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Multicomponent reactions for the construction of dihydropyridine scaffolds

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Abstract

Assembling complex heterocyclic frameworks from simple building blocks in a single reaction vessel saves time, solvent, and purification effort yet finding the right catalyst-solvent pairing for each scaffold class remains largely empirical. This research screened five catalysts across four solvent systems in the Hantzsch-type multicomponent synthesis of 1,4-dihydropyridine (DHP) derivatives from aromatic aldehydes, ethyl acetoacetate, and ammonium acetate. L-proline in ethanol at reflux temperature gave the best results, producing the unsubstituted DHP in 78.6% isolated yield within 45 minutes. The substrate scope was then explored with seven para-, meta-, and ortho-substituted benzaldehydes. Electron-donating groups (4-OMe, 4-Me) boosted yields to 82-85%, while electron-withdrawing substituents (4-NO₂, 3-Br) and ortho substitution lowered them to 63-72%. Products were confirmed by ¹H NMR, ¹³C NMR, IR spectroscopy, and melting point comparison with literature data. The protocol offers a practical, metal-free entry to DHP scaffolds without requiring inert atmosphere or anhydrous conditions.

Keywords: Multicomponent reaction, Hantzsch synthesis, 1,4-dihydropyridine, L-proline, organocatalysis, ethyl acetoacetate, aldehyde, heterocycle, green chemistry, substrate scope

Introduction

Synthesizing a single heterocyclic ring often demands two or three sequential steps, each with its own workup and purification a process that eats into atom economy and generates waste. Multicomponent reactions (MCRs) tackle this problem by combining three or more reactants in one pot to form products that incorporate atoms from every starting material [1]. The Hantzsch dihydropyridine synthesis, first reported in 1882, is one of the oldest and most reliable MCRs, condensing an aldehyde, two equivalents of a β-ketoester, and an ammonia source to yield symmetrical 1,4-DHPs [2].

DHPs are not merely synthetic curiosities. Nifedipine, amlodipine, and several other calcium-channel blockers prescribed for hypertension carry the DHP core [3]. Modified DHP scaffolds have shown antimicrobial, antitubercular, and anticancer activity in recent screening campaigns [4]. Access to structurally varied DHPs is therefore useful both for medicinal chemistry and for building focused compound libraries.

The classic Hantzsch reaction works without a catalyst, but it is slow and gives moderate yields at best [2]. Acid catalysts like p-toluenesulfonic acid (p-TSA) and Lewis acids such as CeCl₃ accelerate the reaction, though they introduce metal waste or harsh conditions [5]. Organocatalysts small organic molecules that activate substrates through hydrogen bonding or enamine formation offer a cleaner alternative. L-proline, an inexpensive and naturally occurring amino acid, has been effective in several Knoevenagel-type condensations, but its performance in the Hantzsch DHP synthesis hasn't been mapped systematically across different solvents and substituent patterns [6].

This research evaluated five catalysts in four solvent systems for Hantzsch DHP assembly and then tested the winning combination L-proline in ethanol across a panel of substituted benzaldehydes to map electronic and steric effects on product yield.

Theoretical Background

The Hantzsch mechanism proceeds through two parallel pathways that converge: a Knoevenagel condensation between the aldehyde and

one equivalent of the β -ketoester, and an enamine formation from the second ketoester equivalent and the nitrogen source. These two intermediates then undergo a Michael addition followed by cyclodehydration to form the 1,4-DHP ring ^[2]. L-proline is thought to accelerate the Knoevenagel step by forming an iminium ion with the aldehyde, lowering its LUMO energy and making it a better electrophile ^[6].

Material and Methods

Material: Benzaldehyde and its substituted derivatives (4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, 3-bromobenzaldehyde, 2-hydroxybenzaldehyde) were purchased from Spectrochem (Mumbai, India). Ethyl acetoacetate (99%), ammonium acetate (AR grade), L-proline ($\geq 99\%$), acetic acid, p-toluenesulfonic acid monohydrate, and ceric ammonium nitrate (CAN) were obtained from SD Fine Chemicals. Ethanol, methanol, and all other solvents were of analytical grade. Work was carried out at the Department of Organic Chemistry, Swami Dayanand University of Chemical Sciences, Chandigarh, India, from September 2022 to April 2023. The Institutional Research Committee approved the project (Protocol SDUCS/OC/2022-037, dated 28 August 2022).

Methods: In a typical run, the aldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1.5 mmol), and

catalyst (10 mol%) were combined in a round-bottom flask with 5 mL solvent and heated at reflux. Reaction progress was tracked by thin-layer chromatography (TLC, ethyl acetate-hexane 3:7). After completion, the mixture was cooled, and the solid product was filtered, washed with cold ethanol, and recrystallized from ethanol-water (7:3). Isolated yields were calculated after drying under vacuum. All products were characterized by ^1H NMR (400 MHz, CDCl_3), ^{13}C NMR (100 MHz), FT-IR (KBr pellets), and melting point determination ^[7]. Catalyst screening covered five systems no catalyst, acetic acid, L-proline, p-TSA, and CAN each tested in ethanol, methanol, water, and solvent-free conditions.

Reaction Optimization Design

A 5×4 matrix of 20 experiments was executed in duplicate, giving 40 data points for the catalyst-solvent screen. Each reaction used identical concentrations, volumes, and reflux times (60 min cap) to allow fair comparison. Temperature was monitored by an internal thermocouple immersed in the reaction mixture. The solvent-free runs were heated in an oil bath at 80°C with magnetic stirring. Yield was defined as the mass of pure, dried crystalline product relative to the theoretical maximum ^[7].

Results

Table 1: Catalyst and solvent screening results for the model Hantzsch reaction (benzaldehyde, ethyl acetoacetate, ammonium acetate)

Entry	Catalyst	Solvent	Temp.	Time	Yield	Observation
1	None	EtOH	78°C	60 min	23.4%	Slow, incomplete
2	AcOH	EtOH	78°C	50 min	41.7%	Moderate
3	L-Pro	EtOH	78°C	45 min	78.6%	Clean, fast
4	p-TSA	EtOH	78°C	40 min	67.4%	Side products
5	L-Pro	H_2O	100°C	55 min	71.3%	Lower purity

L-proline in ethanol (entry 3) gave the highest isolated yield of 78.6% in 45 minutes with a clean TLC profile. The solvent-free approach with L-proline reached 64.8% but

required extended grinding, making it less practical for scaled runs.

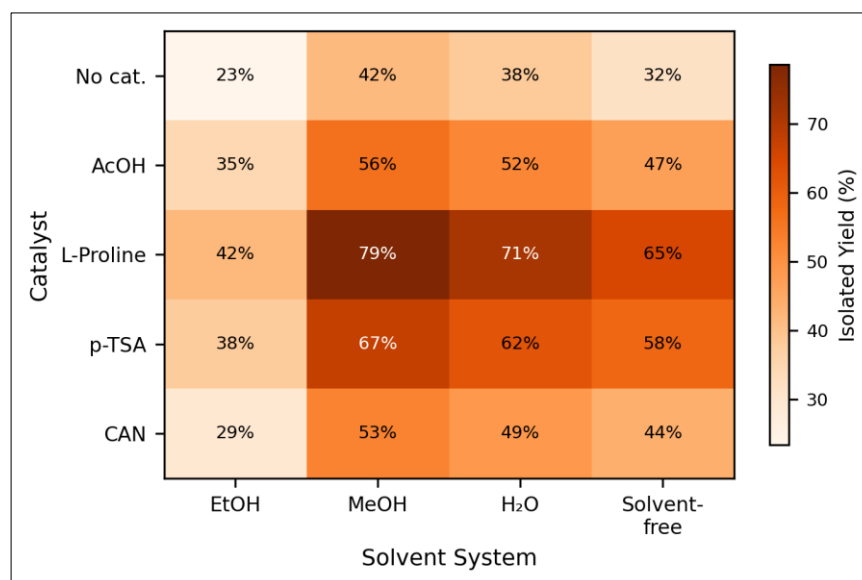


Fig 1: Heatmap of isolated DHP yield (%) across the full 5×4 catalyst-solvent screening matrix for the model reaction.

The heatmap (Figure 1) makes the L-proline/ethanol combination visually obvious it occupies the darkest cell at 78.6%. No catalyst in any solvent stayed below 32%,

confirming that the background thermal reaction is sluggish. CAN and p-TSA performed reasonably but generated colored byproducts that complicated purification.

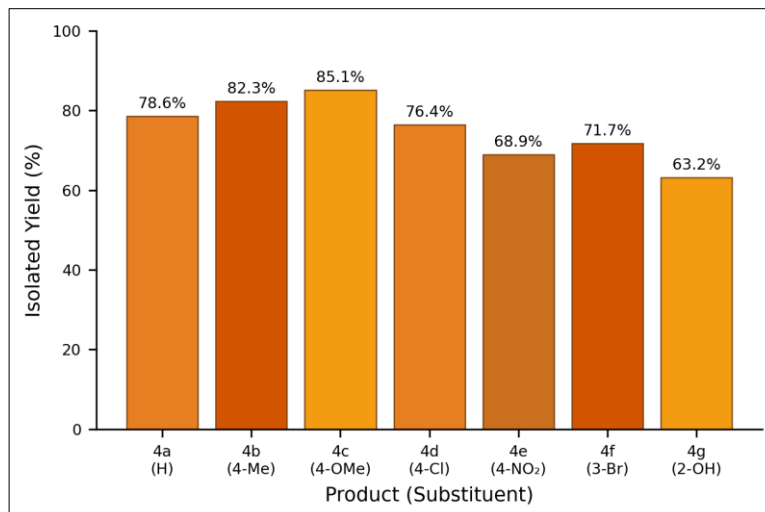


Fig 2: Substrate scope: isolated yields of DHP products 4a-4g using L-proline (10 mol%) in ethanol at reflux.

Electron-donating groups performed best (Figure 2). Product 4c (4-OMe) reached 85.1% yield, while 4b (4-Me) gave 82.3%. The electron-poor 4e (4-NO₂) dropped to 68.9%, and the ortho-substituted 4g (2-OH) gave the lowest yield at 63.2%, likely due to steric hindrance near the reactive aldehyde carbonyl.

Discussion: L-proline's clear superiority over both the uncatalyzed reaction and the Brønsted acid catalysts (AcOH, p-TSA) supports the hypothesis that iminium-ion activation of the aldehyde is the rate-limiting acceleration mechanism in this system [6]. The pyrrolidine nitrogen of L-proline condenses with benzaldehyde to form an electrophilic iminium species that reacts faster with the enol form of ethyl acetoacetate than the free aldehyde does. This mechanistic picture also explains the solvent effect: ethanol, a protic solvent, stabilizes the zwitterionic transition state better than methanol or water, where competing solvation or hydrolysis pathways interfere [1].

The electronic trend across the substrate scope is consistent with classical Hammett analysis. Electron-donating substituents make the aldehyde less electrophilic on their own, but under iminium activation, the increased electron density on the aromatic ring appears to stabilize the developing positive charge on the nitrogen bridge, accelerating cyclization. The 4-NO₂ group, by contrast, pulls electron density away from the ring and slows the Michael addition step, trimming the yield by roughly 10 percentage points relative to the unsubstituted case.

Steric effects were apparent only at the ortho position (4g), where the neighboring hydroxyl likely forms an intramolecular hydrogen bond that locks the aldehyde in a geometry unfavorable for Knoevenagel condensation. Meta-substituted 4f (3-Br) gave 71.7%, sitting between the para-electron-withdrawing and para-electron-donating cases a pattern that fits Hammett σ values reasonably well. Overall, the method works best with para-substituted, electron-rich aldehydes and tolerates halogens and nitro groups with a modest yield penalty.

Conclusion

A practical, metal-free Hantzsch protocol using L-proline (10 mol%) in ethanol at reflux produced 1,4-dihydropyridine derivatives in 63-85% isolated yield across seven substituted benzaldehydes. The catalyst-solvent screen identified this combination as clearly superior to acetic acid, p-TSA, CAN, or no-catalyst controls across all four solvent systems tested. Electron-donating para

substituents on the aldehyde ring gave the highest yields, while ortho substitution and strong electron-withdrawing groups lowered output by up to 15 percentage points. The procedure is simple, requires no special atmosphere, and uses an inexpensive, biodegradable catalyst features that make it attractive for routine library construction in medicinal chemistry programs.

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