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RESEARCH ARTICLE

Efficient and Eco-Friendly Knoevenagel Condensation Catalyzed by L-Phenylalanine–Sodium Acetate Under One-Pot Grinding Approach

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ABSTRACT

A green, efficient, and solvent-free method for the Knoevenagel condensation has been developed using a novel biocompatible catalyst system comprising phenylalanine and sodium acetate under one-pot grinding conditions. The catalyst promotes C=C bond formation between various aromatic aldehydes and active methylene compounds such as malononitrile and dimethyl malonate with excellent yields and short reaction times. This mechanochemical approach eliminates the use of hazardous organic solvents and harsh reaction conditions, aligning well with green chemistry principles. The method offers a simple work-up procedure, good functional group tolerance, and the ability of the catalyst.

Key words: Aromatic aldehydes, Dimethyl malonate, Grinding, L-phenylalanine, Malononitrile, Sodium acetate.

1. INTRODUCTION

The Knoevenagel condensation is one of the most fundamental and widely used carbon–carbon bond-forming reactions in organic synthesis. It involves the condensation of aldehydes or ketones with active methylene compounds, typically in the presence of a basic or acidic catalyst, to yield α, β-unsaturated compounds which serve as valuable intermediates in pharmaceuticals, agrochemicals, and fine chemicals [1]. Over the decades, various homogeneous and heterogeneous catalysts have been employed for the Knoevenagel reaction as LiOH [2], $ZnCl_2$ [3], Cu metal surface [4], LiBr [5], biomass-derived carbon dots [6], and Chitosan in water [7]. Traditional base catalysts such as piperidine, pyridine, and amines, though effective, suffer from issues such as toxicity, volatility, and environmental concerns [8]. To address these limitations, recent research has focused on green and sustainable catalytic systems. Numerous catalysts have been reported for promoting the Knoevenagel reaction by environmental begin such as metal-organic frameworks [9], ionic liquids [10], zeolites [11], and metal oxides like CeO_2 [12] have shown good catalytic activity. Biocatalysts and amino acid-based catalysts are gaining attention due to their biocompatibility and non-toxic nature. For instance, L-proline and its derivatives have been used under mild conditions [13]. Similarly, hybrid catalysts combining amino acids with salts or solid supports have shown synergistic effects in promoting condensation reactions [14]. Mechanochemistry, particularly the grinding method, has emerged as an attractive green alternative, as it avoids the use of solvents, reduces reaction time, and simplifies the reaction setup [15]. Grinding enhances contact between reactants and catalysts, facilitating efficient energy transfer and accelerating the reaction. Combining mechanochemistry with amino acid-based catalysis offers a promising route toward eco-friendly synthesis.

In this context, we report a novel, efficient, and eco-friendly one-pot Knoevenagel condensation catalyzed by a phenylalanine–sodium acetate system under grinding conditions. The phenylalanine acts as a biocompatible organic base, while sodium acetate enhances the deprotonation of the active methylene compound. This synergistic system effectively promotes the formation of α, β-unsaturated carbonyl compounds under solvent-free conditions, offering a simple and sustainable alternative to conventional methods.

2. MATERIAL AND METHOD

All the chemicals used were commercially available and AR grade. Physical constants (m.p.) were determined by the open capillary method and are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR spectrophotometer, and Mass spectra were recorded on a TOF MS ES+ 2.60e7. 1H spectra on a BRUKER AVANCE NEO 500 NMR spectrometer with DMSO-d_6 as a solvent and chemical shift (δ) are expressed in ppm using TMS as an internal standard.

2.1. General Procedure for the Preparation of Dimethyl Benzylidene Malonate and Benzylidene Malononitrile

Equimolar quantities of aryl aldehyde (0.01 mole), diethyl malonate or malononitrile (0.01 mole), and sodium acetate (0.02 mole) with (0.001 mole) phenyl alanine were grinded together in mortal and pestle for 10–15 min at room temperature. The progress of the reaction was checked by TLC. After completion of reaction, content was discharged in 50 mL ice water with stirring. Resulting product was filtered, dried, and recrystallized in ethanol.

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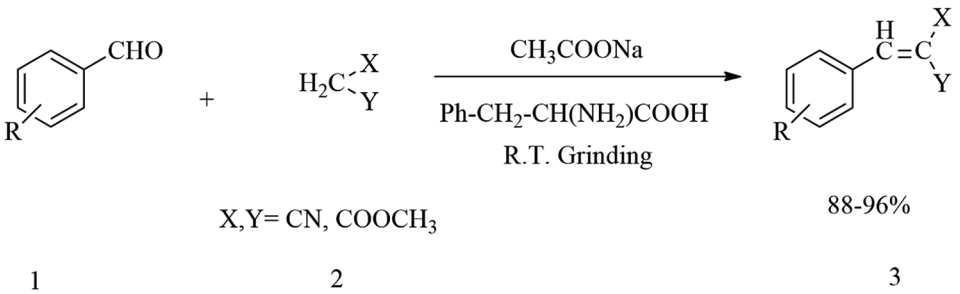

Scheme 1: Reaction condition and yield of desired product

Table 1: Physical Characterization of synthesized compounds

Compounds	R	X and Y	Time	% Yield	M.P. °C
3A	H	$COOCH_3$	12	90	28
3B	3-OH	$COOCH_3$	14	88	72
3C	4-NO_2	$COOCH_3$	10	94	138
3D	4-Cl	$COOCH_3$	12	92	36
3E	4-OCH_3	$COOCH_3$	14	92	oil
3F	4-F	$COOCH_3$	12	90	38
3G	H	CN	12	92	82
3H	3-OH	CN	14	90	188
3I	4-NO_2	CN	10	96	162
3J	4-Cl	CN	12	94	164
3K	4-OCH_3	CN	13	92	114
3L	4-F	CN	13	90	124

2.1.1. 3A: Dimethyl 2-benzylidene malonate

IR (KBr): 2890 (C-H), 1735 (C=O, ester), 1625 (C=C) cm^{-1}; Mass: m/z 220 (M^+); 1H NMR (500 MHZ, DMSO-d_6): δ 3.06 (s, 6H, CH_3), 7.33–7.62 (m, 5H, Ar-H), 8.35 (s, 1H, =C-H); Elemental Analysis, Calculated: $C_{12}H_{12}O_4$: C, 65.45; H, 5.49 %. Found: C, 65.50; H, 5.51%.

2.1.2. 3B: Dimethyl 2-(3-hydroxybenzylidene)malonate

IR (KBr): 3497 (O-H), 2880 (C-H), 1733 (C=O, ester), 1622 (C=C) cm^{-1}; Mass: m/z 236 (M^+); 1H NMR (500 MHz, DMSO-d_6): δ 3.03 (s, 6H, CH_3), 5.35 (s, 1H, Ar-OH), 7.72 (d, 1H, Ar-H), 7.92 (s, 1H, Ar-H), δ 8.15 (d, 1H, Ar-H), 8.30 (d, 1H, Ar-H), 8.35 (s, 1H, =C-H); Elemental Analysis, Calculated: $C_{12}H_{12}O_5$: C, 61.01; H, 5.12%. Found: C, 61.04 H, 5.10%.

2.1.3. 3C: Dimethyl 2-(4-nitrobenzylidene)malonate

IR (KBr): 2885 (C-H), 1740 (C=O, ester), 1527, 1344 (NO_2), 1623 (C=C) cm^{-1}; Mass: m/z 265 (M^+); 1H NMR (500 MHz, DMSO-d_6): δ 3.03 (s, 6H, CH_3), 6.77 (d, 2H, Ar-H), 7.79 (d, 2H, Ar-H), 9.69 (s, 1H, =C-H); Elemental Analysis, Calculated: $C_{12}H_{11}NO_6$: C, 54.34; H, 4.18; N, 5.28 %. Found: C, 54.36 H, 4.20; N, 5.30%.

2.1.4. 3G: 2-Benzylidenemalononitrile

IR (KBr): 2905 (C-H), 2225 (CN), 1622 (C=C) cm^{-1}; Mass: m/z 154 (M^+); 1H NMR (500 MHZ, DMSO-d_6): δ 7.35–7.70 (m, 5H, Ar-H), 7.85 (s, 1H, =C-H); Elemental Analysis, Calculated: $C_{10}H_6N_2$: C, 77.91; H, 3.92; N, 18.17 %. Found: C, 77.93; H, 3.90; N, 18.14%.

2.1.5. 3H: 2-(3-hydroxybenzylidene)malononitrile

IR (KBr): 3510 (O-H), 2888 (C-H), 2233 (CN), 1624 (C=C) cm^{-1}; Mass: m/z 170 (M^+); 1H NMR (500 MHz, DMSO-d_6): δ 5. 45 (s, 1H, Ar-OH), 6.70 (d, 1H, Ar-H), 6.83 (d, 1H, Ar-H), 7.16 (d, 1H, Ar-H), 7.55 (dd, 1H, Ar-H), 8.15 (s, 1H, =C-H); Elemental Analysis, Calculated: $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46%. Found: C, 70.60; H, 3.58; N, 16.42%.

2.1.6. 3I: 2-(4-nitrobenzylidene)malononitrile

IR (KBr): 2895 (C-H), 2230 (CN), 1530, 1345 (NO_2), 1620 (C=C) cm^{-1}; Mass: m/z 199 (M^+); 1H NMR (500 MHz, DMSO-d_6): δ 7.96 (s, 1H, =C-H), 8.07 (d, 2H, Ar-H), 8.28 (d, 2H, Ar-H); Elemental Analysis, Calculated: $C_{10}H_5N_3O_2$: C, 60.31; H, 2.53; N, 21.1%. Found: C, 60.33 H, 2.55; N, 21.4%.

3. RESULTS AND DISCUSSION

We investigated the Knoevenagel reaction under solvent-free conditions by manually grinding aromatic aldehydes with dimethyl malonate or malononitrile, sodium acetate, and L-phenylalanine as a heterogeneous catalyst in a mortar and pestle at room temperature [Scheme 1]. The reaction is typically completed within 10–15 min with excellent yields (88–96%) [Table 1].

Fourier transform infrared (FT-IR), nuclear magnetic resonance (NMR), and mass spectra analysis confirmed the formation of the desired α, β-unsaturated products. In IR spectra, the peak position at 1620–1625 cm^{-1} for C=C of alkene indicates the formation of products 3A-L. In NMR spectra, the peak position at δ 7.85–9.69 of products 3A-L clearly confirm formation of these products. Mass spectra of these compounds further supported for their formation. Melting points of synthesized compounds were matched with reported in the literature. The products were easily purified by simple recrystallization methods, emphasizing the environmental friendliness of the procedure.

Herein, we report a straightforward, effective, and eco-friendly grinding method for the Knoevenagel reaction. This solvent- and catalyst-free approach offers high yields in ambient conditions under brief reaction time.

4. CONCLUSION

We have developed a highly efficient, eco-friendly, and sustainable method for the Knoevenagel condensation using a novel L-phenylalanine–sodium acetate catalytic system under a solvent-free, one-pot grinding approach. The method offers several advantages including mild reaction conditions, short reaction times, excellent yields, simple work-up procedures, and elimination of harmful solvents, aligning well with the principles of green chemistry. The catalytic system exhibited broad substrate compatibility, enabling the synthesis of a variety of α, β-unsaturated compounds with good to excellent yields. The successful application of a biodegradable amino acid and an inexpensive additive as a synergistic catalyst system further highlights the green and cost-effective nature of this protocol.

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6. CONFLICT OF INTEREST

Authors were declared that there is no conflict of interest.

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