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

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(Received January 22, 2021; Revised March 15, 2021; Accepted March 18, 2021)

Abstract: This paper presents a novel Knoevenagel reaction protocol for the condensation of aromatic/heteroaromatic aldehydes with malononitrile to give α, β-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 is one of the most important routes repeated in the synthetic organic chemistry and allows the production of various active pharmaceutical molecules.

Figure 1. Structure of biologically potent benzylidinemalononitrile derivatives

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The article was published by ACG Publications
http://www.acgpubs.org/journal/organic-communications © January-March 2021 EISSN:1307-6175 DOI: http://doi.org/10.25135/acg.oc.99.21.01.1948
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The arylidinemalononitrile derivatives allowed to achieve diverse pharmacologically potent compound such as 2-(4-nitrobenzylidene)malononitrile (1) and 2-(3,4,5-trimethoxybenzylidene)malononitrile (2) well known potential tyrosine kinase inhibitors, 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). 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 an 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 AlPO43-Al2O3, USY Zeolite, MgBr2-0Et2, CTMAB, H3PWO423, I2/K3CO324, [MeHMTA]BF4 ionic liquid25 and LaCl3.H2O26.

The use of greener solvent and catalyst such as ionic liquids are alternative method is well documented, because of their good solubility, non-flammability, less vaporization and recyclability. 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. 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 ash8, water extract of papaya bark ash14, Pineapple juice14, Water extract of banana45 and Water extract of lemon fruit shell ash33. Although microwave-accelerated reactions are reported robust and faster method, there are also limitation on scalability, compatibility and energy usage.

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, 1H and 13C-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 Arylidinemalononitrile Derivatives (3a-3p)

A mixture of aromatic aldehyde (1 mmole), malononitrile (1 mmole) 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, 1H, 13C-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- Benzylidenemalonitrile (3a): Rf =0.56 (7:3 hexane-ethyl acetate); white solid; m.p. 81°C (lit14,82-84°C); 93%. FT-IR (KBr, cm⁻¹): 2223 (CN), 1568 (C=C); ¹H-NMR (CDCl₃): δ (ppm) 7.88 (d, J=7.05 Hz, 2H), 7.76 (s,1H), 7.61 (t, J=7.6 Hz, 2H); ¹³C-NMR (CDCl₃): δ (ppm) 159.9, 134.5, 131.0, 130.5, 129.5,113.8, 112.5, 82.8; LC-MS: m/z found: 154.05 [M+H]+ C₆H₆N₂ Calcd.: 155.06.

2- (2-Hydroxybenzylidene) malononitrile (3b): Rf =0.64 (7:3 hexane-ethyl acetate); light yellow solid; m.p. 160°C (lit27,159-161°C); 90% yield: FT-IR (KBr, cm⁻¹): 3552 (-OH), 2228 (CN), 1607 (C=C), 791 (-C-H). ¹H-NMR (DMSO-d₆): δ (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). ¹³C-NMR (DMSO-d₆): δ (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: 204.11[M+H]^+, C₁₄H₁₃N₂ Calcd.: 204.0.

2- (Naphthalen-1-ylmethylene) malononitrile (3f): Rf =0.72 (7:3 hexane-ethyl acetate); yellow powder solid; m.p. 172°C (lit4,172-174°C); 90% yield: FT-IR (KBr, cm⁻¹): 1455 (C=C), 1743 (furfuryl), 2235 (CN); ¹H NMR (DMSO-d₆): δ (ppm): 6.87-6.88 (m, 1H, furfuryl), 7.09 (m, 1H, furfuryl), 7.19 (s, 1H, CH=C), 7.45 (s,1H, furfuryl); ¹³C-NMR (CDCl₃): δ (ppm) 75.46, 113.89, 115.11, 115.37, 126.44, 145.02, 148.60, 151.80. LC-MS: m/z found: 144.03 [M+H]^+, C₉H₆N₂ Calcd.:145.04.

2- (2-Furfurylmethylene) malononitrile (3m): Rf =0.59 (7:3 hexane-ethyl acetate); black solid; m.p. 64°C (lit4,65-66°C); 92% yield: FT-IR (KBr cm⁻¹): 1455 (C=C), 1743 (furfuryl), 2235 (CN); ¹H NMR (CDCl₃): δ (ppm): 6.79 (d, J=5.3 Hz 2H ArH), 7.83 (s 1H vinyl H), 8.88 (d, J=5.3 Hz, 2H Ar-H); ¹³C NMR (CDCl₃): 89.0, 111.8, 112.9, 123.1, 137.4, 151.9, 158.0. LC-MS: m/z found: 155.05[M+H]^+, C₉H₆N₂ Calcd.:156.05.

2- ((1H-Indol-3-yl) methylene) malononitrile (3): Rf =0.79(7:3 hexane-ethyl acetate); Yellow solid; m.p. 190°C (lit15,187-189°C); 89%. FT-IR (KBr cm⁻¹): 3270(N-H), 2915(=C-H), 2215(CN), 1566(C=C), 1336(C-N); ¹H NMR (DMSO-d₆): 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); ¹³C NMR (DMSO-d₆): 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[M+H]^+, C₁₂H₇N₃ Calcd.: 194.6.
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3. Result and Discussion

Knoevenagel reaction employed organic base, inorganic metal or metal oxides as a catalyst for the formation of a condensed product. Our laboratory initial effort developed a greener protocol "from waste to wealth" concept, which was demonstrated in numerous heterocyclic synthesis catalyzed by agro-waste extracts. To start the required catalytic media for the present work, we have collected orange fruits peel from the local market available and subjected to thermal treatment. The resulted ash was treated with double distilled water to obtain water extract of orange fruit peel ash is named as WEOFPA (manuscript submitted for the publication).

\[ \text{R} - \text{CHO} + \text{CN} \xrightarrow{\text{WEOFPA}} \text{rt} \rightarrow \text{CN} \]

Scheme 1. General reaction of Knoevenagel condensation reaction

The extracted solution pH was examined and found to be 11.7. The ash powder was examined by elemental analysis using XRD, SEM-EDX and flame photometry. The elemental composition present in extract was found rich in Na, K, Ca, Mg and minor contents of Si, Ni, Fe etc. Overall the solution containing rich of potassium and sodium carbonate, and hydroxides of other elements make the solution basic in nature. To explore the utility of the prepared extract, we selected a model Knoevenagel condensation reaction using benzaldehyde with malononitrile at room temperature (Scheme 1) stirring condition for about 45 min gave a solid product isolation, and separated by filtration and purified by recrystallization.

To optimize the amount of WEOFPA volume required for the reaction for 1 mmole scale, we started use of different volumes of 0, 1, 2, 3, 4 and 5 mL of WEOFPA in a model reaction examination at room temperature. The optimization studies revealed that, the gradual increase in the product isolation occurs between 0-3 mL volumes of WEOFPA. Further use of catalyst volume 4 and 5mL, did not see any increase of the product yield. This optimization reaction revealed optimal volume of WEOFPA required for the Knoevenagel reaction is 3 mL at room temperature stirring condition (Table 1).

Table 1. Optimization of WEOFPA volume

| S. No. | Volume (mL) | Reaction time (min) | Yield (%) |
|-------|-------------|---------------------|-----------|
| 1     | 0           | 60                  | 60*       |
| 2     | 1           | 55                  | 70        |
| 3     | 2           | 50                  | 75        |
| 4     | 3           | 45                  | 90        |
| 5     | 4           | 45                  | 90        |
| 6     | 5           | 45                  | 90        |

*S.No.1, reaction performed without catalyst, but gave less yield with long reaction time.
Table 2. Physical constant and reaction data of Knoevenagel product.

| Entry | Aldehyde | Product | Time (min) | Yield (%) | m.p. (°C)  |
|-------|----------|---------|------------|-----------|------------|
|       |          |         | Measured   | Lit.      |
| 1     | CHO      |         | 45         | 93        | 80-82      |
|       |          |         |            |           | 82-84\cite{34} |
| 2     | CHO,OH   |         | 50         | 90        | 159-161    |
|       |          |         |            |           | 160-162\cite{27} |
| 3     | CHO      |         | 60         | 85        | 109-111    |
|       |          |         |            |           | 110-112\cite{34} |
| 4     | CHO      |         | 60         | 88        | 93-95      |
|       | Cl       |         |            |           | 94-96\cite{34} |
| 5     | CHO      |         | 60         | 89        | 161-163    |
|       | NO2      |         |            |           | 159-160\cite{34} |
| 6     | CHO      |         | 55         | 88        | 162-163    |
|       | Br       |         |            |           | 162-163\cite{34} |
| 7     | CHO      |         | 55         | 85        | 125-127    |
|       | F        |         |            |           | 123-125\cite{34} |
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Table 2 continued.

| Entry | Aldehyde | Product | Time (min) | Yield (%) | m.p. (°C) | Measured | Lit.  |
|-------|----------|---------|------------|-----------|-----------|----------|-------|
| 8     | CHO \(\text{C}_6\text{H}_4\text{CHO}\) | \(\text{C}_6\text{H}_4\text{CN}\) | 60         | 82        | 97-99     | 98-100\(^{[34]}\) |
| 9     |CHO \(\text{C}_6\text{H}_4\text{CHO}\) | \(\text{C}_6\text{H}_4\text{CN}\) | 60         | 90        | 113-115   | 114-116\(^{[34]}\) |
| 10    | CHO \(\text{C}_6\text{H}_4\text{CHO}\) | \(\text{C}_6\text{H}_4\text{CN}\) | 55         | 85        | 183-185   | 182-184\(^{[34]}\) |
| 11    |CHO \(\text{C}_6\text{H}_4\text{CHO}\) | \(\text{C}_6\text{H}_4\text{CN}\) | 60         | 85        | 81-83     | 80-82\(^{[34]}\) |
| 12    | CHO \(\text{C}_6\text{H}_4\text{CHO}\) | \(\text{C}_6\text{H}_4\text{CN}\) | 50         | 90        | 157-159   | 158-160\(^{[54]}\) |
| 13    | CHO \(\text{C}_6\text{H}_4\text{CHO}\) | \(\text{C}_6\text{H}_4\text{CN}\) | 55         | 92        | 77-78     | 74-76\(^{[34]}\) |
| 14    | CHO \(\text{C}_6\text{H}_4\text{CHO}\) | \(\text{C}_6\text{H}_4\text{CN}\) | 30         | 90        | 98-100    | 100-102\(^{[16]}\) |
Table 2 continued.

| Entry | Aldehyde | Product | Time (min) | Yield (%) | m.p. (°C) | Measured | Lit. |
|-------|----------|---------|------------|-----------|-----------|----------|------|
| 15    | ![Aldehyde](Image) | ![Product](Image) | 4hr | 89 | 260-262 | 256-259<sup>[15]</sup> |  |
| 16    | ![Aldehyde](Image) | ![Product](Image) | 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      | AlPO₄·Al₂O₃ | -       | 30         | rt                 | 88        | 18        |
| 2      | USY Zeolite | Benzene | 12hr       | reflux             | 92        | 20        |
| 3      | MgBr₂·OEt₂  | THF     | 1-2hr      | rt                 | 98        | 21        |
| 4      | CTMAB      | Water   | 1.5hr      | rt                 | 90.6      | 22        |
| 5      | H₃PWO₄₀     | Water   | 15         | reflux             | 91        | 23        |
| 6      | I₂/K₂CO₃   | EtOH/DMF| 12hr       | rt                 | 80        | 24        |
| 7      | MeHMTA[BF₄] ionic liquid | water | 15         | rt                 | 99        | 25        |
| 8      | LaCl₃·H₂O  | -       | 1hr        | Heated at 80°      | 95        | 26        |
| 9      | SO₄<sup>2-</sup> ion promoted ZrO₄ | N₂ atm, | 180 min    | reflux             | 89        | 28        |
| 10     | Fe₂(SO₄)₃  | DCM,    | 20 min     | rt                 | 93        | 29        |
| 11     | SiO₂·NH₃OAc | DCM,    | 7 hr       | 60 °C              | 87        | 30        |
| 12     | MOF-RNH₂   | Toluene, | 2 hr       | rt                 | 99        | 31        |
| 13     | GaCl₃      | -       | 2 min      | Neat, grinding     | 98        | 32        |
| 14     | Piperidine | -       | 6hr        | reflux             | 94        | 33        |
| 15     | Pineapple juice | - | 1.5hr     | rt                 | 89        | 34        |
| 16     | WEOFPA     | Ethanol | 45 min     | rt                 | 90        | Present Work |
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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). 1H 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). 13C 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]+ and theoretically (C₈H₄N₂O): 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.

Acknowledgement

Authors are thankful to the UGC for the award of Major Research Project {UGC-MRP:F.43-181/2014(SR)} and VGST, Govt. of Karnataka for SMYSR award to Dr. KK. The authors also acknowledges the Department of Science and Technology for the award of DST-FIST programme to the Department of Chemistry, RCUB.

Supporting Information

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

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