

## Knoevenagel condensation reaction catalysed by agro-waste extract as a greener solvent catalyst

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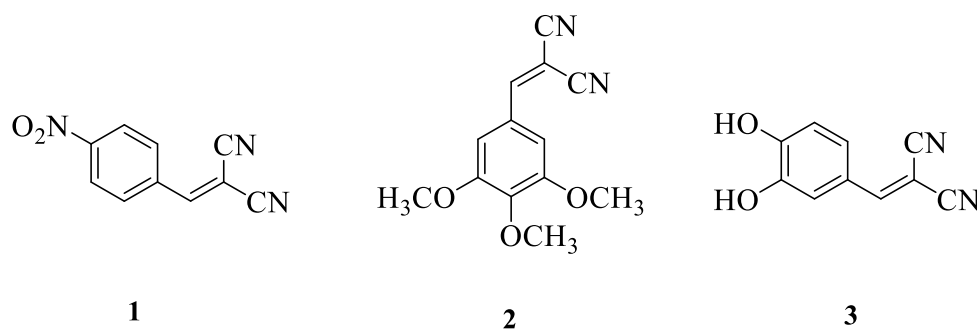
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**Abstract:** This paper presents a novel Knoevenagel reaction protocol for the condensation of aromatic/heteroaromatic aldehydes with malononitrile to give  $\alpha$ ,  $\beta$ -unsaturated benzylidene derivatives. The main focus of this work is to reveal the usability of agro-waste extracts as a catalyst in the Knoevenagel condensation. The present protocol proceeds efficiently for various substituted aromatic and heterocyclic aldehydes in the Knoevenagel reactions. In addition, the present method describes direct isolation of the formed products without using organic solvent extraction gave good yields product.

**Keywords:** one-pot reaction; green chemistry; solvent-free; Knoevenagel condensation reaction; malononitrile; room temperature. ©2021 ACG Publication. All right reserved.

### 1. Introduction

The carbon-carbon bond formation *via* Knoevenagel condensation<sup>1-3</sup> is one of the most important routes repeated in the synthetic organic chemistry and allows the production of various active pharmaceutical molecules.<sup>4</sup>



**Figure 1.** Structure of biologically potent benzylidene malononitrile derivatives

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## Knoevenagel condensation reaction catalysed by agro-waste extract

The aryldinmalononitrile derivatives allowed to achieve diverse pharmaceutically potent compound such as 2-(4-nitrobenzylidene)malononitrile (**1**) and 2-(3,4,5-trimethoxybenzylidene)-malononitrile (**2**) well known potential tyrosine kinase inhibitors<sup>12</sup>, 2-(3,4-dihydroxybenzylidene)-malononitrile derivative (**3**) emerged as a efficient anti-melanogenic agent. Many molecules derived from Knoevenagel condensation are well documented (Figure 1).<sup>13</sup>

Knoevenagel condensation are usually carried out by the reactions of active methylene compound with aliphatic or aromatic or heterocyclic aldehyde in the presence of organic base as a catalyst. Due to environment friendly concerns, the use of a organic base is not desirable and should be replaced. Therefore, synthetic organic chemists developed various inorganic metal and metal oxide derivatives heterogeneous catalyst with reusable such as  $\text{AlPO}_4 \cdot \text{Al}_2\text{O}_3$ <sup>18</sup>, USY Zeolite<sup>20</sup>,  $\text{MgBr}_2 \cdot \text{OEt}_2$ <sup>21</sup>, CTMAB<sup>22</sup>,  $\text{H}_3\text{PWO}_4$ <sup>23</sup>,  $\text{I}_2/\text{K}_2\text{CO}_3$ <sup>24</sup>,  $[\text{MeHMTA}]\text{BF}_4$  ionic liquid<sup>25</sup> and  $\text{LaCl}_3 \cdot \text{H}_2\text{O}$ <sup>26</sup>.

The use of greener solvent and catalyst such as ionic liquids are alternative method is well documented<sup>14</sup>, because of their good solubility, non-flammability, less vaporization and recyclability.<sup>25</sup> However, their application is limited in the macroscale process of the products due to their expensive reagents costs. Another method for Knoevenagel condensation was reported solvent-free condition, which lead environmentally benign, cost effective and gave high yield<sup>18</sup>. The current trend of synthetic organic chemistry is to develop Knoevenagel reaction under greener solvent, which should be environmentally friendly, cost effective, simple operation and efficient. In this context, water as a solvent and many agro-waste derived catalysts were reported by various research group, Water extract of nilgiri bark ash<sup>9</sup>, water extract of papaya bark ash<sup>14</sup>, Pineapple juice<sup>34</sup>, Water extract of banana<sup>45</sup> and Water extract of lemon fruit shell ash<sup>53</sup>. Although microwave-accelerated reactions are reported robust and faster method, there are also limitation on scalability, compatibility and energy usage<sup>7</sup>.

In this study, we have demonstrated a possibility to carry out Knoevenagel reaction of aromatic aldehydes or heterocyclic aldehyde with malononitrile catalyzed agro-waste extract, which served as an environmentally benign catalyst solvent. After completion of the reaction, the reaction mixture filtered to give pure Knoevenagel product in high yields with purity. Furthermore, this study explored the tolerability of the substituents on benzene ring and heterocycles.

## 2. Experimental

### 2.1. Material and Methods

FT-IR spectra were recorded in KBr disk on a Shimadzu FT-IR, <sup>1</sup>H and <sup>13</sup>C-NMR spectra obtained using a Bruker Avance 300MHz spectrometer (DRX). LC-MS spectra recorded in Waters synapt G2 high detection mass spectrometry. The progress of the reaction was monitored by TLC. Melting point of the final product was determined in open capillaries and are uncorrected.

### 2.2. Preparation of WEOFPA

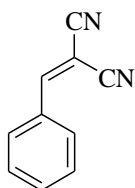
We are adopted our recently developed preparation of Water Extract of Orange Fruit Peel Ash (WEOFPA). Briefly, orange fruits are collected from a local fruit market in Belagavi, India. The outer shell is taken out, washed with tap water, and followed washed with double-distilled water to remove any physical impurities on the surface, it was dried under sunlight and thermal treatment on Bunsen burner (manuscript submitted) to ash. The obtained ash 10 g was suspended in 100 mL of double distilled water and stirred for an hour at room temperature. The suspension was filtered and light brown coloured filtrate is named as a WEOFPA.

### 2.3. Experimental Procedure for the Synthesis of Aryldinmalononitrile Derivatives (**3a-3p**)

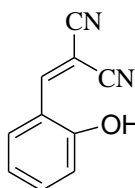
A mixture of aromatic aldehyde (1 mmole), malononitrile (1mmole) and 3 mL of WEOFPA taken in a 50mL round bottom flask, and reaction mixture stirred at room temperature, the reaction progress was monitored by TLC. After the reaction completion, ice cold water (10 mL) was added to reaction mixture, and product was collected by simple filtration, washed with water several times and dried to yield title compounds (**3a-3p**) as a solid. The product was obtained after recrystallization, and confirmed by FT-IR, <sup>1</sup>H, <sup>13</sup>C-NMR and mass spectrometry. The melting point of the obtained products very much comparable with the literature reported.

## 2.4. Spectral Data of Representative Selected Compounds

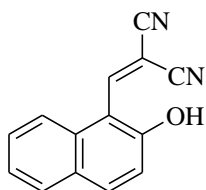
2- *Benzylidenemalononitrile* (**3a**):  $R_f=0.56$  (7:3 hexane-ethyl acetate); white solid; m.p. 81°C (lit<sup>34</sup>.82-84°C); 93%. FT-IR (KBr,  $\text{cm}^{-1}$ ): 2223 (CN), 1568 (C=C); <sup>1</sup>H-NMR ( $\text{CDCl}_3$ ):  $\delta$  (ppm) 7.88 (d,  $J=7.05$  Hz, 2H), 7.76 (s, 1H), 7.61 (t,  $J=7.6$  Hz, 2H); <sup>13</sup>C-NMR ( $\text{CDCl}_3$ ):  $\delta$ (ppm): 159.9, 134.5, 131.0, 130.5, 129.5, 113.8, 112.5, 82.8; LC-MS:  $m/z$  found: 154.05  $[\text{M}+\text{H}]^+$   $\text{C}_{10}\text{H}_6\text{N}_2$  Calcd.: 155.06.



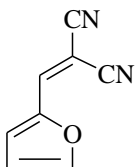
2-(2-*Hydroxybenzylidene*) malononitrile (**3b**):  $R_f=0.64$  (7:3 hexane-ethyl acetate); light yellow solid; m.p. 160°C (lit<sup>27</sup>.159-161°C); 90% yield: FT-IR (KBr,  $\text{cm}^{-1}$ ): 3552 (-OH), 2228 (CN), 1607 (C=C), 791 (-C-H). <sup>1</sup>H-NMR ( $\text{DMSO-d}_6$ ):  $\delta$ (ppm) 5.80-7.50 (m, 4H), 7.55 (s, 1H, Ar-OH), 5.85 (s, 1H); <sup>13</sup>C-NMR( $\text{CDCl}_3$ ):  $\delta$ (ppm) 115.7, 116.1, 116.4, 124.8, 125.29, 129.60, 154.7, 162.5. Please check LC-MS:  $m/z$  found: 170.05  $[\text{M}+\text{H}]^+$   $\text{C}_{10}\text{H}_6\text{N}_2\text{O}$  Calcd.:171.05.



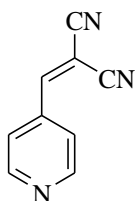
2-(*Naphthalen-1-ylmethylene*) malononitrile (**3l**):  $R_f=0.72$  (7:3 hexane-ethyl acetate); yellow powder solid; m.p. 172°C (lit<sup>54</sup>.172-174°C); 90% yield: FT-IR (KBr,  $\text{cm}^{-1}$ ): 3534 (-OH), 2224 (CN), 1562 (C=C); <sup>1</sup>H-NMR ( $\text{DMSO-d}_6$ ):  $\delta$ (ppm): 9.38 (s, 1H, C-H), 8.27 (m, 2H, Ar-H), 8.20 (t, 1H,  $J = 7.2$  Hz, Ar-H), 8.09 (t, 1H,  $J = 7.2$  Hz, ArH), 7.70 (m, 3H, Ar-H). <sup>13</sup>C-NMR ( $\text{DMSO-d}_6$ ):  $\delta$ (ppm) 157.6, 134.8, 133.4, 131.0, 129.3, 128.5, 128.7, 127.4, 125.3, 124.3, 122.2, 113.6, 112.4, 85.1, LC-MS:  $m/z$  found: 204.1  $[\text{M}+\text{H}]^+$ ,  $\text{C}_{14}\text{H}_8\text{N}_2$  Calcd.: 204.0.



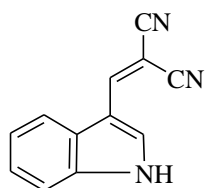
2-(2-*Furfurylmethylene*) malononitrile (**3m**):  $R_f=0.59$  (7:3 hexane-ethyl acetate); black solid; m.p. 64°C (lit<sup>34</sup>.65-66°C); 92% yield: FT-IR (KBr  $\text{cm}^{-1}$ ): 1455 (C=C), 1743 (furfuryl), 2235 (CN); <sup>1</sup>H NMR ( $\text{CDCl}_3$ )  $\delta$ (ppm): 6.87-6.88 (m, 1H, furfuryl), 7.09 (m, 1H, furfuryl), 7.19 (s, 1H, CH=C), 7.45 (s, 1H, furfuryl); <sup>13</sup>C-NMR ( $\text{CDCl}_3$ ):  $\delta$ (ppm) 75.46, 113.89, 115.11, 115.37, 126.44, 145.02, 148.60, 151.80. LC-MS:  $m/z$  found: 144.03  $[\text{M}+\text{H}]^+$ ,  $\text{C}_8\text{H}_4\text{N}_2\text{O}$  Calcd.:145.04.



2-(*Pyridin-4-ylmethylene*) malononitrile (**3n**):  $R_f=0.70$  (7:3 hexane-ethyl acetate); white solid; m.p.102°C (lit<sup>16</sup>.100-102°C); 90% yield. FT-IR: 3023 (HC=C), 2233(CN), 1610, 1548 (C=C), 1403 (C-N); <sup>1</sup>H NMR ( $\text{DMSO-d}_6$ )  $\delta$ (ppm): 7.69 (d,  $J=5.3$  Hz 2H ArH), 7.83 (s 1H vinyl H), 8.88 (d,  $J=5.3$  Hz, 2H Ar-H); <sup>13</sup>C NMR ( $\text{CDCl}_3$ ): 89.0, 111.8, 112.9, 123.1, 137.4, 151.9, 158.0. LC-MS:  $m/z$  found: 155.05  $[\text{M}+\text{H}]^+$ ,  $\text{C}_9\text{H}_5\text{N}_3$  Calcd.:156.05.

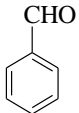
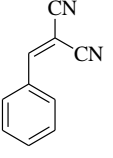
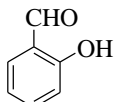
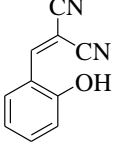
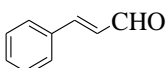
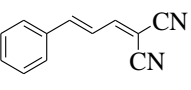
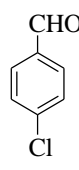
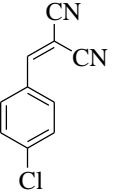
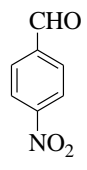
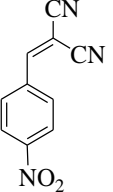
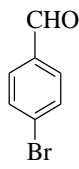
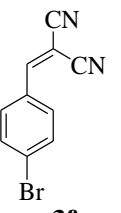
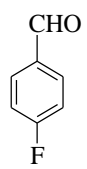
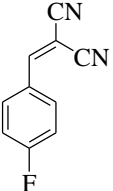


2-((1*H*-Indol-3-yl) methylene) malononitrile (**3**):  $R_f=0.79$ (7:3 hexane-ethyl acetate); Yellow solid; m.p, 190°C (lit<sup>15</sup>.187-189 °C); 89%. FT-IR (KBr  $\text{cm}^{-1}$ ): 3270(N-H), 2915(=C-H), 2215(CN), 1566(C=C), 1336(C-N); <sup>1</sup>H NMR ( $\text{DMSO-d}_6$ ), 7.31(t, 1H, 7.65 Hz), 7.36(t, 1H,  $J=7.23$ ), 7.54(d, 1H,  $J=8$  Hz), 7.92(d, 1H,  $J=8$  Hz), 8.52 (d, 1H,  $J=3.6$  Hz), 9.14 (s, 1H), 11.2 (d, 1H,  $J= 11.0$  Hz); <sup>13</sup>C NMR ( $\text{DMSO-d}_6$ ): 73.45, 110.24, 112.45 (2CN), 115.24, 118.70, 122.40, 123.45, 128.63, 135.6, 137.01, 150.48; LC-MS:  $m/z$  found:193  $[\text{M}+\text{H}]^+$ ,  $\text{C}_{12}\text{H}_7\text{N}_3$  Calcd.: 194.6.





**Table 2.** Physical constant and reaction data of Knoevenagel product.

Entry	Aldehyde	Product	Time (min)	Yield (%)	m.p. (°C)	
					Measured	Lit.
1		 <b>3a</b>	45	93	80-82	82-84 <sup>[34]</sup>
2		 <b>3b</b>	50	90	159-161	160-162 <sup>[27]</sup>
3		 <b>3c</b>	60	85	109-111	110-112 <sup>[34]</sup>
4		 <b>3d</b>	60	88	93-95	94-96 <sup>[34]</sup>
5		 <b>3e</b>	60	89	161-163	159-160 <sup>[34]</sup>
6		 <b>3f</b>	55	88	162-163	162-163 <sup>[34]</sup>
7		 <b>3g</b>	55	85	125-127	123-125 <sup>[34]</sup>

## Knoevenagel condensation reaction catalysed by agro-waste extract

Table 2 continued.

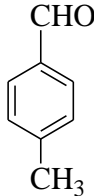
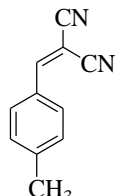
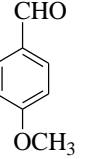
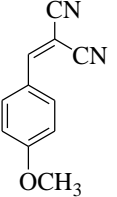
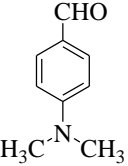
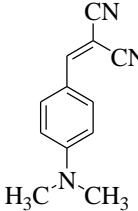
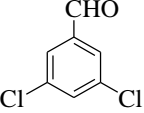
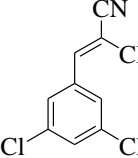
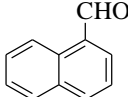
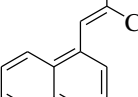
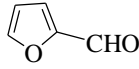
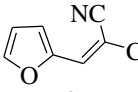
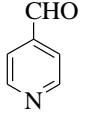
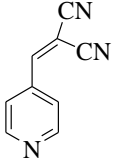
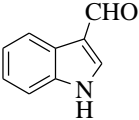
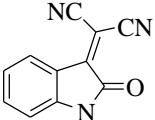
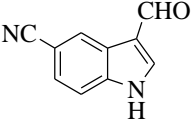
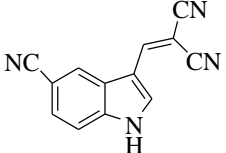
Entry	Aldehyde	Product	Time (min)	Yield (%)	m.p. (°C)	
					Measured	Lit.
8			60	82	97-99	98-100 <sup>[34]</sup>
9			60	90	113-115	114-116 <sup>[34]</sup>
10			55	85	183-185	182-184 <sup>[34]</sup>
11			60	85	81-83	80-82 <sup>[34]</sup>
12			50	90	157-159	158-160 <sup>[54]</sup>
13			55	92	77-78	74-76 <sup>[34]</sup>
14			30	90	98-100	100-102 <sup>[16]</sup>

Table 2 continued.

Entry	Aldehyde	Product	Time (min)	Yield (%)	m.p. (°C)	
					Measured	Lit.
15		 <b>3o</b>	4hr	89	260-262	256-259 <sup>[15]</sup>
16		 <b>3p</b>	2hr	96	290-292	289-291 <sup>[15]</sup>

- All the products were characterized by FT-IR, <sup>1</sup>H and <sup>13</sup>C-NMR and LC-MS
- Yields refer to the isolated yields.

**Table 3.** Comparison of different catalysts reported for the synthesis of arylidinemalononitrile derivatives.

S. No.	Catalyst	Solvent	Time (min)	Reaction condition	Yield (%)	Reference
1	AlPO <sub>4</sub> .Al <sub>2</sub> O <sub>3</sub>	-	30	rt	88	18
2	USY Zeolite	Benzene	12hr	reflux	92	20
3	MgBr <sub>2</sub> .OEt <sub>2</sub>	THF	1-2hr	rt	98	21
4	CTMAB	Water	1.5hr	rt	90.6	22
5	H <sub>3</sub> PWO <sub>40</sub>	Water	15	reflux	91	23
6	I <sub>2</sub> /K <sub>2</sub> CO <sub>3</sub>	EtOH/DMF	12hr	rt	80	24
7	MeHMTA]BF <sub>4</sub> ionic liquid	water	15	rt	99	25
8	LaCl <sub>3</sub> .H <sub>2</sub> O	-	1hr	Heated at 80°	95	26
9	SO <sub>4</sub> <sup>-2</sup> ion promoted ZrO <sub>4</sub>	N <sub>2</sub> atm,	180 min	reflux	89	28
10	Fe <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	DCM,	20 min	rt	93	29
11	SiO <sub>2</sub> -NH <sub>4</sub> OAc	DCM,	7 hr	60 °C	87	30
12	MOF-RNH <sub>2</sub>	Toluene,	2 hr	rt	99	31
13	GaCl <sub>3</sub>	-	2 min	Neat, grinding	98	32
14	Piperidine	-	6hr	reflux	94	33
15	Pineapple juice	-	1.5hr	rt	89	34
<b>16</b>	<b>WEOFPA</b>	<b>Ethanol</b>	<b>45 min</b>	<b>rt</b>	<b>90</b>	<b>Present Work</b>

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To explore the scope of the present method for different aldehyde derivatives such as aliphatic, aromatic and heterocyclic aldehydes are studied. No product formation was observed in the reaction of acetaldehyde with malononitrile for 1 mmole scale using 3 mL catalyst. However, the same reaction condition of benzaldehyde derivatives or heterocyclic aldehydes with malononitrile resulted high yield of condensation product isolation. Therefore, we can conclude, this method is well suitable for the substituted aromatic aldehyde and heterocyclic aldehyde Knoevenagel condensation (Table 2). Further, we also examined method for the bulk synthesis of Knoevenagel product upto 10 mmol scale reaction in a model reaction, and observed isolation of the product in excellent yield and purity.

We also compared the present method with the reported data in the literature, which is tabulated in Table 3. In the literature substrates **1-13** listed in the Table 3 were carried out Knoevenagel reaction in the presence of inorganic composites. These catalysts are expensive and harsh reaction conditions along with longer reaction time reported. Further, S. No. **1-13** used hazardous solvents for the reaction. Overall the present method demonstrated simplicity of the reaction condition and use of environmentally benign, less expensive catalyst for the Knoevenagel reaction compared to literature reported.

Several spectroscopic techniques confirmed the structure of the final products **3a-p**. For example, the isolated product **3m** observed FT-IR using KBr pellet: 3341.09 (CH-H), 2195.17 (C-C triple bond), 1600.11 (C=C), 1379.05 (C-N), 1191.76 (C-O-C) and 761.87 (C-H). <sup>1</sup>H NMR spectrum shows proton variation at 6.87-6.89 (m, H of furfuryl), 7.41 (m, 1H, furfuryl), 7.44 (s, 1H, CH=C), 8.26 (s, 1H, furfuryl). <sup>13</sup>C NMR: δ: 151.80 (C=C, 2-furan), 148.60 (C-C), 145.02 (ethylene -C), 115.37 (nitrile -C=C), 115.11 (nitrile -C=C), 113.81 (2-furan -C=C), 75.46 (1-ethylene). Mass spectrometry data is observed using LC-MS, which gives strong m/z peak at 144.03 [M+H]<sup>+</sup> and theoretically (C<sub>8</sub>H<sub>4</sub>N<sub>2</sub>O): 145.04.

## 4. Conclusion

In summary, we have demonstrated a new green protocol for Knoevenagel condensation catalysed by agro-waste extract as a catalytic media *via* “waste to wealth” concept. The method used agro-waste extract as a catalyst provides efficient application of the reaction with no use of the organic solvents and gives pure final product in good to excellent yields. Further, the reaction can be applied to heterocyclic aldehydes. Thus, an eco-friendly and economic method has been developed for Knoevenagel condensation of aromatic aldehydes and malononitrile to give good yields. The catalyst plays dual role either catalyst or solvent. The reaction procedure does not use any toxic materials to environment, therefore, it as a green approach. This procedure offers more advantages including shorter reaction time, clean reactions, and easy work-up.

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## Supporting Information

Supporting information accompanies this paper on <http://www.acgpubs.org/journal/organic-communications>

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