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ALUM CATALYZED AN ECO-FRIENDLY SYNTHESIS OF BENZYLIDENE MALONONITRILE AND BENZYLIDENE BARBITURIC ACID DERIVATIVES IN AQUEOUS MEDIUM

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ABSTRACT

Alum-catalyzed Knoevenagel reaction of substituted aromatic aldehydes and active methylene compounds such as malononitrile and barbituric acid using green, eco-friendly solvent, water was developed. The protocol is practically simple and found efficient. The condensation is carried out in a short reaction time and the desired products are obtained in excellent yields. Furthermore, The catalyst utilized is readily accessible, cost-effective, environmentally friendly, and safe. The derivatives are among the most frequently used intermediate in heterocyclic synthesis. The synthesized benzylidene derivatives were characterized by spectral analysis.

Keywords: Knoevenagel Condensation, Potassium Alum, Aqueous Medium, Green Catalyst, Active Methylene Compounds, Water, Green Approach.

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INTRODUCTION

Mostly in the formation of carbon-carbon bonds in organic synthetic procedures, the Knoevenagel reactions of aldehydes or ketones and active methylene substances such as malononitrile, malonates, diketones, and 1,3-ketoesters are crucial and often used.[1] The α, β-unsaturated derivatives formed by the condensation reaction are the key intermediates in the number of organic transformations and use for the construction of diverse heterocyclic compounds which find varied applications in pharmaceuticals, cosmetics, dyestuffs, and agrochemicals.[2] The benzylidene malononitrile and benzylidene barbituric acid derivatives show several diverse pharmaceutical activities such as antimicrobial, analgesic, and tyrosine kinase inhibitors to reduce melanogenesis and uridine phosphorylase inhibitors in cancer therapy.[3,4,5] Usually, the reaction is brought out in organic solvents using acids and bases including piperidine, sodium ethoxide, or sodium hydroxide.[6,7] A strong nucleophilic amine, DABCO,[8] (1,4-diazabicyclo [2,2,2] octane) in ethanol was reported for condensation. The other green efforts reported involved the use of several heterogeneous catalysts that are well explored for the condensation reaction such as zeolites,[9] metal oxide nanoparticles[10], and ionic liquids[11] however, these are not desirable due to some limitations such as high catalyst loading, non-recoverable nature, tedious workup, high cost and use of toxic organic solvents or co-solvents as a reaction medium.[12] Literature review revealed that the condensations have been carried out in water using surfactants such as cetyltrimethylammonium bromide (CTMAB)[13], an aqueous extract of *Acacia concinna* pods.[14] The aqueous extract of amla fruit was used for the synthesis of 2-aryl-1,3-benzoxazole derivatives.[15] In an aqueous media, the Knoevenagel reaction of active methylene substances, such as 1,3-dicarbonyl compounds with aromatic aldehydes and carbonyl compounds has been carried out with ease.[16] Alum ($KAl(SO_4)_2.12H_2O$) is a common water purifier, the antiseptic agent and has been reported to be an effective catalyst in a variety of organic reactions, preparation of 5-arylidene-2,4-thiazolidinedione[17], chromene-3-carbonitrile[18], benzylidene malononitrile derivatives under solvent-free condition[19] and in several other transformations[20,21,22] because it is eco-friendly, safe, inexpensive and mild acidic in nature.[23,24] The comparison of reported methodologies disclosed that the green, aqueous-mediated preparation of benzylidene derivatives of malononitrile and barbituric acid needs to develop. Herein, we report the alum-catalyzed, Knoevenagel reaction of substituted aromatic aldehydes with malononitrile and with barbituric acid in an aqueous medium. To the best of our understanding, this is the first illustration in which an alum-

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catalyzed condensation reaction in an aqueous medium has been extended to the Knoevenagel condensation reaction.

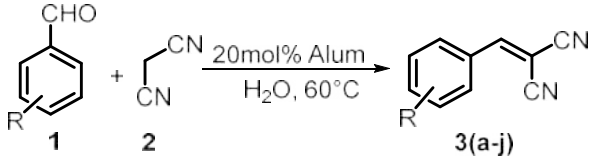
EXPERIMENTAL

Material and Methods

All chemicals and solvents used in the synthesis were from Sigma-Aldrich and Merck. Thin-layer chromatography (TLC) on silica gel plates, 60 F_{254}, was used to monitor the progress of the reaction. The open capillary technique was used to determine the melting points of synthesized compounds. FT-IR spectra were recorded using a Bruker alpha II spectrophotometer. $CDCl_3$ and DMSO-d_6 solvents were used to obtain ^1H and ^{13}C NMR spectra on a Bruker Advance Neo 500 MHz spectrophotometer. The mass spectra were recorded using the LC-MS Spectrometer model Q-ToF Micro Waters.

General Procedure for the Synthesis of Benzylidene Malononitrile (3a-j) and Benzylidene Barbituric Acid Derivatives (5a-j)

In a round bottom flask, an equimolar mixture of substituted aromatic aldehydes (1mmol), active methylene compound malononitrile/barbituric acid (1mmol), and water (10ml) was mixed with 20mol% alum. The reaction mixture was then stirred on a magnetic stirrer at 60°C until the reaction was complete. TLC was used to monitor the progress of the reaction; once the reaction was completed, the reaction mixture was cooled, and the product was precipitated out in the water. It was isolated by simple filtration and recrystallized using ethanol. FT-IR, ^1H NMR, ^{13}C NMR, and LCMS spectral analysis were used to characterize the products (Scheme-1 & 2 respectively).



Scheme-1: Alum-Catalyzed Synthesis of Benzylidene Malononitriles In Aqueous Medium.

Spectral Analysis of Synthesized Benzylidene Malononitrile Derivatives

2-Benzylidenemalononitrile (3a): Yield: 89%, Colourless crystalline, m.p.79-80°C; FT-IR: 3032 (Ar-H), 2213 (CN), 1550 (C=C), 1447 (C=C-Ar), 672, 751 (monosubstituted) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J= 7.4 Hz, 2H), 7.77 (s, 1H), 7.65-7.62 (m, 1H), 7.56-7.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.90, 134.63, 130.96, 130.73, 129.64, 113.66, 112.52, 82.97; ESI-MS (+): $C_{10}H_6N_2$ calc. for M = 154, found: m/z = 154 $[M]^+$

2-(4-Nitrobenzylidene)malononitrile (3b): Yield: 99 %, Ivory crystalline, m. p.158-160°C; FT-IR: 3084 (Ar-H), 2248 (CN), 1577 (C=C-Ar), 1511 (C=C), 827 (para disubstituted) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.39 (dd, J=5.15 & 2.75 Hz, 2H), 8.07 (d, J=7.1 Hz, 2H), 7.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.85, 150.39, 135.80, 131.32, 124.66, 112.62, 111.60, 87.58.

2-(4-Hydroxybenzylidene)malononitrile (3c): Yield: 95 %, Yellow crystalline, m. p.187-189°C; FT-IR: 3362 (OH), 3084 (Ar-H), 2216 (CN), 1562 (C=C),1434 (C=C -Ar) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (dd, J=5.05 & 1.82 Hz, 2H), 7.64 (s, 1H), 6.96 (dd, J= 4.85 & 1.97 Hz, 2H), 6.52 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.36, 158.82, 133.71, 124.23, 116.74, 113.71, 112.31, 82.74.

2-(4-Chlorobenzylidene)malononitrile (3d): Yield: 90 %, White Crystalline, m. p. 94-96°C; FT-IR: 3034 (Ar-H), 2211 (CN), 1569 (C=C),1537 (C=C-Ar), 820 (Para disubstituted) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, J=8.5 Hz, 2H) 7.73 (s, 1H), 7.52 (d, 2H, J= 8.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.25, 141.18, 131.84, 130,10, 129.28, 113.43, 112.33, 83.42.

2-(4-Methylbenzylidene)malononitrile (3e): Yield: 89%, White crystalline , m. p.116-118°C; FT-IR: 3024 (Ar-H), 2216 (CN), 1577 (C=C), 1410 (C=C-Ar), 811 (Para disubstituted) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, J= 8.25 Hz, 2H), 7.71 (s, 1H), 7.33 (d, J= 8.15 Hz, 2H), 2.45 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.74, 146. 38, 130.92, 130.39, 128.49, 114.01, 112.85, 81.30, 22.02.

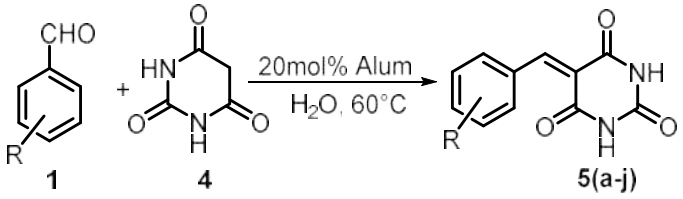
2-(4-Methoxylbenzylidene)malononitrile (3f): Yield: 96 %, Faint yellow crystalline , m. p. 108-110°C; FT-IR: 3039 (Ar-H), 2206 (CN), 1555 (C=C), 1510 (C=C- Ar) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (dd, J=5.15 & 1.85 Hz, 2H), 7.65 (s, 1H), 7.01 (dd, J=5.05 & 1.95 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.84, 158.85, 133.46, 124.05, 115.15, 114.42, 113.34, 78.64, 55.81.

2-(4-Bromobenzylidene)malononitrile (3g): Yield: 95%, Off white crystalline, m. p. 148-150°C; FT-IR: 3116 (Ar-H), 2210 (CN), 1652 (C=C), 1564 (C=C-Ar), 819 (Para disubstituted) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.77-7.75 (m, 2H), 7.71 (s, 1H) 7.70-7.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.42, 133.10, 131.81, 129.94, 129.67, 113.45, 112.33, 83.5; ESI-MS (+): $C_{10}H_5BrN_2$ calc. for M = 233, found: m/z = 233 $[M]^+$.

2-(4-Hydroxy-3-Methoxybenzylidene)malononitrile (3h): Yield: 95%, Yellow crystalline, m. p.133-135°C; FT-IR: 3303 (OH), 3177 (Ar-H), 2223 (CN), 1565 (C=C), 1506 (C=C-Ar) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$,): δ 7.73 (d, J = 1.95 Hz, 1H), 7.62 (s, 1H), 7.30 (dd, J = 6.35 & 1.85 Hz, 1H), 7.02 (d, J= 8.3 Hz, 1H), 6.34 (s, 1H), 3.98 (S, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.21, 152.12, 147.05, 129.02, 124.01, 115.22, 114.38, 113.62, 110.41, 78.77 56.24.

2-(2-Nitrobenzylidene)malononitrile (3i): Yield: 94%, Creamy crystalline, m. p. 135-137°C; FT-IR: 3021 (Ar-H), 2214 (CN), 1567 (C=C), 1512 (C=C-Ar), 1332 (NO_2), 790 (Ortho disubstituted), cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.35 (d, J =8.35 Hz, 1H), 7.89-7.86 (m, 1H), 7.82-7.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.69, 146.83, 134.93, 130.47, 126.71, 125.87, 112.20, 110.96, 88.62; ESI-MS (+): $C_{10}H_5N_3O$ calc. for M = 199, found: m/z = 199 $[M]^+$.

2-(2-Chlorobenzylidene)malononitrile (3j): Yield: 91 %, Faint yellow crystalline, m.p.84-86°C; FT-IR: 3085 (Ar-H), 2204 (CN), 1572 (C=C),1434 (C=C-Ar), 756 (Ortho disubstituted) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.18 (d, J=7.85Hz, 1H), 7.55-7.54 (m, 2H), 7.46-7.43 (m, 1H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.04, 136.36, 135.03, 130.71, 129.51, 129.08, 127.79, 113.21, 111.90, 85.83.



Scheme-2: Alum-Catalyzed Synthesis of Benzylidene Barbituric Acid in Aqueous Medium

Spectral analysis of synthesized benzylidene barbituric acid derivatives

5-Benzylidenepyrimidine-2,4,6(1H,3H,5H)-trione (5a): Yield: 96%, Creamy crystalline, m. p. 248-250°C; FT-IR: 3353, 3177 (NH), 3025 (Ar-H), 1671 (CO amide), 1588 (C=C), 799, 681 (Mono substituted) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 11.38 (s, 1H), 11.22 (s, 1H), 8.28 (s, 1H), 8.08 (d, J= 7.3Hz, 2H), 7.56-7.53 (m, 1H), 7.49-7.46 (m, 2H);^{13}C NMR (125 MHz, DMSO-d_6): δ 161.45, 154.53, 150.08, 132.96, 132.56, 132.07, 127.93, 119.01; ESI-MS (+): $C_{11}H_8N_2O_3$ calc. for M = 216, found: m/z = 216 $[M]^+$.

5-(4-Nitrobenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (5b): Yield: 91 %, Faint yellow amorphous, m.p. 274-275°C; FT-IR: 3235, 3105 (NH), 3089 (Ar-H), 1684 (CO amide), 1512 (C=C), 859 (Para disubstituted) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 11.49 (s, 1H), 11.31 (s, 1H), 8.33 (s, 1H), 8.25 (m, 2H), 8.03 (d, J= 8.45 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.54, 150.99, 150.09, 147.94, 139.91, 132.14, 124.17, 122.77.

5-(4-Hydroxybenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (5c): Yield: 95% Chrome Yellow amorphous, m. p.: > 320°C; FT-IR: 3270, 3181 (NH), 3089 (Ar-H), 1663 (CO amide), 1533 (C=C), 830 (Para disubstituted) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 11.24 (s, 1H), 11.11 (s, 1H), 10.78 (s, 1H), 8.33 (d, J= 8.9 Hz, 2H), 8.21 (S, 1H), 6.88 (dd, J= 8.9 & 2.67 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.90, 162.18, 155.38,150.10, 138.18, 123.69, 115.40, 114.11.

5-(4-Chlorobenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (5d): Yield: 93%, White amorphous, m. p. 287-288°C; FT-IR: 3205 (NH), 3079 (Ar-H), 1672 (CO amide), 1569 (C=C), 800 (Para disubstituted) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.41 (s, 1H), 11.26 (s, 1H), 8.25 (s, 1H), 8.08 (d, J=7.05 Hz, 2H), 7.53 (m, 2H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 163.09, 152.84, 150.06, 136.60, 134.57, 131.49, 127.98, 119.60.

5-(4-Methylbenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (5e): Yield: 98%, Creamy crystalline, m. p. 275-276°C; FT-IR: 3203 (NH), 3079 (Ar-H), 1668 (CO amide), 1569 (C=C), 805 (para disubstituted) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.34 (s, 1H), 11.20 (s, 1H), 8.25 (s, 1H), 8.10 (d, J= 8.3 Hz, 2H), 7.31 (d, J= 8.15 Hz, 2H); 2.39 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d6): δ 161.66, 154.78, 150.06, 143.31, 133.82, 129.75, 128.73, 117.77, 21.23.

5-(4-Methoxybenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (5f): Yield: 96%, Fluorescent yellow amorphous, m.p. 284-286°C; FT-IR: 31955 (NH), 3062 (Ar-H), 1670 (CO amide), 1554 (C=C), 838 (Para disubstituted) cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 11.29 (s, 1H), 11.16 (s, 1H), 8.37 (d, J=7.3 Hz, 2H), 8.25 (s, 1H), 7.07 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d6): δ 163.33, 162.06, 154.82, 150.07, 137.35, 125.05, 115.45, 113.83, 55.58.

5-(4-Bromobenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (5g): Yield: 92 %, Creamy amorphous, m. p. 287-288°C; FT-IR: 3204 (NH), 3084 (Ar-H), 1670 (CO amide), 1570 (C=C), 799 (Para disubstituted) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.40 (s, 1H), 11.26 (s, 1H), 8.22 (s, 1H), 7.99 (d, J=8.5 Hz, 2H), 7.68 (dt, J= 8.55 & 2.1 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d6): δ 161.45, 152.91, 150.05, 134.57, 131.84, 130.92, 125.69, 119.71.

5-(2-Nitrobenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (5h): Yield: 94%, White amorphous, m. p. 266-268°C; FT-IR: 3230 (NH), 3078 (Ar-H), 1600 (CO amide), 1517 (C=C), 1374 (NO_2), 760 (Ortho disubstituted) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.49 (s, 1H), 11.23 (s, 1H), 8.60 (s, 1H), 8.24 (dd, J=7.3 & 0.975 Hz, 1H), 7.81-7.77 (m, 1H), 7.67 (m, 1H), 7.58 (d, J = 7.65 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.07, 152.30, 150.12, 146.17, 133.62, 131.59, 130.28, 130.03, 123.93, 120.43; ESI-MS (+): $C_{11}H_7N_3O_5$ calc. for M = 261, found: m/z = 284 $[M+Na]^+$.

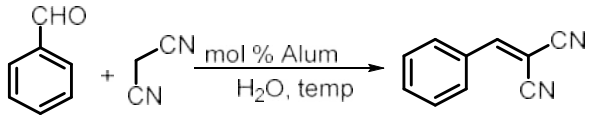
5-(2-Chlorobenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (5i): Yield: 90%, Faint yellow crystalline, m. p. 251-253°C; FT-IR: 3508, 3466 (NH), 3028 (Ar-H), 1668 (CO amide), 1574 (C=C), 749 (Ortho disubstituted) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.47 (s, 1H), 11.25 (s, 1H), 8.30 (s, 1H), 7.75 (dd, J= 6.6 & 1.17 Hz, 1H), 7.55 (dd, J=7.1 &1 Hz, 1H), 7.49-7.46 (m, 1H), 7.39-7.35 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.52, 150.09, 149,58, 133.06, 132.16, 131.84, 131.81, 128.77, 126.21, 121.68; ESI-MS (+): $C_{11}H_7ClN_2O_3$ calc. for M = 250, found: m/z = 250 $[M^+]$.

5-(2-hydroxybenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (5j): Yield: 85%, Faint yellow amorphous, m. p. 249-251°C; FT-IR: 3277, 3219 (NH), 3111 (Ar-H), 1699 (CO amide), 1503 (C=C), 766 (ortho disubstituted) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.96 (s, 1H), 11.28 (s, 1H), 11.16 (s, 1H), 10.97 (s, 1H), 7.36-7.32 (m, 1H), 7.22 (m, 1H),7.15 (d, J=7.15 Hz, 1H), 7.09 (d, J= 8.2 Hz,1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.38, 155.28, 150.41, 149.41, 149.01, 129.10, 127.91, 125.46, 120.66, 116.35.

RESULTS AND DISCUSSION

To investigate the catalytic activity of alum in water as a green media for the Knoevenagel reaction, the reaction of benzaldehyde (1a) and malononitrile (2) was performed with varied amounts of catalyst and reaction temperatures (Tables-1 and 2) (Scheme-3). Surprisingly, stirring equimolar proportions of benzaldehyde (1a) and malononitrile (2) in water yielded 89% of the product (Table-1; entry 3) within 2 h in the presence of alum. The model reaction performed well at 20 mol% alum (Table-2; entry 4), with the highest yield reached in 2h, however, no significant improvement in yield was found at higher alum concentrations. At rt, the reaction runs smoothly, but when the temperature is raised to 60°C, the yield of the reaction is found to increase. (Entry 3 in Table-1)With the best reaction condition for the model reaction in hand, the reaction of a series of aromatic aldehydes (1a-j) with malononitrile (2) in equimolar amounts was carried out to investigate the substrate scope of the reaction. The substituents present in aromatic

aldehydes have no noticeable effect on the yields of the derivatives, but in terms of reaction time, aldehydes with electron-withdrawing substituents react faster under the reaction conditions (Table-3; entries 2, 9) than the benzaldehydes with electron-releasing substituents (Table-3; entries 3, 5, 6).



1a **2** **3a**

Scheme-3: Model Reaction for Benzylidene Malononitrile Synthesis

Table-1: Effect of temperature on Synthesis of Benzylidene Malononitrile(3a) Using 20 Mol% Alum

Entry	Temperature(° C)	Time (h)	Yield (%)
1	RT	5	79
2	40	3	78
3	60	2	89
4	80	2	78

Table-2: Effect of Alum loading on Synthesis of Benzylidene Malononitrile (3a) at 60°C

Entry	Benzylidene Catalyst (mol%)	Time (h)	Yield (%)
1	-	8	10
2	10	5	15
3	15	3	56
4	20	2	89
5	25	2:15	80
6	30	2:15	82

Table-3: Physical Data of Substituted Benzylidene Malononitrile Derivatives 3a-3j[a]

Entry	Substituent	Product	Time (min)	Yield[b] (%)	M.P.(°C)	
					Observed	Reported
1	H	3a	120	89	79-80	80-82[4]
2	4-NO_2	3b	10	99	158-160	161-163[4]
3	4-OH	3c	50	95	187-189	189-190[25]
4	4-Cl	3d	10	90	94-96	93-95[4]
5	4-CH_3	3e	90	89	116-118	118-119[26]
6	4-OCH_3	3f	120	96	108-110	110-113[27]
7	4-Br	3g	75	95	148-150	155[28]
8	4-OH, 3-OCH_3	3h	45	95	133-135	134-135[28]
9	2-NO_2	3i	40	94	135-137	136-138[29]
10	2-Cl	3j	60	91	84-86	82-85[27]

[a]Reaction conditions: Substituted benzaldehyde(1mmol), malononitrile(1mmol), and water (10 ml) catalyzed by 20mol% alum at 60°C.
[b]Isolated yields in percentage.

Table-4: Physical Data of Substituted Benzylidene Barbituric Acid Derivatives 5a-5j[a]

Entry	Substituent	Product	Time (min)	Yield[b] (%)	M.P.(°C)	
					Observed	Reported
1	H	5a	10	96	248-250	250-252[30]
2	4-NO_2	5b	5	91	274-275	272-274[4]
3	4-OH	5c	10	95	>320	>320[28]
4	4-Cl	5d	5	93	287-288	292-293[30]
5	4-CH_3	5e	10	98	275-276	274-278[31]
6	4-OCH_3	5f	10	96	284-286	287-289[30]
7	4-Br	5g	10	92	287-288	288-290[10]
8	2-NO_2	5h	5	94	266-268	271-273[32]
9	2-Cl	5i	5	90	251-253	250-252[10]
10	2-OH	5j	10	85	249-251	248-250[32]

[a]Reaction conditions: Substituted benzaldehyde (1mmol), barbituric acid (1mmole), and water (10 ml) catalyzed by 20mol% alum at 60°C; [b]Isolated yields in percentage.

The good results obtained in the synthesis of benzylidene malononitrile derivatives motivated us to apply the methodology to the synthesis of benzylidene barbituric acid derivatives. To examine the scope of the methodology, we performed the condensation reaction of 4-chlorobenzaldehyde (1d) with barbituric acid (4) to yield the 4-chlorobenzylidene barbituric acid derivative (5d). The electron-withdrawing and electron-donating substituted aromatic aldehyde react equally well in a short reaction time, producing high product yields (Table-4). The results showed the efficient application of catalyst for the series of substituted aldehydes. The melting points of the products were compared with the literature value and are close matches. TLC was used to monitor the reaction completion using the solvent system n-hexane-ethyl acetate (7:3).

CONCLUSION

The present study provides an easy, effective, and environmentally friendly practical approach to generate an important key intermediate of organic multistep synthesis as well as biologically significant benzylidene malononitrile and benzylidene barbituric acid derivatives. The protocol avoids the use of hazardous organic solvents, costly catalysts, and tedious workup involved in their use.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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