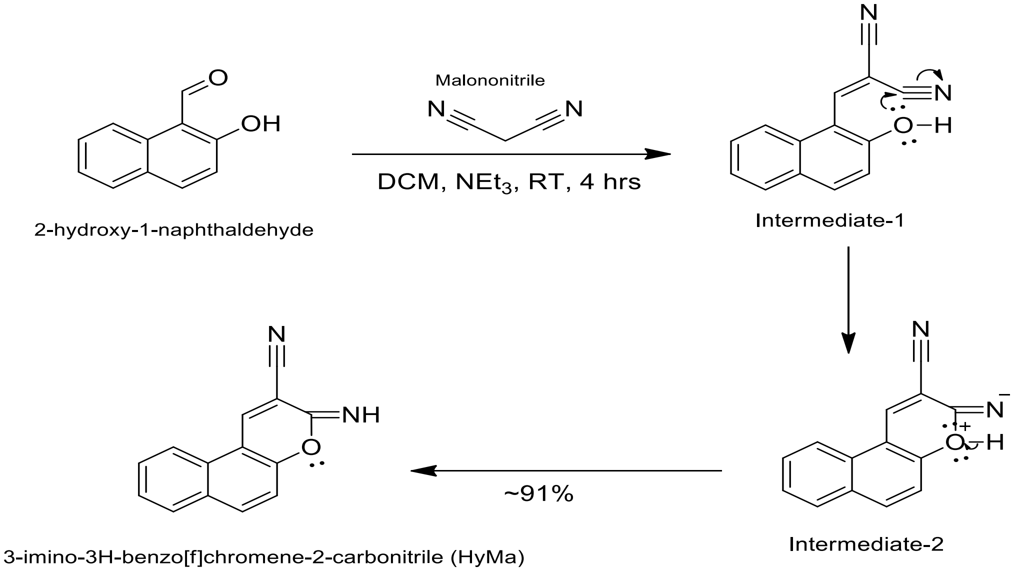
In literature, number of methods (ball milling, simple grinding, microwave and ultrasonic irradiation, photochemical assisted) were reported for a greener Knoevenagel condensation reactions under mild or solvent-free conditions and number of review articles were published by different researchers [13]. In this review, we discuss the recent development for the synthesis of different alkenes by the use of different catalysts or different reaction conditions in Knoevenagel condensation reaction. Surly this review will provide a better understanding to researchers for further development in electrophilic alkenes through Knoevenagel condensation reaction.

2. RECENT DEVELOPMENTS IN KNOEVENAGEL CONDENSATION REACTION

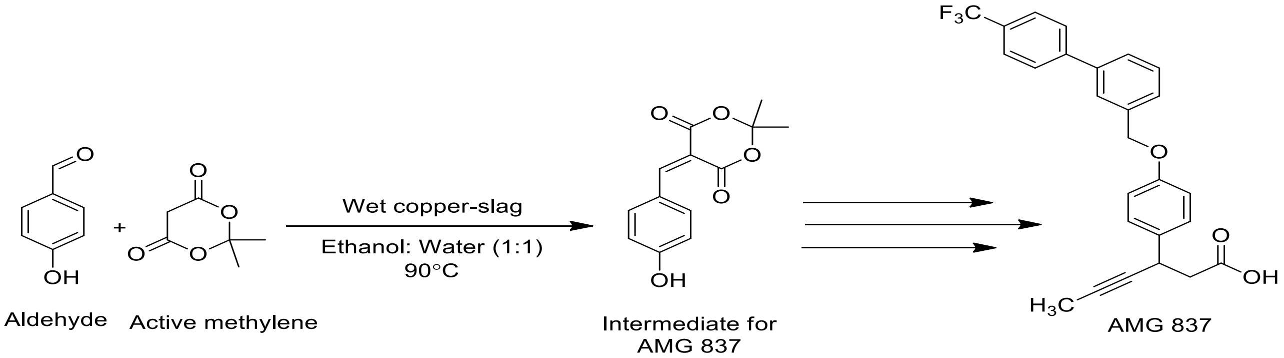
S. Bej and group synthesized an oxene based sensory receptor 3-amino-3H-benzo[f]chromene-2-carbonitrile (HyMa) *via* Knoevenagel condensation reaction. It involved 2-hydroxy-1-naphthaldehyde (172.18 mg, 1 mmol) and NEt_3 (200 μL) in dehydrated culture media (DCM), after 4 hour stirring at room temperature a yellow crude product (90.7%) was yielded as shown in **Scheme 1**. The completion of reaction was monitored by various instruments like FT-IR, ESI-MS (m/z=221), FE-SEM, UV-Vis and 1H NMR. Numerous applications of chemosensory HyMa were found like as for development of molecular keypad lock, in real field water sample analysis, *in vitro* toxicity study and MTT assay of HyMa showed low cytotoxicity and membrane permeability indicating its attractive capability for bio-imaging towards triple negative breast cancer [14].

P. Ganwir *et al* used Wet Copper slag (copper slag is a waste material produced from copper refining) as a catalyst for Knoevenagel condensation reaction of aldehydes or ketones with malononitrile as well as active methylenes in environmentally-benign solvents water: ethanol (1:1) at room temperature or 90°C in a short reaction time respectively, high yield of the products were obtained as shown in **Scheme 2**. After completion of reaction, catalyst was easily separated with the help of magnet and reused for three times without significant loss of catalytic activity. Many advantages of current protocols were found such as catalyst leaves no residues, mild reaction conditions required at low temperature, environment friendly and used to synthesized the intermediate of AMG 837, a novel GPR40 agonist [15]. Comparative studies of wet copper slag with literature reported catalysts discussed in table 1.

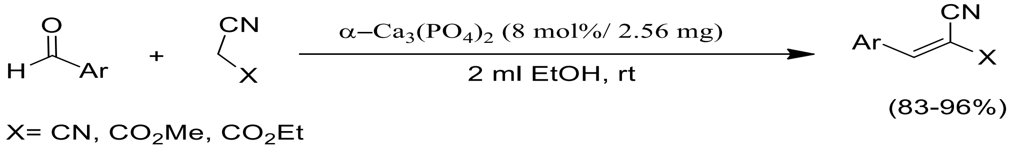
To catalyze the Knoevenagel condensation reaction of aromatic aldehydes with active methylene compounds under mild reaction condition, H. Anahmadi and group prepared a catalyst alpha-tricalcic phosphate (α-$Ca_3(PO_4)_2$), which provided high yield of the product at room temperature. Furthermore, current protocol had several beneficial including, drifts under sustainable conditions, shorter reaction time (30-60 min), small quantity of catalyst required and catalyst recovered very easily and gave excellent yield of the product without significant loss of catalytic performance in more than five times reuse. Catalytic amount of alpha-tricalcic phosphate also used to prepared 2,3-diphenylquinoxalines [27].



Scheme 1: Synthesis of 3-amino-3H-benzo[f]chromene-2-carbonitrile



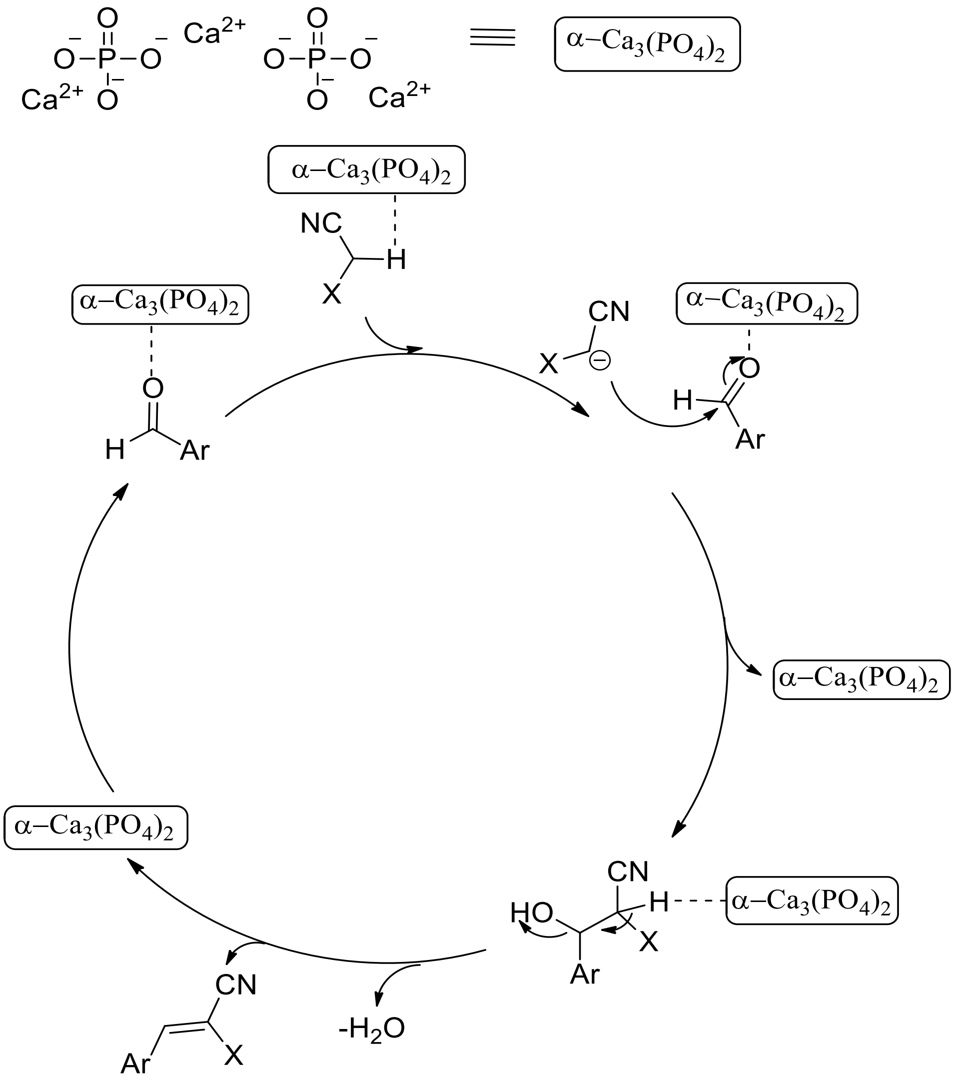
Scheme 2: Synthesis of AMG 837 intermediate



Scheme 3: Synthesis of electrophilic alkenes

Table 1: Comparative study between Wet copper slag catalyst and other literature reported catalysts for the synthesis of 2-benzylidene malononitrile

Entry	Catalysts	Reaction condition	Time (h)	Yield (%)	Ref
1	Powdered Magnetized copper-slag	EtOH: H_2O/rt	1	0	[15]
2	**Wet copper slag**	**EtOH: H_2O/rt/90°C**	**0.25**	**98**	**[15]**
3	Commercial MgO	EtOH/rt	0.3	99	[16]
4	$[Gd_2(tnbd)_3(DMF)_4].4DMF.3H_2O$	C_6H_5/rt	0.3	96	[17]
5	TMU-5	Water/rt	0.5	100	[18]
6	$Ce(PO_2NH)_3.5H_2O$	EtOH/100°C	2	95	[19]
7	Unannealed ZrO_2	EtOH/78°C	2	95	[20]
8	FeNPs/PPD@rGO	Toluene/40°C	3.5	100	[21]
9	MOF-NH_2	DMF/80°C	4.5	51	[22]
10	Cu-metal surface	EtOH/56°C	6	99	[23]
11	$Pb(cpna)_2.DMF.6H_2O$	MeCN/rt	24	100	[24]
12	NHCu(II)@MNP	Ethanol/80°C	1	91	[25]
13	MIL-53 (Fe)@SiO_2@$NiFe_2O_4$	Solvent-free/rt	1	99	[26]



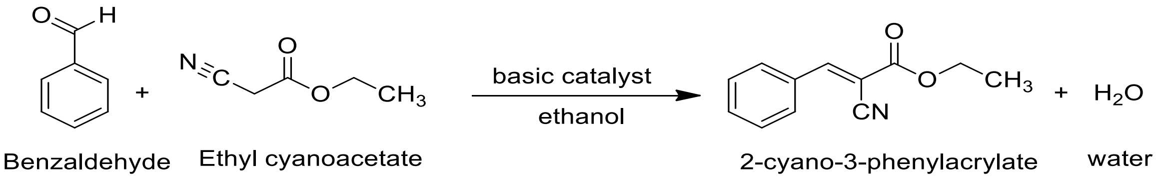
Scheme 4: Mechanism suggested for the synthesis of alkenes by α-$Ca_3(PO_4)_2$

Table 2: Comparative study between catalytic activity of α-Ca_3 $(PO_4)_2$ catalyst and other literature reported catalyst for the synthesis of electrophilic alkenes as shown in Scheme 3

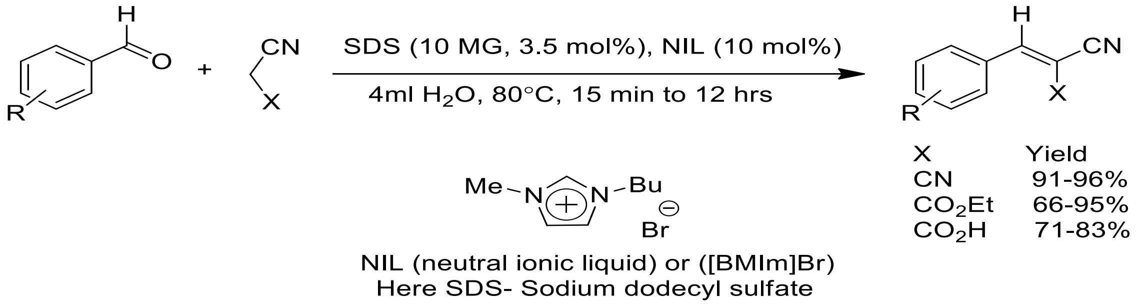
Entry	Catalyst	Reaction conditions	Yield (%)	Ref.
1	**α-$Ca_3(PO_4)_2$**	**2.56 mg/8 mol%, 2 mL EtOH, rt, 30-60 min**	**83-96**	**[27]**
2	Mesoporous Amino-silica	20 mg, EtOH, rt, 6h	64-90	[28]
3	HAP-γ-Fe_2O_3	0.025 g, H_2O, 30°C, 1h	60-99	[29]
4	mpg-C_3N_4-tBu	50 mg, CH_3CN, 70°C, 2h	48-98	[30]
5	Na-A-PW_9	0.25 mol%, MeOH, rt, 6h	80-98	[31]
6	$R_2(1MCl\text{-}2NaPO_3)$ (2%)	6 mg, 3 ml EtOH, rt, 3-30 min	85-98	[32]
7	$(N_2H_5)_2SiF_6$	0.1 mol%, 2 ml EtOH, rt, 30-60 min	54-98	[33]
8	$CaHPO_4$, $2H_2O$ (DCPD)	10 mg, 3ml EtOH, rt, 10 min	84-96	[34]
9	$Na_2Ca(HPO_4)_2$	6 mg, 3ml EtOH, rt, 10-65 min	82-97	[35]

J. Floriano da Silva *et al* reported a catalyst, zeolite 4A (LTA-x) using the [3-(trimethoxysilyl) propyl] octadecyldimethylammonium chloride (TPOAC) organosilane surfactant to formed mesopores for bulky molecules. In Knoevenagel condensation reaction, a high conversion of benzaldehydes were achieved using zeolites 4A containing mesopores, which provided higher external surface area for bulky molecules by using different concentration of TPOAC (0-0.09) compared to conventional zeolite 4A [36]. Furthermore reaction acierated by the zeolite containing mesopores had lower activation energy (33.6 $KJmol^{-1}$) compared to use of the conventional zeolite 4A (40.9 $KJmol^{-1}$) [37].

S. Chakraborty *et al* reported first base and metal free protocol for Knoevenagel condensation reaction in a neutral medium including water-SDS-[BMIm]Br composite system. The developed protocol provided good to excellent yield of the Knoevenagel condensation products from different aromatic aldehydes and active methylenes compounds (malononitrile ethyl cyanoacetate or cyano acetic acid). Waste of the reaction also acted as a good catalyst after six recycling process. All aldehydes gave very high yield of the product with malononitrile under given reaction conditions in Scheme 6, but some aldehydes (naphthaldehyde, thiophene-2-carboxaldehyde and indole 3-carboxaldehyde) take little more time to give desired products. Moreover, current protocol had many advantages such as free from chromatography and use of volatile organic solvents and environment benign. Light scattering study proved that the reaction proceeds in the hydrophobic cavity of the micelle formed in the medium [38].



Scheme 5: Synthesis of 2-cyano-3-phenylacrylate



Scheme 6: Synthesis of functionalized α, β-unsaturated compounds

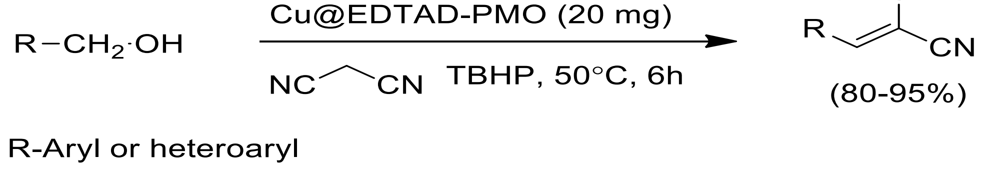
Table 3: Comparative study between catalytic performance of water-SDS-NIL system and other literature reported catalysts for the synthesis of functionalized α, β- unsaturated compounds as shown in Scheme 6

Entry	Catalyst	Solvent	Temp (°C)	Malononitrile		Ethyl cyanoacetate	
				Time	Yield (%)	Time	Yield (%)
1[38]	**SDS and 1-Butyl-3-methy-limidazolium bromide**	**Water**	**80**	**15-120 min**	**90-96**	**4-8 hr**	**66-95**
2 [39]	Microporous polyurethane material	THF	50	14 hr	80-99	-	-
3 [40]	Metal organic framework	THF	50	4 hr	35-100	-	-
4 [41]	Cu metal	EtOH	56	-	-	6 hr	68-98
5 [42]	ZnO Catalyst	Water	rt	85-94	85-94	4-24 hr	82-92
6 [43]	Polyacrylamide functional polymers	Water	80	-	-	75-270 min	90-99
7 [44]	Calcium hydroxyapatite	DCM	MW	87-93	87-93	5 min	46-98
8 [45]	Hydroxyapatite encapsulated γ-Fe_2O_3 nanoparticles- ionic liquid	Water	30-80	89-99	89-99	3 hr	88
9 [46]	Molecular complex of N-methylpiperidine-(2,4-Dinitrophenol)	No	rt	60-98	60-98	10-20 min	50-95
10 [47]	KF-Montmorillonite	DMF	80	73-92	73-92	3 hr	74-90
11 [48]	$Bi(NO_3)_3.5H_2O$	Water	Reflux	88-95	88-95	-	-
12 [49]	L-Histidine/L-Arginine	Water	rt	83-92	83-92	5-8 min	85-97
13 [50]	Urea-functionalized mesoporous polymers	Water	50	-	-	4 hr	72-99
14 [51]	3-aminopropylated silica	Water	rt	93-98	93-98	1.5-3 hr	76-100
15 [52]	DABCO with pyridinium ionic liquid	Water	50	-	-	20-40min	83-99
16 [53]	TiO_2	No	80	70-95	70-95	14 hr	70

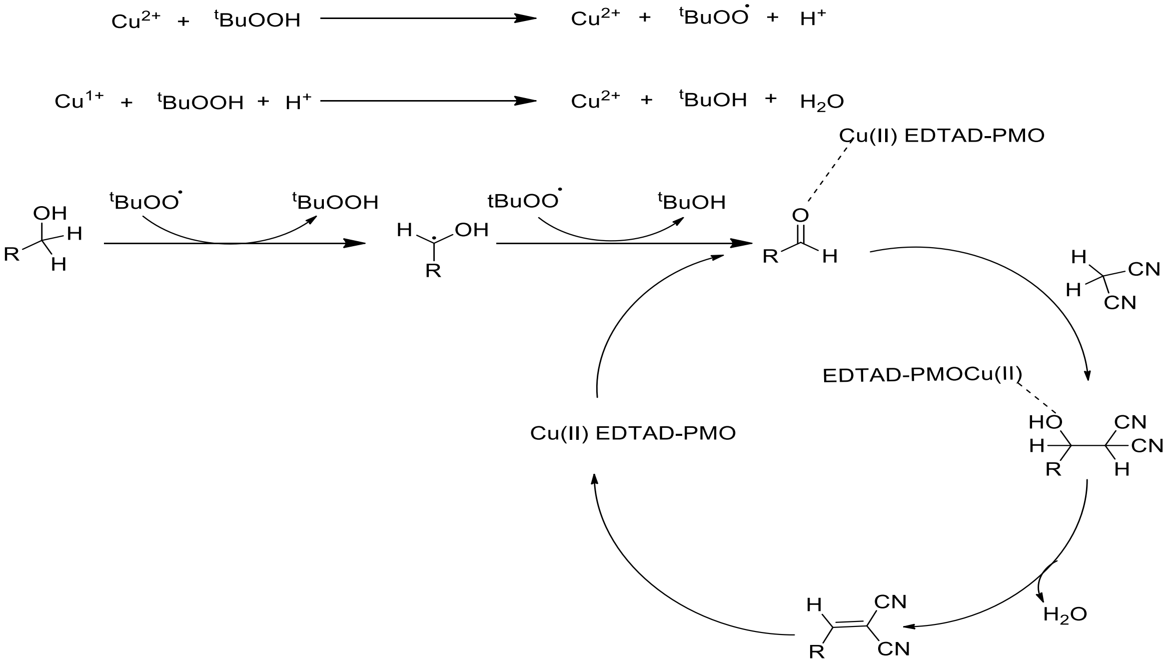
E. Valiey and M. G. Dekam reported a new catalyst Cu@EDTAD-PMO (Cu(II) species on ethylene-diaminetetraacetic dianhydried-bridged periodic mesoporous organosilica), which catalyzed the oxidation of benzyl alcohols into corresponding aldehydes followed by subsequent Knoevenagel condensation with malononitrile (one pot multistep synthesis or cascade synthesis), provided corresponding α,β-unsaturated nitriles using TBHP(tert-butyl hydro peroxide) as a green oxidant under mild reaction conditions as shown in Scheme 7. The current protocol had many advantages such as good selectivity of the product was obtained by using nano-ordered and reusable Cu@EDTAD-PMO catalyst [54].

Lulu Chen and group used first time sodium alginate as catalyst for Knoevenagel condensation of furfural with acetylacetone produced high quality fuel precursor (3-(furan 2-ylmethylene) pentane-2,4-dione with 86.47% yield) as shown in Scheme 9. One of the important advantage of sodium alginate catalyst observed, it provided high yield of the product on six times recycling without loss of catalytic performance [55].

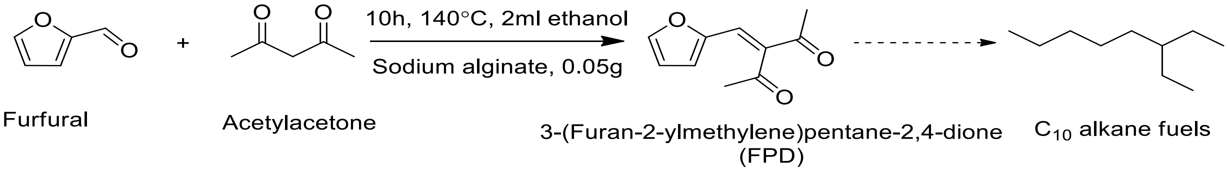
F Hajizadeh et al synthesized a (covalent bonded $Fe_3O_4SiO_2$@PAMAM-G2) magnetic cored amino group terminated dendrimer catalyst for Knoevenagel condensation of aldehydes with malononitrile under solvent-free and mild reaction conditions. The given catalyst provided high yield of the product under given reaction condition in Scheme 11 and separated very easily from reaction mixture by an external magnet and recycled five times without loss of catalytic activity [56].



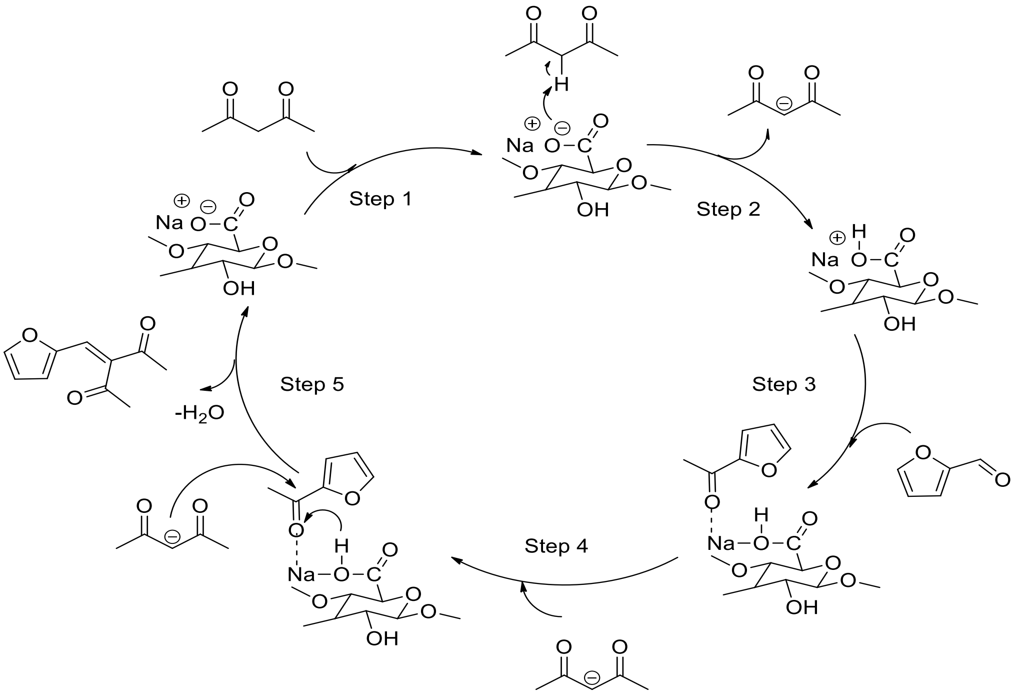
Scheme 7: Synthesis of α,β-unsaturated nitriles



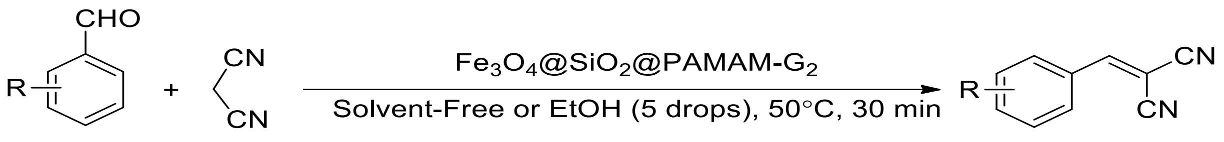
Scheme 8: A plausible mechanism for the synthesis of α,β-unsaturated nitriles



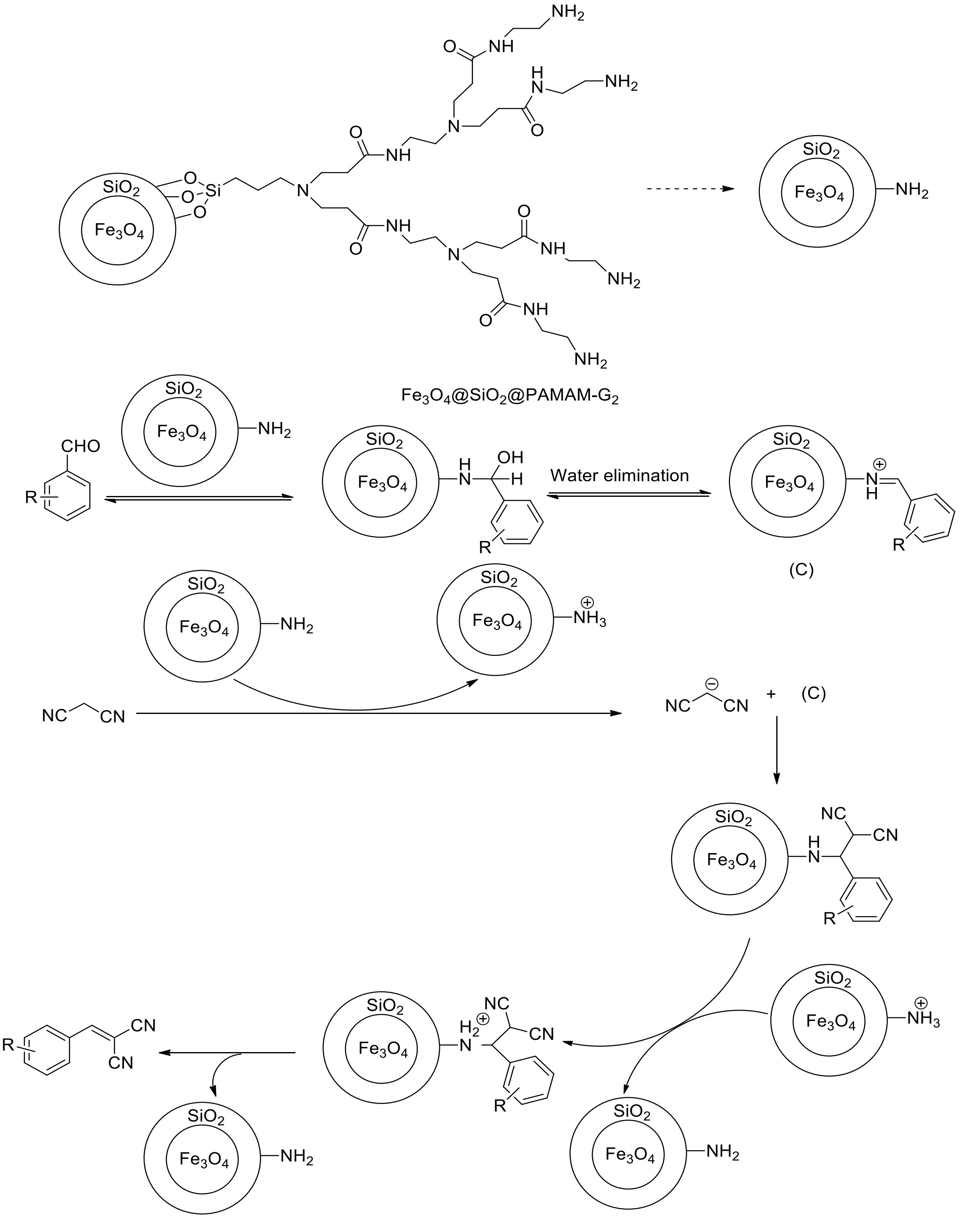
Scheme 9: Synthesis of fuel precursors from furfural and acetylacetone



Scheme 10: Plausible reaction mechanism for Knoevenagel condensation of furfural with acetylacetone by using sodium alginate



Scheme 11: Synthesis of 2-benzylidene malononitrile derivatives



Scheme 12: Possible mechanism for the synthesis of 2-benzylidene malononitrile derivatives

Table 4: Comparative studies of catalytic efficiency of Fe_3O_4@SiO_2@PAMAM-G_2 catalyst with other literature reported catalyst for the synthesis of benzylidene malononitrile as shown in Scheme 11

Entry	Conditions	Time (min)	Yield (%)
1 [56]	**Fe_3O_4@SiO_2@PAMAM-G_2/Solvent-free/50°C**	**30**	**95**
2 [57]	RE(72%)NaY/CH_3CN/rt	720	78
3 [58]	CTMAB/H_2O/rt	90	91
4 [58]	MgO/ZrO_2/Solvent-free/60°C	20	93
5 [59]	Znβ/Solvent-free/140°C	360	16
6 [60]	PVC-TEPA/EtOH/reflux	60	75
7 [61]	Na_2S/Al_2O_3/CH_2Cl_2/reflux	20	90
8 [62]	MgF_2/EtOH/rt	150	93
9 [63]	Ni-SiO_2/Toluene/reflux	900	100
10 [64]	C/Z-30/70/EtOH/reflux	50	82
11 [65]	Fe_3O_4@UiO-66-NH_2-3/DMF/80°C	60	73
12 [66]	Fe_3O_4@SiO_2-3N/Water/75°C	12	93
13 [67]	Fe_3O_4@P4VP@ZIF-8/Toluene/23°C	120	99
14 [68]	Fe_3O_4@SiO_2@Ni-Zn-Fe/EtOH/reflux	90	92

3. CONCLUSION

From above discussion it was found many applications of Knoevenagel condensation reaction between different aromatic aldehydes with active methylenes compounds with different catalysts. In this review we discussed some recent developments in Knoevenagel condensation reaction which has many applications in total synthesis of natural products, fine chemicals, pharmaceutical products, functional polymers and various important drugs intermediates. Certainty this review will provide a great help to research community for synthesizing the new material in Knoevenagel condensation reaction.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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