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Sustainable Knoevenagel Condensation through L-Phenylalanine Sodium Acetate Catalysis under Solvent Free Grinding Conditions

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Abstract

A convenient and environmentally compatible protocol has been developed for the synthesis of α,β -unsaturated compounds through Knoevenagel condensation under solvent-free mechanochemical conditions. The reaction employs a combination of L-phenylalanine and sodium acetate as an efficient catalytic system and is performed by simple grinding at room temperature. A range of aromatic aldehydes was reacted with active methylene compounds including dimethyl malonate and malononitrile. The transformations proceeded rapidly, generally requiring only 10-15 min, and afforded the corresponding condensation products in 88-96% yields. The protocol avoids hazardous organic solvents and does not require complicated reaction equipment or elevated temperatures. Product isolation was accomplished through a simple aqueous work-up followed by recrystallization from ethanol. Spectroscopic and analytical investigations using FT-IR, ^1H NMR, mass spectrometry and elemental analysis confirmed the structures of the synthesized compounds. The combination of an inexpensive salt, a biocompatible amino acid and mechanochemical activation provides a practical approach for greener Knoevenagel condensation.

Keywords: Aromatic aldehydes, dimethyl malonate, grinding, L-phenylalanine, malononitrile, sodium acetate

1. Introduction

The Knoevenagel condensation represents an important carbon-carbon bond-forming transformation in organic chemistry. The reaction generally involves the condensation of aldehydes or ketones with active methylene compounds in the presence of a suitable acidic or basic catalyst, producing α,β -unsaturated products that are important intermediates in pharmaceutical, agrochemical and fine-chemical synthesis [1]. A wide variety of catalytic systems have been explored for this transformation. Reported examples include lithium hydroxide [2], zinc chloride [3], copper surfaces [4], lithium bromide [5], biomass-derived carbon dots [6], and chitosan in aqueous media [7]. Although conventional organic bases such as piperidine, pyridine and related amines can efficiently promote the reaction, their volatility, toxicity and environmental impact have encouraged the development of more sustainable alternatives [8]. Green catalytic approaches have subsequently attracted considerable attention. Metal-organic frameworks [9], ionic liquids [10], zeolitic materials [11], and metal oxide catalysts such as CeO_2 [12] have all demonstrated useful catalytic activity in Knoevenagel-type transformations. At the same time, amino acids have emerged as attractive catalytic materials because of their comparatively benign nature, availability and compatibility with environmentally responsible synthetic approaches. L-Proline and related amino-acid-based systems have, for example, been employed under relatively mild reaction conditions [13]. Amino acids combined with salts or other solid materials can also exhibit synergistic catalytic behavior [14].

Mechanochemical synthesis provides another important strategy for improving the environmental profile of organic reactions. Grinding-based reactions can substantially reduce or eliminate the requirement for organic solvents, while intimate physical contact between

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reactants can promote efficient reaction and energy transfer [15]. Such processes can also shorten reaction times and simplify product isolation. The combination of amino-acid catalysis with mechanochemical activation is therefore particularly attractive for developing simple and sustainable synthetic methodologies. In the present study, an L-phenylalanine-sodium acetate catalytic system was employed for the one-pot grinding synthesis of Knoevenagel condensation products. L-Phenylalanine provides a biocompatible catalytic component, while sodium acetate assists the deprotonation of the active methylene substrate. The resulting system enables efficient C=C bond formation under solvent-free conditions at room temperature.

2. Materials and Methods

2.1 Materials and Instrumentation

All chemicals employed in the synthesis were commercially available and of analytical reagent grade. Melting points were measured by the open-capillary method and are reported without correction. Infrared spectra were obtained using a SHIMADZU FT-IR spectrophotometer. Mass spectra were recorded using a TOF MS ES+ instrument. ^1H NMR spectra were acquired on a BRUKER AVANCE NEO 500 MHz spectrometer using DMSO- d_6 as the solvent. Chemical shifts are reported in ppm (δ) with tetramethylsilane (TMS) used as the internal standard.

2.2 General Synthetic Procedure

Equimolar quantities of the selected aromatic aldehyde (0.01 mol) and either dimethyl malonate or malononitrile (0.01 mol) were combined with sodium acetate (0.02 mol) and L-phenylalanine (0.001 mol). The mixture was subjected to manual grinding in a mortar and pestle at room temperature for approximately 10-15 min. Reaction progress was monitored by thin-layer chromatography. Following completion of the reaction, the reaction mixture was transferred into 50 mL of ice-cold water with stirring. The solid product was separated by filtration, dried and subsequently purified by recrystallization from ethanol.

2.3 Characterization of Synthesized Products

2.3.1 Dimethyl 2-benzylidene malonate 3A

IR (KBr): 2890 cm^{-1} (C-H), 1735 cm^{-1} (C=O, ester), 1625 cm^{-1} (C=C). 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 for $\text{C}_{12}\text{H}_{12}\text{O}_4$: C, 65.45; H, 5.49%. Found: C, 65.50; H, 5.51%.

2.3.2 Dimethyl 2-(3-hydroxybenzylidene)malonate 3B

IR (KBr): 3497 cm^{-1} (O-H), 2880 cm^{-1} (C-H), 1733 cm^{-1} (C=O, ester), 1622 cm^{-1} (C=C). 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), 8.15 (d, 1H, Ar-H), 8.30 (d, 1H, Ar-H), 8.35 (s, 1H, =C-H). Elemental analysis: Calculated for $\text{C}_{12}\text{H}_{12}\text{O}_5$: C, 61.01; H, 5.12%. Found: C, 61.04; H, 5.10%.

2.3.3 Dimethyl 2-(4-nitrobenzylidene)malonate 3C

IR (KBr): 2885 cm^{-1} (C-H), 1740 cm^{-1} (C=O, ester), 1527 and 1344 cm^{-1} (NO_2), 1623 cm^{-1} (C=C). 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 for $\text{C}_{12}\text{H}_{11}\text{NO}_6$: C, 54.34; H, 4.18; N, 5.28%. Found: C, 54.36; H, 4.20; N, 5.30%.

2.3.4 2-Benzylidenemalononitrile 3G

IR (KBr): 2905 cm^{-1} (C-H), 2225 cm^{-1} (CN), 1622 cm^{-1} (C=C). 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 for $\text{C}_{10}\text{H}_6\text{N}_2$: C, 77.91; H, 3.92; N, 18.17%. Found: C, 77.93; H, 3.90; N, 18.14%.

2.3.5 2-(3-Hydroxybenzylidene)malononitrile 3H

IR (KBr): 3510 cm^{-1} (O-H), 2888 cm^{-1} (C-H), 2233 cm^{-1} (CN), 1624 cm^{-1} (C=C). 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 for $\text{C}_{10}\text{H}_6\text{N}_2\text{O}$: C, 70.58; H, 3.55; N, 16.46%. Found: C, 70.60; H, 3.58; N, 16.42%.

2.3.6 2-(4-Nitrobenzylidene)malononitrile 3I

IR (KBr): 2895 cm^{-1} (C-H), 2230 cm^{-1} (CN), 1530 and 1345 cm^{-1} (NO_2), 1620 cm^{-1} (C=C). 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 for $\text{C}_{10}\text{H}_5\text{N}_3\text{O}_2$: C, 60.31; H, 2.53; N, 21.1%. Found: C, 60.33; H, 2.55; N, 21.4%.

3. Results and Discussion

The Knoevenagel condensation was investigated under solvent-free mechanochemical conditions by combining aromatic aldehydes with either dimethyl malonate or malononitrile in the presence of sodium acetate and L-phenylalanine. The reaction mixtures were manually ground using a mortar and pestle at room temperature. Under these conditions, the condensation proceeded efficiently, with reaction completion generally occurring within 10-15 min. The experimental results demonstrate that the catalytic system provides consistently high product yields. The synthesized compounds were obtained in the range of 88-96%, indicating that the L-phenylalanine-sodium acetate combination is effective for promoting condensation between aromatic aldehydes and active methylene compounds.

The results also demonstrate the compatibility of the procedure with different aromatic substituents. Aldehydes containing hydroxy, nitro, chloro, methoxy and fluoro substituents participated successfully in the reaction. Both electron-withdrawing and electron-donating substituents were therefore accommodated under the reaction conditions. Spectroscopic investigations supported the formation of the desired α,β -unsaturated products. The FT-IR spectra showed characteristic alkene C=C absorptions in the 1620-1625 cm^{-1} region. For products derived from dimethyl malonate, the ester carbonyl absorption occurred around 1733-1740 cm^{-1} , whereas the malononitrile derivatives displayed the characteristic nitrile absorption near 2225-2233 cm^{-1} . Nitro-substituted products exhibited additional characteristic NO_2 absorptions.

The ^1H NMR spectra provided further evidence for product formation. The vinylic proton signals occurred in the δ 7.85-9.69 region, consistent with formation of the benzylidene products. Additional signals associated with methoxycarbonyl, hydroxy and aromatic groups were also observed according to the structure of each product. Mass spectral data were consistent with the expected molecular masses, while elemental analysis values were in close agreement with the calculated compositions. The physical

characteristics and yields of the synthesized compounds are summarized in Table 1.

Table 1: Physical Characterization of the Synthesized Compounds

Compound	R	X and Y	Time (min)	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

3.1 Effect of the Reaction Conditions

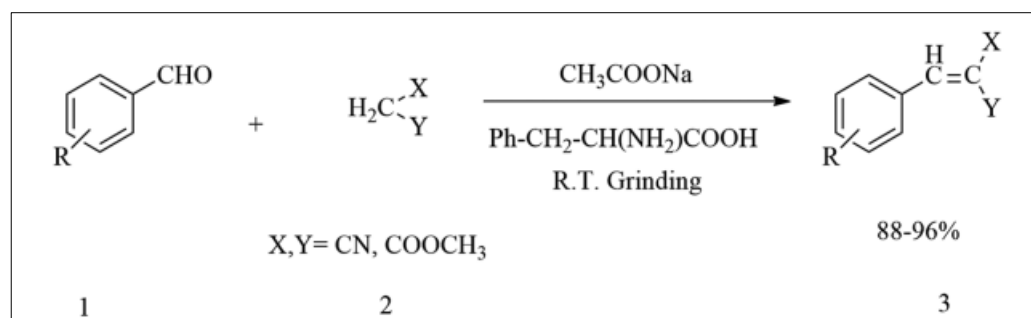
The mechanochemical approach offers several practical advantages. The reaction takes place without the addition of an organic solvent, and mechanical grinding facilitates intimate contact among the reactants and catalytic components. The use of room temperature conditions further reduces the energy requirements of the synthesis. The relatively short reaction times, ranging from 10 to 15 min, together with yields of 88-96%, demonstrate the efficiency of the protocol. The procedure also avoids complicated reaction apparatus and provides a straightforward method for isolating the products.

3.2 Structural Confirmation of the Products

The formation of the α,β -unsaturated products was established using complementary analytical techniques. FT-IR spectroscopy confirmed the characteristic functional groups, particularly the C=C stretching vibration in the 1620-1625 cm⁻¹ range. The ¹H NMR spectra showed the expected vinylic proton resonances between δ 7.85 and 9.69. Mass spectral measurements provided molecular-ion signals consistent with the assigned structures. The observed melting points were also compared with reported literature values, providing additional support for the identity of the synthesized compounds. Simple recrystallization from ethanol was sufficient for purification, contributing to the practical simplicity of the overall procedure.

3.3 Green Chemistry Features of the Protocol

The present methodology incorporates several features desirable in sustainable organic synthesis. It operates under solvent-free conditions, uses room-temperature mechanical activation, employs an amino acid as a biocompatible catalytic component and utilizes inexpensive sodium acetate as an additive. The short reaction time and simple isolation procedure further reduce the operational requirements. The successful condensation of several substituted aromatic aldehydes demonstrates useful substrate compatibility. The combination of mechanochemistry and amino-acid-based catalysis consequently provides a promising alternative to conventional solvent-dependent Knoevenagel procedures.



Scheme 1: Reaction conditions and formation of the desired Knoevenagel condensation products

4. Conclusion

An efficient and environmentally preferable protocol has been established for Knoevenagel condensation using an L-phenylalanine-sodium acetate catalytic system under solvent-free grinding conditions. The method enables the reaction of aromatic aldehydes with dimethyl malonate and malononitrile at room temperature, providing the corresponding α,β -unsaturated products in good to excellent yields. The principal advantages of the procedure include short reaction times, mild conditions, high yields, avoidance of hazardous organic solvents and a simple purification procedure. The successful conversion of aromatic aldehydes bearing hydroxy, nitro, chloro, methoxy and fluoro substituents demonstrates the broad applicability of the approach within the investigated substrate series. The use of L-phenylalanine, a biocompatible amino acid, together with inexpensive sodium acetate provides an attractive catalytic combination for sustainable organic synthesis. The mechanochemical mode of operation additionally minimizes solvent consumption and simplifies the experimental setup. Overall, this procedure represents a practical and greener

approach to the preparation of α,β -unsaturated carbonyl and dicyano compounds.

5. Acknowledgment

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6. Conflict of Interest

The authors declare that there is no conflict of interest.

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