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Green and Efficient BPA-Catalyzed Synthesis of 1,4- Dihydropyridine-3,5-Dicarboxylates via One-Pot Hantzsch Reaction

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Abstract:

An environmentally benign and efficient Banana Perchloric Acid (BPA)-catalyzed Hantzsch multicomponent reaction has been developed for the synthesis of 1,4- dihydropyridine-3,5-dicarboxylate derivatives. The protocol involves a one-pot condensation of aldehydes, β-keto esters, and ammonium acetate in a green water–ethanol solvent system under reflux conditions. BPA, a biodegradable and recyclable Brønsted acid catalyst, efficiently promotes the transformation, affording the desired products in excellent yields within short reaction times and with high atom economy. The methodology avoids hazardous mineral acids and toxic organic solvents, thereby aligning with the principles of green chemistry. The catalyst can be recovered and reused multiple times without significant loss of activity. The synthesized derivatives were characterized by standard spectroscopic techniques, including FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. This protocol provides a sustainable, operationally simple, and environmentally compatible approach for the synthesis of pharmacologically important dihydropyridine frameworks.

Keywords: Hantzsch reaction; 1,4-Dihydropyridine-3,5-dicarboxylates; Green chemistry; Banana Perchloric Acid (BPA); Multicomponent reaction; Recyclable catalyst.

Introduction:

Multicomponent reactions (MCRs) are powerful synthetic tools that allow the rapid construction of complex molecules from simple starting materials in a single operational step. Among them, the Hantzsch reaction is one of the most widely used methodologies for the synthesis of 1,4-dihydropyridines (1,4-DHPs). These compounds represent an important class of heterocycles with diverse biological and pharmacological properties, including antihypertensive, antianginal, vasodilatory, and calcium channel blocking activities[1].

1,4-Dihydropyridine-3,5-dicarboxylates form the structural core of several clinically important drugs. Consequently, the development of efficient, sustainable, and environmentally friendly methods for their synthesis remains highly desirable[2].

Traditional Hantzsch synthesis typically employs strong mineral acids, organic solvents, and prolonged heating, which may lead to environmental concerns and reduced atom economy. In recent years, green chemistry principles have encouraged the replacement of hazardous reagents with biodegradable catalysts and benign solvent systems[3-4].

In this context, Banana Perchloric Acid (BPA), a natural-derived Brønsted acid catalyst, has emerged as a promising green alternative. BPA is biodegradable, inexpensive, easy to handle, and recyclable. Herein, we report an efficient BPA-catalyzed one-pot Hantzsch reaction in a water–ethanol solvent system for the synthesis of 1,4-dihydropyridine-3,5-dicarboxylate derivatives under mild conditions [5].

Literature Review:

The Hantzsch multi-component reaction (MCR) has long been recognized as a versatile and efficient route for the synthesis of 1,4-dihydropyridine (1,4-DHP) derivatives, which are pivotal heterocyclic scaffolds in medicinal chemistry due to their diverse pharmacological properties, including antihypertensive[6], antianginal, and calcium channel blocking activities[7]. Traditional Hantzsch protocols typically employ strong mineral acids and volatile organic solvents, which pose environmental and safety concerns, in addition to limiting their broad utility in sustainable synthesis[8]. Consequently, there has been significant interest in developing greener and more efficient catalytic systems that conform to the principles of green chemistry while maintaining high product yields and operational simplicity[9].

Recent research has explored a wide range of heterogeneous and homogeneous catalysts for Hantzsch reactions to improve efficiency and sustainability. Nanostructured catalysts such as Fe_3O_4-based magnetic catalysts have been investigated to promote 1,4-DHP synthesis with facile separation and recyclability[10]. For example, Fe_3O_4@phenyl@Cu magnetic catalysts demonstrated excellent activity in one-pot Hantzsch syntheses, offering ease of catalyst recovery and reuse with minimal loss of activity. Similarly, $MnFe_2O_4$ nanocatalysts have been shown to effectively catalyze multicomponent dihydropyridine formation under mild conditions, highlighting the potential of magnetic nanomaterials in sustainable organic synthesis[11-13].

In addition to nanocatalysts, polymer-supported and hybrid organic-inorganic catalysts have gained attention due to their tunable acidity and high surface area. Polyindole–TiO_2 composite catalysts were successfully utilized for solvent-free one-pot Hantzsch reactions, providing good yields without the need for hazardous solvents[14-16]. Solid acid catalysts such as $AlCl_3$@ZnO have also been reported to facilitate 1,4-DHP synthesis under green conditions, producing high yields and demonstrating excellent stability over multiple cycles[17]. These studies underscore the progress in designing recyclable catalytic systems that reduce waste and improve atom economy[18-20].

Parallel to catalyst development, significant efforts have been directed toward adopting greener reaction media[21-22]. Water and water–alcohol solvent systems have emerged as preferred alternatives to conventional organic media due to their low toxicity, safety, and environmental compatibility[23]. Subcritical ethanol, for instance, has been used effectively for Hantzsch synthesis, minimizing solvent waste while enhancing reaction rates. Likewise, glycerol and biomass-derived solvents have been explored as benign media, aligning synthetic protocols more closely with green chemistry goals[24].

Despite these advancements, there remains a need for versatile catalysts that combine operational simplicity, recyclability, and compatibility with benign solvents. Natural acid catalysts, including bio-derived Brønsted acids, offer an attractive solution due to their biodegradability, low cost, and minimal environmental footprint. In this context, Banana Perchloric Acid (BPA) represents a promising catalyst for multicomponent syntheses. Its ability to efficiently catalyze Hantzsch-type MCRs in aqueous ethanol under mild conditions has not been extensively studied, and its application could significantly enhance the sustainability of dihydropyridine synthesis.

Collectively, these developments illustrate a clear trend toward greener and more sustainable methodologies for 1,4-DHP synthesis, with emphasis on recyclable catalysts and benign solvent systems. Building on this foundation, the current investigation explores the application of

BPA as an eco-friendly catalyst for the construction of 1,4-dihydropyridine-3,5-dicarboxylate frameworks using an efficient one-pot Hantzsch reaction.

Experimental Section:

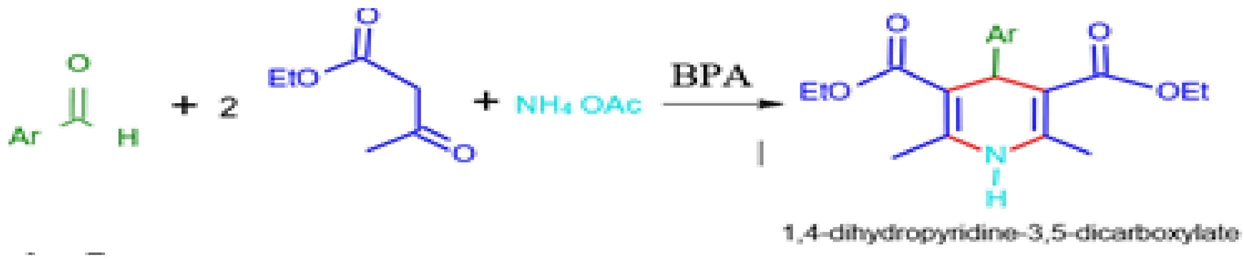
Materials and Methods:

All chemicals were commercially available and used without further purification.

Aldehydes, β-keto esters (such as ethyl acetoacetate), and ammonium acetate were obtained from Sigma-Aldrich. Reactions were monitored by thin-layer chromatography (TLC).

General Procedure for the Synthesis of 1,4-Dihydropyridine-3,5-Dicarboxylates:

A mixture of aldehyde (1 mmol), β-keto ester (2 mmol), ammonium acetate (1.5 mmol), and BPA catalyst (10 mol%) was taken in a round-bottom flask containing a water–ethanol mixture (1:1, 10 mL). The reaction mixture was refluxed with constant stirring for an appropriate time (30–60 min). The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature. The solid product formed was filtered, washed with cold ethanol, and recrystallized to afford pure 1,4-dihydropyridine derivative.



Catalyst Recovery:

After separation of the solid product by filtration, the aqueous layer containing Banana Perchloric Acid (BPA) was subjected to concentration under reduced pressure to recover the catalyst. The isolated catalyst was subsequently reused in successive reaction cycles under identical experimental conditions to evaluate its recyclability and stability. The results demonstrated that BPA retained significant catalytic activity over four consecutive cycles. The product yields showed only a marginal decrease from 92% in the first cycle to 88% in the fourth cycle, indicating minimal loss of efficiency. This slight reduction in yield may be attributed to minor handling losses during recovery rather than catalyst deactivation. Overall, the recyclability study confirms the robustness and sustainability of BPA as an effective green catalyst for the Hantzsch reaction.

Entry	Catalyst (mol%)	Solvent	Time (min)	Yield (%)
1	5	EtOH	90	72
2	10	H_2O	70	80
3	10	$EtOH:H_2O$ (1:1)	45	92
4	15	$EtOH:H_2O$	45	92

Optimal condition: 10 mol% BPA in $EtOH:H_2O$ (1:1).

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Collectively, these developments illustrate a clear trend toward greener and more sustainable methodologies for 1,4-DHP synthesis, with emphasis on recyclable catalysts and benign solvent systems. Building on this foundation, the current investigation explores the application of BPA as an eco-friendly catalyst for the construction of 1,4-dihydropyridine-3,5-dicarboxylate frameworks using an efficient one-pot Hantzsch reaction.

Entry	Aldehyde (R-CHO)	Time (min)	Yield (%)	M.P (°C)
1	Benzaldehyde	45	92	155–157
2	4-Cl-benzaldehyde	40	94	168–170
3	4-NO_2-benzaldehyde	35	95	178–180
4	4-OCH_3-benzaldehyde	50	88	150–152
5	3-CH_3-benzaldehyde	55	85	148–150

Proposed Mechanism:

The reaction proceeds through the well-established classical Hantzsch mechanism involving a sequence of condensation and cyclization steps. Initially, the aldehyde undergoes a Knoevenagel condensation with one molecule of β-keto ester in the presence of the acidic catalyst to generate an activated α,β-unsaturated carbonyl intermediate. Simultaneously, a second molecule of β-keto ester reacts with ammonium acetate to form an enamine intermediate. This enamine then participates in a Michael addition to the previously formed Knoevenagel adduct, resulting in the formation of a key open-chain intermediate. Subsequent intramolecular cyclization followed by tautomerization leads to the formation of the substituted 1,4- dihydropyridine ring system.

Banana Perchloric Acid (BPA) functions as a Brønsted acid catalyst throughout the process by protonating the carbonyl groups, thereby enhancing their electrophilicity and facilitating both the condensation and cyclization steps. Its acidic nature accelerates intermediate formation while maintaining mild and environmentally compatible reaction conditions.

Characterization (Representative Example):

The FT-IR spectrum confirms the presence of N–H stretching at 3300 cm^{-1} and strong ester carbonyl absorption at 1685 cm^{-1}. The ^1H NMR spectrum shows characteristic triplet and quartet signals corresponding to the ethyl ester groups. The singlet at δ 5.05 ppm confirms the presence of the NH proton of the dihydropyridine ring. Aromatic protons appear as a multiplet between δ 7.20–7.40 ppm. The molecular ion peak observed at m/z 330 $[M+H]^+$ in the mass spectrum supports the proposed molecular structure. All spectral data are consistent with the assigned structure of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate.

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate

Yield: 92%

Melting point: 155–157°C

Infrared Spectroscopy (FT-IR, KBr, νmax cm^{-1})

3300 (N–H stretching), 1685 (ester C=O stretching), 1600 (C=C aromatic stretching), 1510 (C=C heterocyclic ring), 1250 (C–O stretching, ester), 750–700 (aromatic C–H bending)

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

1.20 (t, J = 7.2 Hz, 6H, CH_3 of ethyl ester), 2.30 (s, 6H, 2 × CH_3 at C-2 and C-6), 4.10 (q, J = 7.2 Hz, 4H, CH_2 of ethyl ester), 5.05 (s, 1H, NH proton), 7.20–7.40 (m, 5H, aromatic protons)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

14.2 (CH_3, ethyl), 18.8 (C-2, C-6 methyl carbons), 59.6 (CH_2, ethyl ester), 100.4 (C-4 of dihydropyridine ring), 126.8–128.9 (aromatic carbons), 144.2 (quaternary aromatic carbon), 147.5 (C-3 and C-5), 167.8 (C=O, ester carbonyl)

Mass Spectrometry (ESI-MS)

m/z: 330 $[M + H]^+$ (calculated for $C_{19}H_{24}NO_4^+$: 330.17)

Conclusion:

An efficient and environmentally friendly BPA-catalyzed Hantzsch multicomponent reaction has been successfully developed for the synthesis of 1,4-dihydropyridine-3,5- dicarboxylates. The protocol features mild reaction conditions, short reaction times, excellent yields, and catalyst recyclability. The use of a green solvent system and biodegradable catalyst makes this method an attractive alternative to traditional procedures. This strategy provides a sustainable and practical approach for synthesizing pharmacologically relevant dihydropyridine derivatives.

References:

1. Silva, W. A.; Takada, S. C. S.; Gatto, C. C. Microwave-Assisted Synthesis of 1,4-Dihydropyridines Using a Recyclable HPW/PEG-400 Catalytic System. Catalysts 2026, 16 (1), 96. https://doi.org/10.3390/catal16010096
2. Singh, V.; Rajput, K.; Singh, S.; Srivastava, V. Montmorillonite K-10 Catalyzed Synthesis of 1,4-Dihydropyridine Derivatives under Microwave Irradiation. RSC Adv. 2024, 14, 27086–27091. https://doi.org/10.1039/D4RA04990J
3. Pachipulusu, S.; Merugu, K. S.; Bhonsle, R. R.; Kurnool, A. Facile Microwave-Mediated Synthesis of 1,4-Dihydropyridine Carboxylates by Multicomponent Reaction.
4. J. Heterocycl. Chem. 2024, 61 (6), 1009–1014. https://doi.org/10.1002/jhet.4817
5. Dolatyari, K.; Khodaei, M. M. Ultrasound-Assisted One-Pot Synthesis of 1,4-Dihydropyridines Using Magnetic CuO Nanocatalyst. J. Organomet. Chem. 2024, 1021, 123352. https://doi.org/10.1016/j.jorganchem.2024.123352
6. Phasage, D. B.; Sharma, S. K.; Tripathi, B.; Srivastava, S. C. Polyindole-TiO_2 Nanocatalyst for Solvent-Free One-Pot Synthesis of 1,4-Dihydropyridines. Open J. Compos. Mater. 2024, 14, 109–123.
7. Anchan, H. N.; Naik, C. P.; Bhat, N. S.; Kumari, M.; Dutta, S. Green Synthesis of Novel Biginelli and Hantzsch Products from Biorenewable Furfurals Using Gluconic Acid Aqueous Solution. ACS Omega 2023, 8 (37), 34077–34083. https://doi.org/10.1021/acsomega.3c05106
8. Efficient and Green Synthesis of Hantzsch 1,4-Dihydropyridine Derivatives in Subcritical Ethanol. J. Supercrit. Fluids 2021, 176, 105303. https://doi.org/10.1016/j.supflu.2021.105303

9. Green Approach for Synthesis of 1,4-Dihydropyridines through Catalyst-Free Multicomponent Hantzsch Reaction (ACS J. Chem. Educ.) 2025, 102, 1215–1222. https://doi.org/10.1021/acs.jchemed.4c01069
10. Soni, A. A Decade of Catalytic Progress in 1,4-Dihydropyridines: Recent Trends in Catalysis and Green Synthesis. J. Taiwan Inst. Chem. Eng. 2025.
11. Recent Advances in the Synthesis of Dihydropyridine and Related Derivatives. Chem. Select. 2024. https://doi.org/10.1002/slct.202403664
12. Willong, L.; Gangshin, S. Eco-Friendly Synthesis of 1,4-DHP Derivatives Using Fe_3O_4@Phen@Cu Magnetic Catalyst. J. Synth. Chem. 2023, 2, 252–264.
13. Ichie, S.; Soler, F. Magnetic Nanoparticle-Functionalized Catalysts for 1,4-Dihydropyridine Synthesis. J. Synth. Chem. 2023, 2, 275–287.
14. Zhang, H. F.; Jialon, R. $MnFe_2O_4$ Nanocatalyst for Hantzsch Synthesis of 1,4-DHP. Bioorg. Mol. Chem. 2023, 1, 82–93.
15. $AlCl_3$@ZnO Nanostructured Material: Efficient Green Catalyst for Solvent-Free 1,4- DHP Synthesis. RSC Adv. 2023, 13 (35), 24767–24776. https://doi.org/10.1039/D3RA04277D
16. One Pot Multicomponent Synthesis of 1,4-DHP Derivatives by Hantzsch Reaction (IJCRT). 2024, 12 (5).
17. Efficient Synthesis of Polyhydroquinoline Derivatives via Hantzsch Reaction, Arab J. Chem. 2025.
18. Green Catalysts and Solvents for Sustainable Multicomponent Reactions. Catalysts (MDPI) 2022, 14 (9).
19. Recent Developments in Nanomaterial-Catalyzed Green Synthesis of 1,4-DHPs. RSC Adv. 2021 (review background).
20. Recent Progresses in the Multicomponent Synthesis of Dihydropyridines. Front. Chem. 2021, Article 800236.
21. Catalyst- and Solvent-Free Multicomponent Synthesis of Dihydropyridines from Biomass-Derived Building Blocks. Sci. Prog. 2025. https://doi.org/10.1016/j.scp.2025.102123
22. Ultrasound-Assisted Synthesis of 1,4-DHPs Using Cellulose/Pumice Nanocomposite. Solid State Sci. 2020.
23. Tiwari, S. K.; Shivhare, K. N.; Patel, M. K.; et al. Glycerol Promoted Sustainable Hantzsch Synthesis. Polycycl. Aromat. Compd. 2020.
24. Sayahi, M. H.; Saghanezhad, S. J.; Mostafa-Shehni, L. One-Pot Preparation of Novel 1,4-DHPs with SBA-15-SO_3H. Org. Prep. Proced. Int. 2020.
25. Ghosh, A.; Kavitha, C. S.; Keri, R. S. Fe_3O_4@Cysteine Nanocomposite
26. Catalyst for 1,4- DHP Synthesis. Chem. Data Collec. 2021.

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