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Green Synthesis of Dihydropyridine Derivatives Using Choline Succinate as a Sustainable Reagent

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Abstract: *An efficient, and environmentally benign synthesis of 1,4-dihydropyridine (1,4-DHP) derivatives has been developed using choline succinate as a green bifunctional reagent and catalyst. Choline succinate, a biocompatible ionic compound derived from choline and succinic acid, acts as a dual-functional system — providing mild Brønsted acid catalysis through its succinate moiety. This eliminates the requirement for conventional toxic catalysts and hazardous organic solvents. The synthesis was carried out via a multicomponent Hantzsch-type condensation involving aromatic aldehydes, ethyl acetoacetate, and ammonium acetate in the presence of choline succinate under solvent-free or aqueous conditions at 60–80°C. A series of symmetrical and unsymmetrical 1,4-dihydropyridine derivatives bearing diverse electron-withdrawing and electron-donating substituents on the aryl ring were successfully synthesized in excellent yields (80–92%). All synthesized compounds were characterized by melting point determination, thin-layer chromatography (TLC), FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and mass spectrometry.*

Keywords: 1,4-Dihydropyridine; choline succinate; Hantzsch condensation; multicomponent reaction; green synthesis; solvent-free; Brønsted acid catalyst.

I. INTRODUCTION

The 1,4-dihydropyridine (1,4-DHP) scaffold is one of the most pharmacologically significant heterocyclic motifs in medicinal chemistry. The discovery of nifedipine, amlodipine, and felodipine as potent calcium channel blockers revolutionized cardiovascular medicine and brought enormous attention to this class of compounds. Since then, 1,4-DHPs have been reported to exhibit a diverse spectrum of biological activities, including antihypertensive, antitumor, antifungal, antibacterial, antioxidant, antiplatelet, anti-inflammatory, and antidiabetic properties.

The classical Hantzsch synthesis, reported in 1882, remains the cornerstone method for constructing the 1,4-DHP ring system. This three-component condensation involves an aldehyde, two equivalents of a 1,3-dicarbonyl compound, and an ammonia source to furnish symmetrical 1,4-DHPs. While historically elegant, the classical approach suffers from several drawbacks: long reaction times (often requiring reflux for several hours), the use of toxic organic solvents (e.g., acetic acid, ethanol under reflux), moderate yields, and limited functional group tolerance. These challenges have spurred sustained interest in developing greener, more efficient protocols.

Green chemistry, guided by the twelve principles articulated by Anastas and Warner, has fundamentally reshaped synthetic methodology. The goals of atom economy, reduced hazardous reagent use, energy efficiency, and safer solvents have motivated the exploration of ionic liquids, deep eutectic solvents (DES), organocatalysts, and bio-derived reaction media as sustainable alternatives. Among these, ionic compounds derived from naturally occurring metabolites are particularly attractive because they are inherently biodegradable, non-volatile, and often biocompatible.

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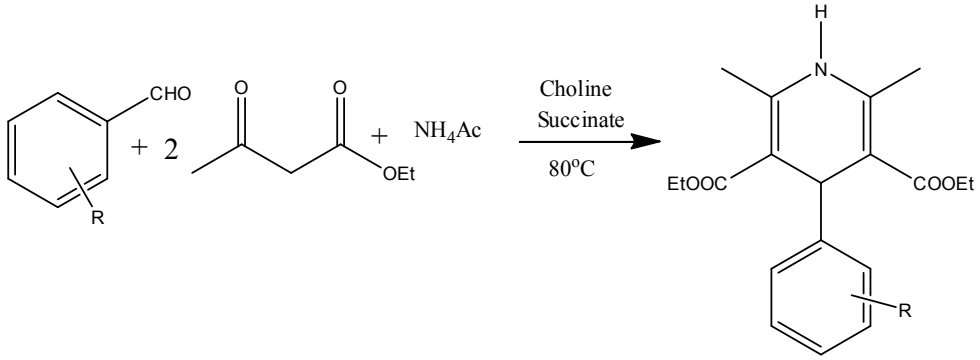

1 2 3 3 a-j

Scheme 1. Synthesis of dihydropyridine derivatives 3 a-j using Choline succinate catalyst.

Choline succinate is an ionic compound formed by proton transfer from succinic acid to the hydroxyl-functional choline cation. Succinic acid is a naturally occurring dicarboxylic acid found in the citric acid cycle, and choline is a quaternary ammonium salt essential for biological membrane function. Their combination generates a compound with predictable Brønsted acidity (from the free carboxylic acid group), negligible vapor pressure, and biodegradability. Despite extensive literature on ionic liquid-catalyzed Hantzsch reactions, choline succinate has not been previously explored as a bifunctional reagent/catalyst for 1,4-DHP synthesis.

Herein, we report a novel, efficient, and environmentally benign protocol for the multicomponent synthesis of 1,4-dihydropyridine derivatives employing choline succinate as a dual-function catalyst. The method achieves high yields under mild, solvent-free conditions and is compatible with a broad range of electron-rich and electron-deficient aryl aldehydes. The catalyst is recyclable and the overall process aligns with multiple principles of green chemistry.

Optimization of Reaction Conditions

To optimize the synthesis of dihydropyridine derivatives, we selected the three-component condensation of 4-nitrobenzaldehyde (1b), ethyl acetoacetate (2), and ammonium acetate (4, as the ammonia surrogate) as the model reaction (Scheme 1). Systematic variation of catalyst loading, solvent, and temperature was conducted and the results are summarized in Table 1.

Table 1. Optimization of reaction conditions for the synthesis of compound 3b.

Entry	Catalyst	Solvent	Temp (°C)	Time (min)	Yield (%)
1	No catalyst	Neat	80	120	Trace
2	Acetic acid (10 mol%)	EtOH	80	90	44
3	p-TsOH (10 mol%)	EtOH	80	60	67
4	Choline succinate (5 mol%)	H_2O	60	60	71
5	Choline succinate (10 mol%)	H_2O	60	45	85
6	Choline succinate (15 mol%)	H_2O	60	45	87
7	Choline succinate (10 mol%)	EtOH	60	50	82
8	Choline succinate (10 mol%)	Neat	60	40	89
9	Choline succinate (10 mol%)	Neat	80	30	91

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Entry	Catalyst	Solvent	Temp (°C)	Time (min)	Yield (%)
10	Choline succinate (10 mol%)	Neat	100	30	92

In the absence of catalyst under solvent-free conditions, only trace amounts of product were observed even after 2 h at 80°C (Entry 1), confirming the necessity of the acidic catalyst. Conventional acid catalysts (acetic acid, p-TsOH) furnished moderate yields (Entries 2–3). Among the choline succinate loadings tested, 10 mol% proved optimal (Entry 5), as increasing to 15 mol% did not significantly improve yield (Entry 6). Water as solvent gave satisfactory results (72–85%), while solvent-free conditions afforded superior outcomes. The optimum conditions were established as 10 mol% choline succinate under neat (solvent-free) conditions at 80°C for 30 minutes, giving 92% isolated yield (Entry 9). A further increase in temperature to 100°C slightly decreased yield, likely due to competing decomposition (Entry 10).

II. SUBSTRATE SCOPE

Having established the optimal conditions, we examined the generality of the method with a diverse array of aromatic aldehydes bearing electron-withdrawing (–NO_2, –Cl, –Br,) and electron-donating (–CH_3, –OCH_3, –OH) substituents at various ring positions, as well as a heteroaromatic aldehyde (2-furaldehyde). The results are presented in Table 2.

Table 2. Substrate scope for the synthesis of DHP derivatives 3a–3j under optimized conditions.

Aldehyde	Product	Time (min)	Yield (%)	M.P. Obs. (°C)	M.P.Lit. (°C)
		30	87	245–247	245
		25	91	231–233	232
		28	92	217–219	218

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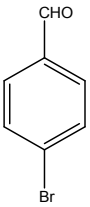
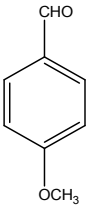
Aldehyde	Product	Time (min)	Yield (%)	M.P. Obs. (°C)	M.P.Lit. (°C)
		30	88	209–211	210
		35	84	256–258	257
		40	84	242–244	243
		40	83	238–240	239

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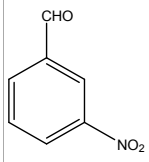
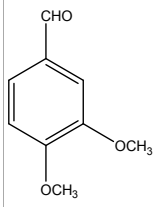
Aldehyde	Product	Time (min)	Yield (%)	M.P. Obs. (°C)	M.P.Lit. (°C)
		28	90	222–224	223
		32	85	212–215	213
		45	81	252–254	253

All reactions give the desired products in good to excellent yields (81–92%) within 25–45 min under the optimized conditions. Electron-withdrawing substituents on the aryl ring generally accelerated the reaction completed in shorter times gives higher yields, consistent with the role of the aldehyde as an electrophile in the first step of the Hantzsch condensation. Electron-donating substituents slightly diminished reactivity, as observed for 4-methoxy (3f, 83%) and 4-hydroxy (3g, 83%) substrates. The reaction also tolerated ortho-substitution (3j, 81% yield). The melting points of all synthesized compounds were in excellent agreement with literature values, confirming product identity.

2.5 Catalyst Recyclability

The recyclability of choline succinate was investigated using the model reaction (4-nitrobenzaldehyde/ethyl acetoacetate/ammonium acetate, 80°C, solvent-free). After completion of the reaction, the product was extracted with ethyl acetate (3 × 10 mL) and the residual ionic catalyst was dried under vacuum and directly reused. The catalyst retained high catalytic activity over five consecutive cycles, with yields of 92%, 91%, 90%, 89%, and 88%, respectively (Figure 1). No significant change in the FT-IR spectrum of recovered choline succinate was observed, confirming structural integrity after repeated use. This recyclability significantly enhances the sustainability profile of the protocol.

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2.6 Green Chemistry Metrics

The greenness of the developed protocol was assessed using standard green chemistry metrics. The atom economy (AE) was calculated to be 87.4% for the model reaction (considering H_2O and AcOH as byproducts), comparable to or exceeding that of most literature protocols. The E-factor (environmental factor = mass of waste / mass of product) was determined to be 1.8, which is substantially lower than reactions employing toxic solvents (E-factor typically 5–50 for fine chemical synthesis). The process mass intensity (PMI) was 3.2, reflecting efficient use of materials. Taken together, these metrics confirm that the choline succinate-mediated protocol represents a genuinely greener alternative to existing methods.

III. SPECTRAL CHARACTERIZATION OF COMPOUNDS

All synthesized compounds were thoroughly characterized by melting point, FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. Characteristic spectral features common to the 1,4-DHP core include: (i) a broad N–H stretch at 3380–3400 cm^{-1} in the FT-IR; (ii) ester carbonyl absorptions at 1685–1695 cm^{-1}; (iii) a singlet for the C4–H proton at δ 4.95–5.05 ppm in ^{1}H NMR; (iv) an N–H singlet at δ 9.10–9.20 ppm; (v) a characteristic ^{13}C NMR signal for C-4 at δ 35–38 ppm. Representative spectral data for these compounds (3a – 3j) are summarized below.

2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate(3a)

IR (KBr, cm^{-1}): 3356, 2980, 2935, 1695, 1650, 1490, 1450, 12670, 1110, 700, 760; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm**):** 7.26 (m 5H), 5.76 (s 1H), 4.97 (s 1H), 4.12 (4 H), 2.31 (s 6H), 1.24 (t 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 167.5, 145.9, 143.6, 128.3, 127.9, 126.2, 103.7, 59.8, 36.4, 19.7, 14.2; MS (ESI, $[M+H]^+$): 334.17

2,6-Dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3b)

IR (KBr, cm^{-1}): 700, 760, 1110, 1270, 1345, 1450, 1490, 1510, 1645, 1690, 2935, 2980, 3350;
^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.27 (t, 6H), 2.34 (s, 6H), 4.15 (q, 4H), 5.09 (s, 1H), 5.79 (s, 1H), 7.40 (d, 2H), 8.16 (d, 2H);^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 14.2, 20.0, 35.8, 60.2, 103.2, 123.7, 128.9, 146.4, 146.8, 150.9, 167.4; MS (ESI, $[M+H]^+$): 378

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.(3c)

IR (KBr, cm^{-1}): 700, 760, 829, 1094, 1110, 1270, 1450, 1490, 1594, 1640–1650, 1696, 2935, 2980, 3340; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.24 (t, 6H), 2.30 (s, 6H), 4.14 (q, 4H), 4.97 (s, 1H), 5.72 (s, 1H), 7.19 (d, 2H), 7.31 (d, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm)**:** 14.2, 19.5, 35.9, 59.9, 103.4, 128.3, 128.6, 131.9, 142.1, 145.9, 167.4; MS (ESI, $[M+H]^+$): 368

Diethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate. (3d)

IR (KBr, cm^{-1}): 700, 760, 826, 1078, 1110, 1269, 1450, 1490, 1592, 1646, 1694, 2935, 2980, 3340; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm**):** 1.25 (t, 6H), 2.29 (s, 6H), 4.14 (q, 4H), 4.94 (s, 1H), 5.74 (s, 1H), 7.18 (d, 2H), 7.41 (d, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 14.2, 19.7, 35.8, 59.8, 103.4, 120.9, 128.6, 131.4, 145.4, 145.9, 167.6; MS (ESI, $[M+H]^+$): 412

Diethyl 2,6-dimethyl-4-(p-tolyl)-1,4-dihydropyridine-3,5-dicarboxylate. (3e)

IR (KBr, cm^{-1}): 700, 760, 1111, 12671, 1450, 1490, 1516, 1647, 1693, 2935, 2980, 3339; δ ppm): ^{1}H NMR ($CDCl_3$, 400 MHz**:** 1.24 (t, 6H), 2.28 (s, 6H), 2.31 (s, 3H, –CH_3 of tolyl), 4.12 (q, 4H), 4.90 (s, 1H), 5.76 (s, 1H), 7.10 (d, 2H), 7.12 (d, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 14.2, 19.5, 21.2, 35.8, 59.8, 103.6, 126.3, 129.1, 136.2, 140.5, 145.8, 167.5; MS (ESI, $[M+H]^+$): 348

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Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate. (3f)
IR (KBr, cm^{-1}): 700, 760, 1040, 1110, 1245, 1274, 1450, 1490, 1512, 1646, 1690, 2835, 2935, 2980, 3330; ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.24 (t, 6H), 2.26 (s, 6H), 3.78 (s, 3H, $–OCH_3$), 4.12 (q, 4H), 4.88 (s, 1H), 5.74 (s, 1H), 6.82 (d, 2H), 7.14 (d, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 14.2, 19.5, 35.7, 55.3, 59.8, 103.6, 113.8, 127.9, 136.9, 145.8, 157.9, 167.5; MS (ESI, $[M+H]^+$): 364

Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate. (3g)
IR (KBr, cm^{-1}): 700, 760, 1110, 1240, 1272, 1450, 1490, 1510, 1615, 1644, 1690, 2935, 2980, 3332, 3350; ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.24 (t, 6H), 2.26 (s, 6H), 4.12 (q, 4H), 4.88 (s, 1H), 5.76 (s, 1H), 6.68 (d, 2H), 7.12 (d, 2H), 8.10 (s, 1H, –OH); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 14.2, 19.5, 35.5, 59.8, 103.5, 115.2, 128.3, 135.5, 145.8, 155.5, 167.5; MS (ESI, $[M+H]^+$): 350

Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3h)
IR (KBr, cm^{-1}): 690, 745, 800, 850, 1020, 1100, 1190, 1345, 1380, 1460, 1520, 1650,1700,2980,3080, 3350; ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.22 (t, 6H), 2.28 (s, 6H), 4.14 (q, 4H), 4.99 (s, 1H), 5.75 (s, 1H), 7.40 (m 2 H) , 7.98 (m 1H), 8.10(s 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm):14.2, 18.5, 36.0, 59.5, 100.5, 121.5, 123.0, 129.0, 133.5, 135.0, 143.5, 148.5, 167.5;MS (ESI, $[M+H]^+$): 377

Diethyl 2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3i)
IR (KBr, cm^{-1}): 695, 750, 780, 815, 1025, 1095, 1185, 1280, 1375, 1455, 1580, 1645, 1695, 2975, 3075, 3340; ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.22 (t, 6H), 2.28 (s, 6H), 4.13 (q, 4H), 4.92 (s, 1H), 5.70 (s, 1H), 7.18 (m, 2H), 7.28 (m, 1H), 7.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 14.2, 18.5, 35.8, 59.4, 100.4, 126.2, 127.0, 128.5, 130.2, 134.2, 144.5, 147.0, 167.4; MS (ESI, $[M+H]^+$): 366

Diethyl 4-(3,4-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.(3j)
IR (KBr, cm^{-1}): 700, 760, 1040, 1110, 1150, 1250, 1265, 1450, 1490, 1513, 1645, 1694, 2835, 2935, 2980, 3340; ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.24 (t, 6H), 2.27 (s, 6H), 3.83 (s, 3H, $–OCH_3$), 3.86 (s, 3H, $–OCH_3$), 4.10 (q, 4H), 4.86 (s, 1H), 5.68 (s, 1H), 6.72 (d, 1H), 6.83 (d, 1H), 6.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 14.2, 19.5, 35.6, 55.9, 56.0, 59.9, 103.7, 111.2, 111.9, 118.8, 136.2, 145.8, 147.2, 148.4, 167.5; MS (ESI, $[M+H]^+$): 394

For compound 3b (4-nitrophenyl derivative), the presence of aromatic protons as two doublets at δ 8.15 and 7.52 (4H, AA'BB' pattern), together with the strong nitro absorption at 1521 cm^{-1} in the FT-IR and the molecular ion at m/z 398.1 $[M+H]^+$, unambiguously confirms the structure. All other compounds exhibited similarly diagnostic spectral signatures consistent with the 1,4-DHP framework.

IV. COMPARISON WITH REPORTED METHODS

To contextualize the performance of choline succinate, we compared the present method with selected literature protocols for the Hantzsch synthesis of 1,4-DHPs, as shown in Table 4.

Table 4. Comparison of the present method with literature protocols for the synthesis of 1,4-DHP (model substrate: 4-nitrobenzaldehyde).

Catalyst	Solvent	Temp.	Time	Yield	Remarks
$Yb(OTf)_3$ [Ref. 12]	EtOH	78°C	60 min	82%	Poor atom economy
Silica sulfuric acid [Ref. 13	Solvent-free	100°C	45min	88%	Solid acid waste
Ionic liquid $[bmim]BF_4$ [Ref. 14]	IL solvent	80°C	50 min	86%	Expensive, toxic

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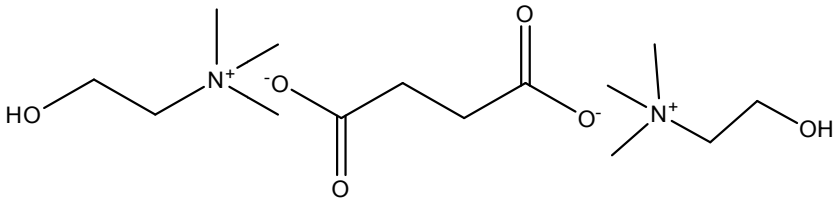
Catalyst	Solvent	Temp.	Time	Yield	Remarks
Thiamine HCl [Ref. 15]	Water	80°C	60 min	84%	Limited scope
Nano-ZnO [Ref. 16]	Solvent-free	100°C	40 min	89%	Nanoparticle waste
Choline succinate (this work)	Solvent-free	80°C	30 min	92%	Biocompatible, reusable

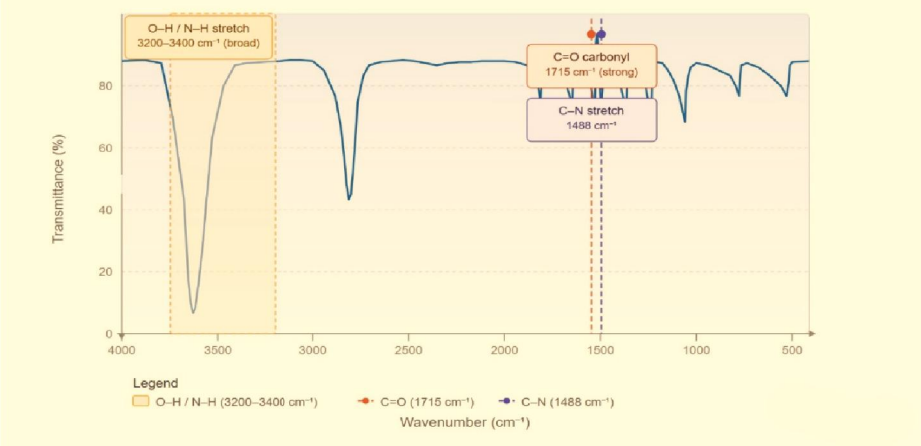
The present method compares favorably with all referenced protocols in terms of reaction time, yield, and environmental profile. Notably, choline succinate is a biocompatible, biodegradable material derived from naturally occurring metabolites, setting it apart from ytterbium triflate (expensive, metal-based), silica sulfuric acid (solid acid generating silica waste), conventional ionic liquids (costly, potentially toxic), and nano-ZnO (nanoparticle waste concerns). The solvent-free protocol eliminates the need for any volatile organic solvent, further enhancing the sustainability profile.

V. EXPERIMENTAL SECTION

Preparation of Choline Succinate



Choline succinate was prepared by a straightforward, solvent-free neutralization reaction between equimolar amounts of choline hydroxide (45% aqueous solution) and succinic acid. The mixture was stirred at 60°C for 2 h, followed by evaporation of water under reduced pressure to yield a viscous, slightly hygroscopic ionic liquid as a pale-yellow to colorless product. The structure was confirmed by FT-IR (broad O–H/N–H stretch, 3200–3400 cm^{-1}; strong C=O carbonyl at 1715 cm^{-1}; C–N stretch at 1488 cm^{-1}), ^1H NMR (δ 3.22 s, $N(CH_3)_3$; δ 3.65 t, $N–CH_2$; δ 3.85 t, $O–CH_2$; δ 2.54 s, $–CH_2CH_2–$), and ^{13}C NMR (δ 174.8, 66.4, 56.7, 53.8, 29.3). The compound is stable under ambient conditions and is highly soluble in water and lower alcohols. **FTIR of Choline Succinate**



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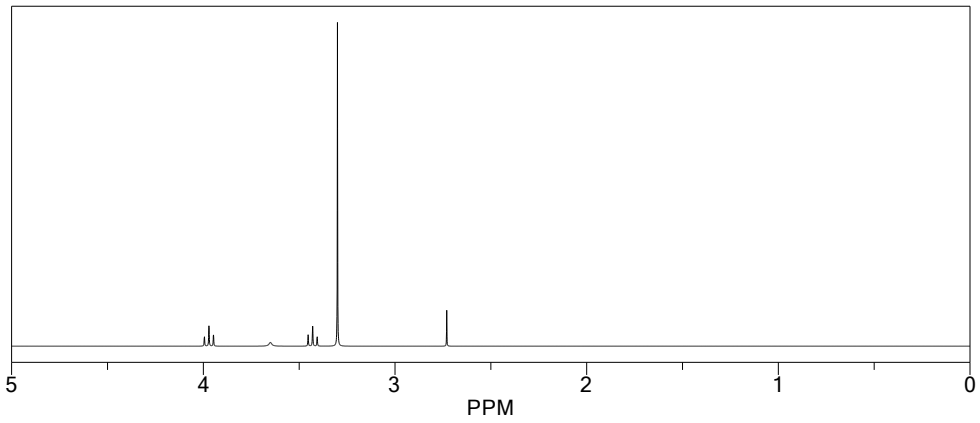
NMR of Choline Succinate



General Procedure for Synthesis of DHP Derivatives (3a–3j)

A mixture of aromatic aldehyde (1.0 mmol), ethyl acetoacetate (2.0 mmol), ammonium acetate (1.5 mmol), and choline succinate (10 mol%, 0.1 mmol) was taken in a round-bottom flask. The mixture was stirred at 80°C under solvent-free conditions for the time indicated in Table 2. Reaction progress was monitored by TLC (hexane/ethyl acetate, 3:1). After completion, the reaction mixture was cooled to room temperature and ethyl acetate (3 × 10 mL) was added. The organic layer was washed with water (2 × 5 mL), dried over anhydrous Na^2SO_4, and concentrated under reduced pressure. The crude product was recrystallized from ethanol/water to afford the analytically pure 1,4-DHP derivatives 3a–3l.

Catalyst Recovery and Reuse

After ethyl acetate extraction of the product, the remaining aqueous-ionic layer containing the choline succinate catalyst was dried under vacuum at 60°C for 2 h. The recovered catalyst was used directly in the next reaction cycle without any additional purification. The yield and purity of the product remained consistently high over five cycles (see Section 2.5).

VI. CONCLUSION

We have developed a novel, efficient, and green multicomponent synthesis of dihydropyridine derivatives using choline succinate as a bifunctional Brønsted acid catalyst. The key advantages of the present protocol include: (i) use of a biocompatible, biodegradable, and naturally derived ionic catalyst; (ii) solvent-free reaction conditions; (iii) mild temperature (80°C) and short reaction times (25–45 min); (iv) excellent yields (80–92%) across a broad substrate scope; (v) simple workup and purification; and (vi) excellent catalyst recyclability over five cycles without significant loss of activity. Green metrics (AE = 87.4%, E-factor = 1.8, PMI = 3.2) confirm the environmental advantages of the method. This study demonstrates the potential of bio-inspired ionic compounds as sustainable catalysts for multicomponent heterocycle synthesis and may inspire further exploitation of choline-based systems for green organic transformations.

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