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ORIGINAL ARTICLE

DBUHI$_3$-catalyzed efficient synthesis of 1,4-dihydropyridines

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Cite This: *Org. Commun.* 2026, 19(1): e26013780

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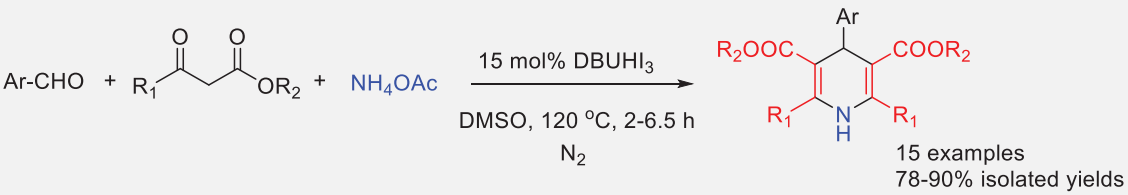
Abstract: A process-optimized, one-pot multicomponent reaction catalyzed by DBUHI$_3$ was developed, enabling the synthesis of diverse 1,4-dihydropyridines (1,4-DHPs), a class of bioactive nitrogen heterocycles from substituted benzaldehydes, ethyl acetoacetate, and ammonium acetate under mild conditions in DMSO. The methodology afforded good to excellent yields for a variety of aryl aldehyde substrates bearing both electron-donating and electron-withdrawing groups. Structural confirmation was achieved through IR, ^{1}H NMR, ^{13}C NMR, and HRMS analyses. This work not only summarizes key synthetic strategies but also provides a practical, sustainable route to the preparation of 1,4-DHPs, supporting further medicinal and synthetic exploration.



Keywords: 1,4-dihydropyridines (1,4-DHPs), DBUHI$_3$, organocatalyst, multicomponent reaction (MCR)

1 Introduction

Heterocyclic compounds have attracted significant scientific research due to their numerous important biological and medicinal uses.[1–5] They are found in more than 90% of novel drugs and act as a bridge between chemistry and biology, the domains where most scientific discoveries and applications occur. Although nitrogen, oxygen, and sulfur are the most common heteroatoms, heterocyclic rings with additional heteroatoms, including phosphorus, iron, magnesium, selenium, and others, are also commonly seen. Because of their many uses, nitrogen-containing heterocyclic molecules are particularly crucial to medical chemistry.[6–9]

The earliest multicomponent reaction, dating to 1850 and credited to Strecker,[10] initiated a sequence of reactions documented in the literature. Multicomponent reactions (MCRs) are a unique class of synthetically useful organic reactions that combine one or more different starting materials in a single pot to produce a final product. These reactions have been widely used in a number of synthetic transformations, where traditional methods typically require a lengthy, multi-stage processes.

High yields, atom-/step economy, shorter reaction times, environmental friendliness, and a useful tool for building a library of novel chemical entities (NCEs) are just a few of the benefits that make the MCR technique so beneficial in the drug development process.[11–19] Heterocyclic chemistry has consistently produced highly convergent syntheses because heterocyclic scaffolds often comprise more than two building units. The effective conversion of heterocycles into functional compounds has been closely linked to their synthesis by multicomponent reactions (MCRs) from the early days of organic chemistry.

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Received: January 02, 2026
Revised: January 26, 2026
Accepted: February 02, 2026
Published: February 19, 2026

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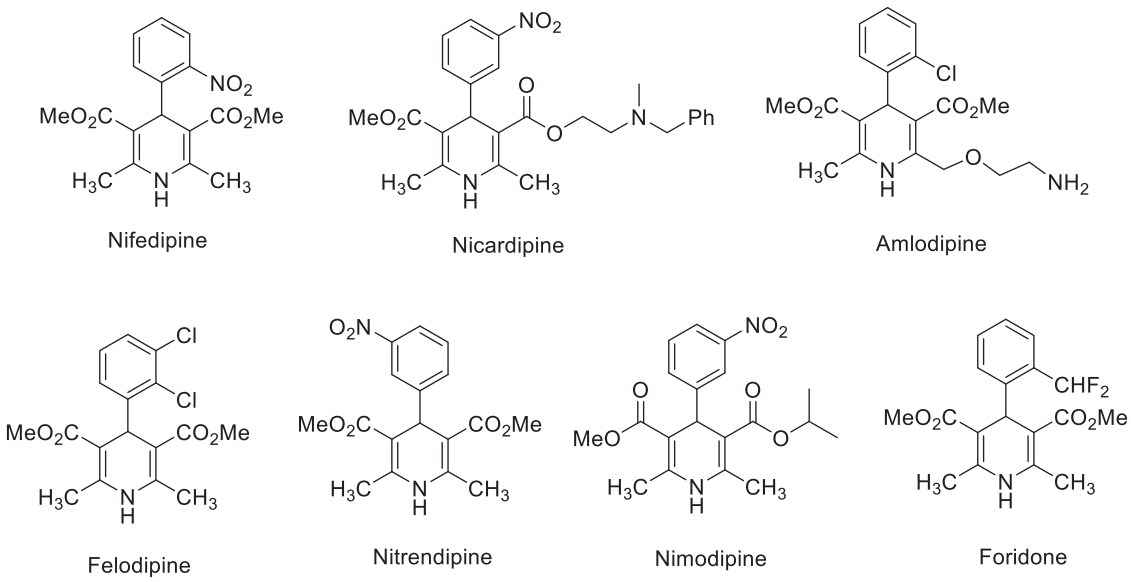


Figure 1. Marketed antihypertensive drugs (vasodilators)

Since 1,4-dihydropyridine is a common constituent of many physiologically active compounds, it occupies a significant place among the many heterocyclic scaffolds. Hantzsch was the first to synthesize dihydropyridines.[20] The Hantzsch synthesis, the most traditional technique for creating 1,4-dihydropyridines, is a one-pot cyclo-condensation of a β-ketoester with an aldehyde and a nitrogen supply (formate or ammonium acetate). Dihydropyridines play a significant role in natural products and biological activities, including the treatment of Alzheimer's disease, cardiovascular disorders, hypertension, nephroprotection in hypertensive types I and II in diabetic patients, chemosensitizers, neuroprotectants, anticoagulants, and cerebral anti-ischemic.[21–27] Commercial dihydropyridine compounds were produced and are in use all over the world, including Bay K 8644, diludine, felodipine, amlodipine, nimodipin, nifedipine, nitredipin, nislodipin, and nimopidipin (Figure 1).

Synthetic chemists' interest in developing novel, environmentally friendly synthetic methods for the synthesis of 1,4-dihydropyridine molecules using Lewis acid, Bronsted acid, biocatalysts, ionic liquids, and organocatalysts has increased due to the substantial pharmaceutical applications.[28–36] Numerous studies concentrate on modifying the Hantzsch process to boost product yield while lowering reaction time and byproduct production. The use of volatile organic solvents, longer reaction times, high reaction temperatures, the use of ecologically harmful reagents, low yield, narrow scope, and the use of hazardous solvents are the unpleasant aspects of these changes. and creation of ancillary products. Therefore, in order to produce target libraries with specific building blocks for our different heterocyclic scaffolds, this idea requires greater diversity.

$DBUHI_3$ was initially synthesized in our lab in recent years, and it was used as a novel organocatalyst to create a variety of heterocyclic frameworks, such as benzimidazoles, arylidenepyrazoles, and benzothiazoles.[37–39] In light of these advancements, we report our initial results on the synthesis of 1,4-dihydropyridines using $DBUHI_3$, an effective chalcone-derived organocatalyst. The use of the amine-iodine-iodide complex as a catalyst in the synthesis of title compounds has not been reported, as far as we are aware. The current method provides a sustainable and environmentally beneficial strategy because to its excellent substrate and functional group compatibility, cheap cost, benign reaction conditions, simple and quick product separation, and reliance on an organocatalyst.

2 Results and Discussion

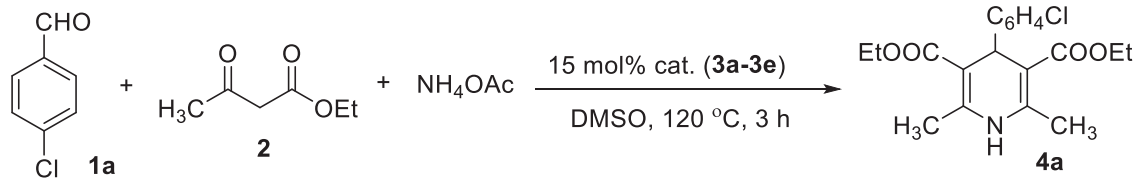
We screened all amineH-I_3 complexes (**3a–e**, Table 1) for the synthesis of **4a** and the outcome was summarized in Table 1, which indicated that all amineH-I_3 showed good catalytic activity but $DBUHI_3$ (**3e**) was found slightly better.

Different solvent mediums such as acetonitrile, DCE, water, DCM, DMF and ethanol were also tried, but the expected results were not produced. Now, the same reaction was preceded with $DBUHI_3$ in DMSO medium at room temperature and different temperatures (60°C, 80°C and 100°C), and the results were found to be not effective. Open air, nitrogen conditions were tested and the yield of the product seemed to be far better while performing the reaction under nitrogen atmosphere. The catalyst was used in various amounts (5, 10, and 20 mol%) for the synthesis of title compounds and resulted in optimum (45, 68, and 84%) product yields. Thus, we concluded the optimized reaction parameters for the synthesis of 1,4-DHPs are as follows: $DBUHI_3$ (15 mol%) in DMSO at 120 °C under N_2.

A number of 1,4-DHP derivatives were produced using different aldehydes, including both electron-donating and electron-withdrawing substituents, in order to investigate the reaction's range once the reaction conditions were optimized (Table 2). All of the aldehydes containing both

http://doi.org/10.25135/org.2601.3780
Org. Commun. 2026, 19(1):e26013780

Table 1. Study of the effect of catalysts (3a–3e) in the synthesis of 4a[a]



Entry	AmineH-I_3 complexes	Yield (%)[b]
1	No catalyst	0
2	morpholineH-I_3 (**3a**)	78
3	urotropineH-I_3 (**3b**)	81
4	piperazineH-I_3 (**3c**)	75
5	*N*-Me piperazineH-I_3 (**3d**)	71
6	I_2	66
7	**DBUH-I_3 (3e)**	**85**

Note: [a]Reaction condition: 4-chlorobenzaldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1.5 mmol), amineH-I3catalyst (**3a–3e**), DMSO (2 mL); [b]isolated yield after purification.

electron-donating and electron-withdrawing groups had excellent reactions, producing high yields of the intended products in brief reaction periods (entries **4a–o**, 2–6.5 h). As anticipated, compared to substituted aldehydes with electron-donating groups, those with electron-withdrawing groups require a shorter reaction time. Aldehydes bearing electron-withdrawing substituents increase the electrophilicity of the carbonyl carbon, thereby facilitating faster nucleophilic attack during the condensation process. In contrast, electron-donating groups reduce carbonyl electrophilicity, leading to comparatively longer reaction times and slightly reduced reaction rates. This electronic effect accounts for the observed trend in yields and reaction times.

Since aliphatic aldehydes, such as acetaldehyde and isobutyraldehyde, could not react under optimum conditions to yield any desired product, only aromatic aldehydes were investigated. Aliphatic aldehydes generally exhibit lower electrophilicity and lack conjugative stabilization of reaction intermediates, which is crucial for efficient cyclocondensation. Additionally, their higher tendency toward enolization and side reactions under the reaction conditions may suppress the desired transformation, resulting in poor or no product formation.

The IR spectrum of above the product shows characteristic signal ~3354 cm^{-1} N-H stretching, ~1693 cm^{-1} and 1651 cm^{-1} signal indicate carbonyl group and C=C bond stretching respectively indicates cyclic ring formation of 1,4-DHP **4a**. The structure was confirmed by two important signals of ^{1}HNMR 1 & 4 dihydro carbon proton singlet at ~5.69 and ~4.96. The structure was further authenticated by ^{13}C-NMR and HRMS analysis. The $DBUHI_3$-catalyzed Hantzsch reaction mechanism probably proceeds through a Michael addition, followed by an intramolecular tandem sequence, that may take place in the formation of the final product.

The proposed mechanism highlights the role of the active catalytic species, which facilitates carbonyl activation, intermediate formation, and subsequent cyclocondensation leading to the final product (Figure 2).

Although $DBUHI_3$ is frequently reported in iodination and oxidation-related transformations, in the present multicomponent reaction it primarily functions as a mild ionic promoter and bifunctional catalyst rather than as an iodinating agent. The $DBUHI_3$ system provides a unique combination of Brønsted acidity and hydrogen-bonding capability, which facilitates activation of the carbonyl group and enhances the formation of key intermediates during the Hantzsch-type condensation process. The presence of the iodide species assists in improving electrophilic activation without leading to side iodination, thereby promoting smooth cyclocondensation under mild conditions.

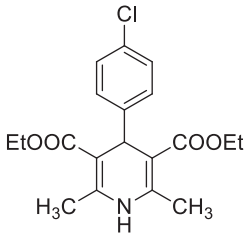
Furthermore, $DBUHI_3$ was preferred over conventional acidic or Lewis acid catalysts due to several advantages, including: mild and metal-free reaction conditions, operational simplicity and easy handling, avoidance of harsh acids or toxic metal salts, and excellent chemoselectivity without formation of halogenated by-products. These features make $DBUHI_3$ particularly suitable for the synthesis of 1,4-dihydropyridine derivatives in an environmentally benign and efficient manner. Since, hypo wash is given during workup, this catalyst is deactivated and henceforth, no scope for its resue and recyclability.

3 Experimental Detail

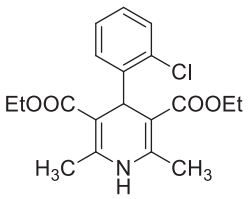
Typical procedure for the synthesis of 1,4-dihydropyridine synthesis (4a–o)

A mixture of aryl aldehyde (1 mmol), ammonium acetate (1.5 mmol), ethylacetoacetate (2 mmol), and $DBUHI_3$ (15 mol%) in 2 mL DMSO solvent was taken in a round-bottom flask reaction mixture was heated and maintained 120°C under nitrogen atmosphere for the time specified in Table 2. The progress of the reaction was monitored by TLC in ethyl acetate and hexane. As soon as aryl aldehyde vanishes in TLC, cooled the reaction mixture to room

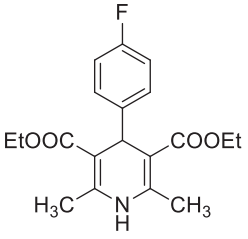
Table 2. DBUH-I_3 catalyzed synthesis of divergent dihydropyridines



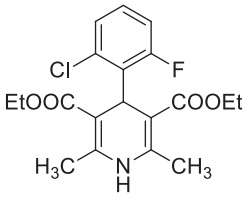
4a (3 h, 85%)



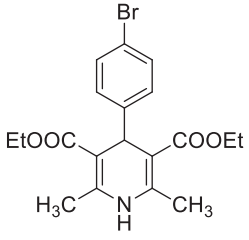
4b (3.5 h, 82%)



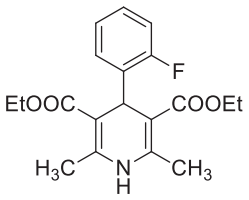
4c (2.5 h, 85%)



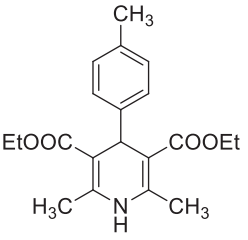
4d (2 h, 90%)



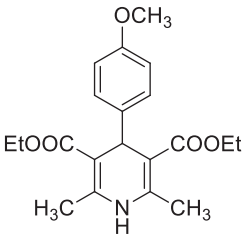
4e (4 h, 81%)



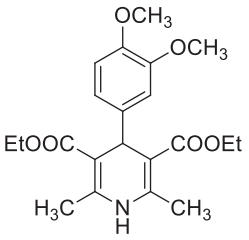
4f (2.5 h, 79%)



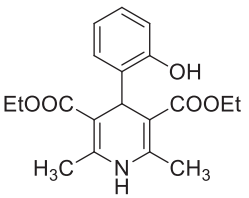
4g (5 h, 82%)



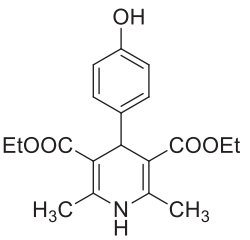
4h (4.5 h, 85%)



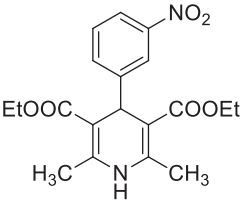
4i (6 h, 79%)



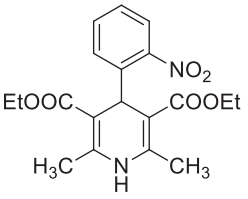
4j (6.5 h, 78%)



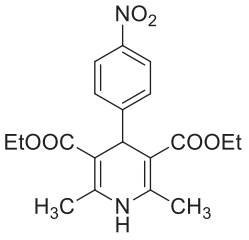
4k (5.5 h, 81%)



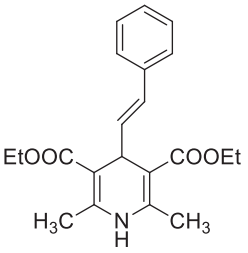
4l (3 h, 83%)



4m (2.5 h, 87%)



4n (3 h, 89%)



4o (4 h, 80%)

temperature and added 20% ice-cold sodium thiosulphate solution to quench the reaction. Solid product was obtained, filter and dry the product. The product was recrystallized in absolute ethanol, solvent and yield, and melting point was reported.

4 Spectral Analysis

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4a): White Solid; mp 147–148°C; **FT IR** (cm^{-1}): 3354.8, 2981.7, 1693.4, 1651.1, 1485.5, 1209.9, 829.1; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ: 7.21–7.22 (d, 2H, Ar-H, J = 8.0 Hz), 7.00–7.04 (d, 2H, Ar-H, J = 8.0 Hz), 5.64 (s, 1H, NH), 4.92 (s, 1H, CH), 4.02–4.11 (q, 4H, -O-CH_2-, J = 7.0 Hz), 2.31 (s, 6H,-CH_3), 1.18–1.21 (t, 6H, -CH_2-**CH**$_3$, J = 7.0 Hz); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ: 167.44 (-**C**OOEt), 146.34 (Cl-**C**-Ar), 143.99 (Ar-C), 131.70 (Ar-C), 129.44 (Ar-C), 127.95 (SP^2-**C**-NH-), 103.90 (SP^2-**C**-COOEt), 59.84 (-O**C**H_2-CH_3), 39.26 (CH), 19.63 (-CH_3), 14.27 (-O-CH_2-**C**H_3); HRMS (ESI): m/z $[M+H]^+$ calcd. for: $C_{19}H_{22}ClNO_4$, 363.1237, found, 364.1235.

http://doi.org/10.25135/org.2601.3780
Org. Commun. 2026, 19(1):e26013780

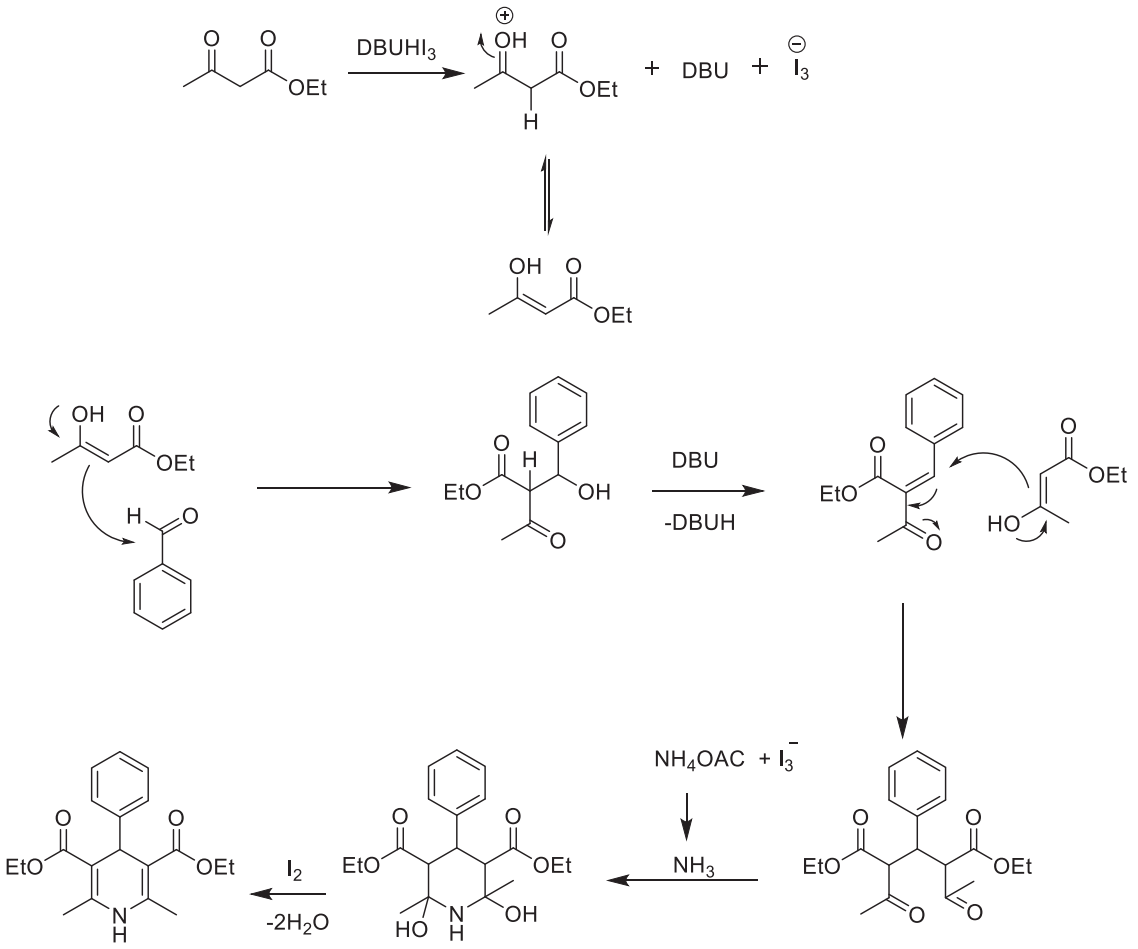


Figure 2. Plausible reaction mechanism for the $DBUHI_3$-catalyzed synthesis of dihydropyridines

Diethyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4b): White Solid; mp 81–82°C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.20–7.40 (m, 3H, Ar-H), 6.01 (q, 1H, Ar-H), 5.66 (s, 1H, NH), 4.63 (s, 1H, CH), 4.11–4.13 (q, 4H, -O-CH_2-), 2.33 (s, 6H, -CH_3, J = 7.0 Hz), 1.20–1.21 (t, 6H, -CH_2-**CH_3**, J = 7.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 168.12 (-**C**OOEt), 149.00 (Cl-**C**-Ar), 132.36 (Ar-C), 130.18 (Ar-C), 129.75 (Ar-C), 129.13 (Ar-C), 127.54 (Ar-C), 126.89 (SP^2-**C**-NH-), 104.31 (SP^2-**C**-COOEt), 60.00 (-O-CH_2-), 40.11 (CH), 19.67 (-CH_3), 14.00 (-O-CH_2-**CH_3**); HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{19}H_{22}ClNO_4$, 363.1237, found, 364.1236.

Diethyl 4-(5-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4c): White Solid; mp 154–155°C; FT IR (cm^{-1}): 3341.9, 2984.2, 1688.5, 1650.4, 1492.1, 1372, 1301.6, 1207.8, 1166.7, 1125.7, 1090.5, 1020.2, 858.94, 788.53, 753.4, 697.7, 677.19, 515.96; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.21–7.26 (m, 2H, Ar-H), 6.86–6.89 (m, 2H, Ar-H), 5.65 (s, 1H, NH), 4.96 (s, 1H, CH), 4.04–4.12 (m, 4H, -O-CH_2-, J = 7.5 Hz), 2.32 (s, 6H, -CH_3), 1.20–1.23 (t, 6H,-CH_2-CH_3, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.52 (-COOEt), 162.33 (F-C-Ar), 160.39 (Ar-C), 143.77 (Ar-C), 143.65 (Ar-C), 129.48 (Ar-C), 129.42 (Ar-C), 114.58 (SP^2-C-NH-), 104.19 (SP^2-C-COOEt), 59.78 (-O-CH_2-), 39.06 (CH), 19.60 (-CH_3), 14.26 (-CH_2-CH_3); HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{19}H_{22}FNO_4$, 347.1533, found, 348.1535.

Diethyl 4-(2-chloro-6-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5- dicarboxylate (4d): Pale yellow Solid; mp 142–143°C; **FT IR** (cm^{-1}): 3333, 2987.2, 1664.4, 1693.9, 1660.5, 1498, 1454, 1372, 1278, 1213.6, 1117, 1020.2, 894.12; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.08–7.10 (m, 1H, Ar-H), 7.01–7.05 (m, 1H, Ar-H), 6.84–6.88 (m, 1H, Ar-H), 5.83 (s, 1H, NH), 5.66 (s, 1H, CH), 4.02–4.06 (q, 4H, -O-CH_2-, J = 7.0 Hz), 2.26 (s, 6H, -CH_3), 1.13–1.16 (t, 6H, -CH_2-**CH_3**, J = 7.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 167.62 (**C**OOEt), 163.59 (F-**C**-Ar), 161.59 (Cl-**C**-Ar), 145.28 (Ar-C), 135,55 (Ar-C), 131.61 (Ar-C), 127.42 (Ar-C), 114.05 (SP^2-**C**-NH-), 100.10 (SP^2-**C**-COOEt), 59.61 (-O-CH_2-), 33.67 (CH), 19.59 (-CH_3), 14.11 (-CH_2-**CH_3**); HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{19}H_{21}ClFNO_4$, 381.1143, found 382.1415.

Diethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4e): White Solid; mp 159–161°C; FT IR (cm^{-1}): 3359.5, 2990.1, 1694.4, 1650.4, 1486.3, 1372, 1301.6, 1213.6, 1117, 1014.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.26–7.32 (m, 2H, Ar-H), 7.14–7.17 (m, 2H, Ar-H), 5.65 (s, 1H, NH), 4.94 (s, 1H, CH), 4.05–4.12 (m, 4H, O-CH_2-, J = 7 Hz), 2.32 (s, 6H, -CH_3), 1.20–1.23 (t, 6H, -CH_2-CH_3, J = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.39 (COOEt), 146.81 (Br-C-Ar), 143.97 (Ar-C), 130.89 (Ar-C), 129.84 (Ar-C), 119.87 (SP^2-C-NH-), 103.83 (SP^2-C-COOEt), 59.83 (-O-CH_2-), 39.33

(CH), 19.62 (-CH_3), 14.26 (-CH_2-CH_3); HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{22}BrNO_4$, 407.0732, found 408.0812.

Diethyl 4-(2-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4f): White Solid; mp 157–159°C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.26–7.27 (t, 2H, Ar-H, *J* = 8.6 Hz), 7.21–7.22 (t, 2H, Ar-H, *J* = 8.6 Hz), 7.13–7.14 (t, 1H, Ar-H, *J* = 8.6 Hz), 5.63 (s, 1H, NH), 4.91 (s, 1H, CH), 4.07–4.08 (q, 4H, -O-CH_2-, *J* = 7 Hz), 2.34 (s, 6H, -CH_3), 1.21–1.22 (t, 6H, -CH_2-CH_3, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 167.64 (COOEt), 157.76 (F-C-Ar), 153.82 (Ar-C), 142.14 (Ar-C), 130.83 (Ar-C), 128.03 (Ar-C), 127.84(Ar-C), 126.11 (SP^2-C-NH-), 104.21 (SP^2-C-COOEt), 59.74 (-O-CH_2-), 39.63 (CH), 19.63 (-CH_3), 14.26 (-CH_2-CH_3); HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{22}FNO_4$, 347.1533, found 348.1419.

Diethyl 2,6-dimethyl-4-(*p*-tolyl)-1,4-dihydropyridine-3,5-dicarboxylate (4g): White Solid; mp 163–165°C; FT IR (cm^{-1}): 3359.5, 2990.1, 1694.4, 1653.4, 1489.2, 1372, 1298.7, 1207.8, 1119.8, 1090.5, 1020.2; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.15–7.17 (d, 2H, Ar-H, *J* = 8 Hz), 7.00–7.01 (d, 2H, Ar-H, *J* = 7.5 Hz), 5.67 (s, NH, 1H), 4.95 (s, 1H, CH), 4.05–4.11 (s, 4H, -O-CH_2-, *J* = 7 Hz), 2.31 (s, 6H, -CH_3), 2.27 (s, 3H, Ar-CH_3), 1.21–1.24 (t, 6H, -CH_2-CH_3, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 167.68 (COOEt), 144.87 (Ar-C), 143.76 Ar-C), 135.51 (Ar-C), 128.57 (Ar-C), 127.83 (SP^2-C-NH-), 104.28 (SP^2-C-COOEt), 59.71 (-O-CH_2-), 39.11 (CH), 21.06 (Ar-CH_3), 19.60 (-CH_3), 14.27 (-CH_2-CH_3); HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{20}H_{25}NO_4$, 343.1784, found 344.1955.

Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4h): White Solid; mp. 162–164°C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.18–7.20 (dd, 2H, Ar-H, *J* = 7 & 2 Hz), 6.73–6.75 (dd, 2H, Ar-H, *J* = 6.5 & 2Hz), 5.66 (s, 1H, NH), 4.92 (s, 1H CH), 4.05–4.12 (q, 4H -O-CH_2-, *J* = 7 Hz), 3.75 (s, 3H, -CH_3), 2.31 (s, 6H, -CH_3), 1.21–1.23 (t, 6H, -CH_2-CH_3, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 167.70 (COOEt), 157.87 (MeO-C-Ar), 143.56 (Ar-C), 140.33 (Ar-C), 128.96 (Ar-C), 127.70 (Ar-C), 113.19 (SP^2-C-NH-), 104.39 (SP^2-C-COOEt), 59.70, (-O-CH_2-), 55.14 (-OCH_3), 38.74 (CH), 19.58 (-CH_3), 14.28 (-CH_2-CH_3); HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{20}H_{25}NO_5$, 359.4162, found, 360.4201.

Diethyl 4-(3,4-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4i): White Solid; mp 148–149°C; **^{1}H NMR** (500 MHz, $CDCl_3$) *δ*: 6.71–6.80 (m, 3H, Ar-H), 5.61 (s, 1H, NH), 4.97 (s, 1H, CH), 4.08–4.10 (q, 4H, -O-CH_2-, *J* = 7.2 Hz), 3.69 (s, 6H, -CH_3), 2.33 (s, 6H, -CH_3), 1.21–1.22 (t, 6H, -CH_2-**CH_3**, *J* = 7.2 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) *δ*: 167.95 (**CO**OEt), 157.32 (MeO-C-Ar), 156.61 (MeO-C-Ar), 143.55 (Ar-C) 140.39 (Ar-C), 129.00 (Ar-C), 128.54 (Ar-C) 113.85 (SP^2-**C**-NH-), 104.17 (SP^2-**C**-COOEt), 60.01 (-O-CH_2-), 55.45 (-OCH_3), 39.10 (CH), 19.28 (-CH_3), 14.56 (-CH_2-**CH_3**); HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{21}H_{27}NO_6$, 389.1838, found, 390.2012.

Diethyl 4-(2-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4j): White Solid; mp 118–120°C; **^{1}H NMR** (500 MHz, DMSO-d_6) *δ*: 8.97 (s, 1H, -OH), 8.63 (s, 1H, Ar-H), 6.50-7.00 (m, 3H), 5.14 (s, 1H, NH), 4.71 (s, 1H, CH), 3.93–4.11 (q, 4H, -O-CH_2-, *J* = 7.10 Hz), 2.21 (s, 6H, -CH_3), 1.11–1.13 (t, 6H, -CH_2-**CH_3**, *J* = 7.10 Hz); **^{13}C NMR** (125 MHz, DMSO-d_6) *δ*: 167.40 (**CO**OEt), 154.00 (HO-**C**-Ar), 145. (91Ar-C), 135.12 (Ar-C), 133.88 (Ar-C), 124.36 (Ar-C), 120.42 (Ar-C), 112.54 (SP^2-**C**-NH-), 102.00 (SP^2-**C**-COOEt), 59.08 (O-CH_2-), 37.14 (CH), 18.31 (-CH_3), 14.20 (-CH_2-**CH_3**); HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{23}NO_5$, 345.1576, found, 346.4650.

Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4k): Off white Solid; mp 226-228°C; FT IR (cm^{-1}): 3350.7, 2993, 1662.2, 1489.2, 1369, 1228.3, 1131.6, 1023.1; **^{1}H NMR** (500 MHz, DMSO-d_6) *δ*: 9.07 (s, 1H, -OH), 8.70 (s, 1H, NH), 6.91–6.93 (d, 2H, Ar-H, *J* = 8.0 Hz), 6.56–6.58 (d, 2H, Ar-H, *J* = 8.5 Hz), 4.73 (s, 1H, CH), 3.93–4.01 (q, 4H, -O-CH_2-, *J* = 7.0 Hz), 2.23 (s, 6H,-CH_3), 1.11–1.14 (t, 6H, -CH_2-**CH_3**, *J* = 7.0 Hz); **^{13}C NMR** (125 MHz, DMSO-d_6) *δ*: 167.56 (**CO**OEt), 155.89 (HO-C-Ar) 145.22 (Ar-C), 139.36 (Ar-C), 128.73 (Ar-C), 114.98 (SP^2-**C**-NH-), 102.75 (SP^2-**C**-COOEt), 59.34 (-O-CH_2-), 38.32 (CH), 18.66 (-CH_3), 14.67 (-CH_2-**CH_3**); HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{23}NO_5$, 345.1576, found, 346.4650.

Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4l): Yellow Solid; mp 162–164°C; **^{1}H NMR** (500 MHz, $CDCl_3$) *δ*: 7.95 (s, 1H, Ar-H), 7.55–7.92 (m, 3H, Ar-H), 5.74 (s, 1H, NH), 5.20 (s, 1H, CH), 3.98–4.03 (q, 4H -O-CH_2^-, *J* = 7.0 Hz), 2.30 (s, 6H, -CH_3), 1.12–1.14 (t, 6H, CH_2-**CH_3**, *J* = 7.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) *δ*: 167.00 (**CO**OEt), 154.27 (O_2N-C-Ar), 148.12 (Ar-C), 145.63 (Ar-C), 134.81 (Ar-C), 129.75 (Ar-C), 122.14 (Ar-C), 121.59 (SP^2-**C**-NH-), 101.77 (SP^2-**C**-COOEt), 60.13 (-O-CH_2-), 18.92 (-CH_3), 14.49 (-CH_2-**CH_3**); HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{22}N_2O_6$, 374.1478, found, 375. 1520.

Diethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4m): Yellow Solid; mp 168–170°C; **^{1}H NMR** (500 MHz, $CDCl_3$) *δ*: 7.72–7.74 (dd, 1H, Ar-H, *J* = 8 & 1 Hz), 7.52–7.54 (dd, 1H, Ar-H, *J* = 8 & 1.5 Hz), 7.44–7.47 (m, 1H, Ar-H), 7.22–7.26 (m, 1H, Ar-H), 5.84 (s, 1H, NH), 5.71 (s, 1H, CH), 4.09–4.14 (q, 4H, -O-CH_2, *J* = 7 Hz), 2.32 (s, 6H, -CH_3), 1.14–1.17 (t, 6H, CH_2-**CH_3**, *J* = 7 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) *δ*: 167.24 (**CO**OEt), 156.96 (O_2N-C-Ar), 147.81 (Ar-C), 144.44, 142.60 (Ar-C), 132.76 (Ar-C), 131.35 (Ar-C), 129.49 (Ar-C), 124.00 (SP^2-**C**-NH-), 104.01 (SP^2-**C**-COOEt), 60.05 (-O-CH_2-), 34.68 (CH), 19.65 (-CH_3), 14.14 (-CH_2-**CH_3**); HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{22}N_2O_6$, 374.1478, found, 375. 1520.

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4n): Yellow Solid; MP. 130–132°C; **^{1}H NMR** (500 MHz, $CDCl_3$) *δ*: 8.07–8.09 (dd, 2H, Ar-H, *J* = 7 & 2 Hz), 7.44–7.45 (dd, 2H, Ar-H, *J* = 6.5 & 2 Hz), 5.72 (s, 1H, NH), 5.09 (s, 1H, CH), 4.06–4.11 (q, 4H, -O-CH_2-, *J* = 7 Hz), 2.35 (s, 6H, -CH_3), 1.20–1.23 (t, 6H, -CH_2-**CH_3**, *J* = 7 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) *δ*: 167.05 (-**CO**OEt), 155.08 (O_2N-C-Ar), 146.36 (Ar-C), 144.59 (Ar-C), 128.91 (Ar-C), 123.30 (SP^2-**C**-NH-), 103.24 (SP^2-**C**-COOEt), 60.01 (-O-CH_2-), 40.14 (CH) 19.68 (-CH_3), 14.26 (-CH_2-**CH_3**); HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{22}N_2O_6$, 374.1478, found, 375. 1520.

http://doi.org/10.25135/org.2601.3780
Org. Commun. 2026, 19(1):e26013780

Diethyl-2,6-dimethyl-4-styryl-1,4-dihydropyridine-3,5-dicarboxylate (4o): White Solid; mp 147–148°C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ: 7.14–7.32 (m, 5H, Ar-H), 6.23–6.24 (d, 1H, Olefinic H, J = 11.01 Hz), 6.18–6.21 (q, 1H, Olefinic H, J = 10.96 & 7 Hz), 5.71 (s, 1H, NH), 4 .65 (s, 1H, CH), 4.19–4.21 (q, 4H, -O-CH_2-, J = 7.5 Hz), 2.31 (s, 6H -CH_3), 1.28–1.30 (t, 6H, -CH_2-**CH_3**, J = 7.5 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 167.96 (**C**OOEt), 145.52 (Ar-C), 139.03 (Ar-C), 132.28 (Ar-C), 128.87 (Ar-C), 128.44 (Olefinic C), 127.31 (Olefinic C), 126.19 (SP^2-**C**-NH-), 101.85 (SP^2-**C**-COOEt), 60.17 (-O-CH_2-), 37.00 (CH), 20.21 (-CH_3), 14.42 (-CH_2-**CH_3**); HRMS (ESI): m/z $[M+H]^+$ calcd. for$C_{21}H_{25}NO_4$, 355.1784, found, 356.2012.

5 Conclusion

Utilizing a newly prepared organocatalyst DBUHI3, we have successfully accomplished a one-pot multi component synthesis of dihydropyridine molecules. This method offers numerous advantages over traditional approaches, including easy workup, the broad scope of the substrate, short reaction time, high yield, and the use of environmentally friendly catalyst.

Acknowledgement

Dr. RV is thankful to Dr. Ch. V. Rajasekhar, Scrips Pharma, Hyderabad, for his continued support and encouragement.

Author Contributions

RG: Execution of work; PK: Supervision; RV: Writing the manuscript and final draft.

Availability of Data and Materials

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information files. Should any raw data files be needed in another format they are available from the corresponding author upon reasonable request. Source data are provided with this paper.

Conflicts of Interest

The authors declare that they do not have any conflict of interest.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/Journal/organiccommunications.

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References

[1] Kabir, E. & Uzzaman, M. (2022). A review on biological and medicinal impact of heterocyclic compounds. *Results in Chemistry*, *4*, 100606. DOI: 10.1016/j.rechem.2022.100606.

[2] Taylor, A. P., Robinson, R. P., Fobian, Y. M., Blakemore, D. C., Jones, L. H. & Fadeyi, O. (2016). Modern advances in heterocyclic chemistry in drug discovery. *Organic & Biomolecular Chemistry*, *14*, 6611–6637. DOI: 10.1039/C6OB00936K.

[3] Karthikeyan, S., Grishina, M., Kandasamy, S., Mangaiyarkarasi, R., Ramamoorthi, A., Chinnathambi, S. & Kennedy, L. J. (2023). Medicinally important heterocyclic compounds and the biophysical approach to mechanism in biological environments. *Journal of Biomolecular Structure and Dynamics*, *41*(23), 14599–14619. DOI: 10.1080/07391102.2023.2187640.

[4] Qadir, T., Amin, A., Sharma, P. K., Jeelani, I. & Abe, H. (2022). Medicinally important heterocyclic compounds: A review. *The Open Medicinal Chemistry Journal*, *16*(1), e187410452202280. DOI: 10.2174/18741045-v16-e2202280.

[5] Varala, R. (2016). *Scope of Selective Heterocycles from Organic and Pharmaceutical Perspective*. Rijeka: InTechOpen. DOI: 10.5772/60890.

[6] Aatif, M., Raza, M. A., Javed, K., Nashre-ul-Islam, S. M., Farhan, M. & Alam, M. W. (2022). Potential nitrogen-based heterocyclic compounds for treating infectious diseases: A literature review. *Antibiotics*, *11*(12), 1750. DOI: 10.3390/antibiotics11121750.

[7] Kerru, N., Gummidi, L., Maddila, S., Gangu, K. K. & Jonnalagadda, S. B. (2020). Recent advances in nitrogen-containing molecules and their biological applications. *Molecules*, *25*, 1909. DOI: 10.3390/molecules25081909.

[8] Luo, W., Liu, Y., Qin, H., Zhao, Z., Wang, S., He, W., Tang, S. & Peng, J. (2024). Nitrogen-containing heterocyclic drug products approved by the FDA in 2023: Synthesis and biological activity. *European Journal of Medicinal Chemistry*, *279*, 116838. DOI: 10.1016/j.ejmech.2024.117087.

[9] Amin, A., Qadir, T., Sharma, P. K., Jeelani, I. & Abe, H. (2022). Medicinal and industrial applications of N-containing heterocycles: A review. *The Open Medicinal Chemistry Journal*, *16*(1), e187410452209010. DOI: 10.2174/18741045-v16-e2209010.

[10] Strecker, A. (1850). Ueber die künstlicheBildung der Milchsäure und einen neuen, demGlycocoll homologen Körper. *Liebigs Annalen Der Chemie*, *75*(1), 27–45. DOI: 10.1002/jlac.18500750103.

[11] Zarganes-Tzitzikas, T., Ajay, L. C. & Alexander, D. (2015). Multicomponent reactions, union of MCRs and beyond. *Chemical Record*, *15*(5), 981–996. DOI: 10.1002/tcr.201500201.

[12] Zarganes-Tzitzikas, T. & Dömling, A. (2014). Modern multicomponent reactions for better drug syntheses. *Organic Chemistry Frontiers*, *1*(7), 834–837. DOI: 10.1039/C4QO00088A.

[13] Cores, Á., Clerigué, J., Orocio-Rodríguez, E. & Menéndez, J. C. (2022). Multicomponent reactions for the synthesis of active pharmaceutical ingredients. *Pharmaceuticals*, *15*(8), 1009. DOI: 10.3390/ph15081009.

[14] Younus, H. A., Al-Rashida, M., Hameed, A., Uroos, M., Salar, U., Rana, S. & Khan, K. M. (2021). Multicomponent reactions in medicinal chemistry: A patent review (2010–2020). *Expert Opinion on Therapeutic Patents*, *31*(3), 267–289. DOI: 10.1080/13543776.2021.1858797.

[15] Graziano, G., Stefanachi, A., Contino, M., Prieto-Díaz, R., Ligresti, A., Kumar, P., Scilimati, A., Sotelo, E. & Leonetti, F. (2023). Multicomponent reaction-assisted drug discovery: A green approach for anticancer agents. *International Journal of Molecular Sciences*, *24*(7), 6581. DOI: 10.3390/ijms24076581.

[16] Graebin, C. S., Ribeiro, F. V., Rogério, K. R. & Kümmerle, A. E. (2019). Multicomponent reactions for the synthesis of bioactive compounds: A review. *Current Organic Synthesis*, *16*(6), 855–899. DOI: 10.2174/1570179416666190718153703.

[17] John, S. E., Shivani, G. & Nagula, S. (2021). Recent advances in multi-component reactions and their mechanistic insights: A triennium review. *Organic Chemistry Frontiers*, *8*, 4237–4287. DOI: 10.1039/D0QO01480J.

[18] Godsi, M. Z., Moradi, R. & Mahammadkhani, L. (2019). Application of multicomponent reactions in the total synthesis of natural peptides. *Arkivoc*, part i, 18–40. DOI: 10.24820/ark.5550190.p010.779.

[19] Müller, T. J. J. (2017). Multicomponent reactions in the synthesis of heterocycles. *Chemistry of Heterocyclic Compounds*, *53*(4), 381–400. DOI: 10.1007/s10593-017-2064-2.

[20] Hantzsch, A. (1882). Ueber die synthese pyridinartiger verbindungen aus acetessigäther und aldehydammoniak. *European Journal of Organic Chemistry*, *215*(1), 1–82. DOI: 10.1002/jlac.18822150102.

[21] Anaikutti, P. & Makam, P. (2020). Dual active 1,4-dihydropyridine derivatives: Design, green synthesis and *in vitro* anti-cancer and anti-oxidant studies. *Bioorganic Chemistry*, *105*(7), 104379. DOI: 10.1016/j.bioorg.2020.104379.

[22] de Fátima Silva Lago, A., de Benedicto, D. F. C., da Silva, L. & Thomasi, S. s. (2023). 1,4-Dihydropyridine derivatives: An overview of synthesis conditions and biological tests. *Current Organic Chemistry*, *27*(18), 1567–1610. DOI: 10.2174/0113852728264228231013074432.

[23] Jindal, D., Sohal, H. S. & Malhi, D. S. (2022). A review on 1,4-dihydropyridines as anti-tuberculosis agent. *Materials Today: Proceedings*, *68*(4), 950–955. DOI: 10.1016/j.matpr.2022.07.325.

[24] Parthiban, A., Makam, P. (2022). 1,4-Dihydropyridine: Synthetic advances, medicinal and insecticidal properties. *RSC Advances*, *12*(45), 29253–29290. DOI: 10.1039/D2RA04589C.

[25] De Luca, M., Ioele, G. & Ragno, G. (2019). 1,4-Dihydropyridine antihypertensive drugs: Recent advances in photostabilization strategies. *Pharmaceutics*, *11*(2), 85. DOI: 10.3390/pharmaceutics11020085.

[26] Khedkar, S. A. & Auti, P. B. (2014). 1,4-Dihydropyridines: A class of pharmacologically important molecules. *Mini Reviews in Medicinal Chemistry*, *14*(3), 282–290. DOI: 10.2174/1389557513666131119204126.

[27] Sri, C. D., Beeraka, N. M., Ramachandrappa, H. V. P., Bidye, D. P., Prashantha Kumar, B. R., Nikolenko, V. N. & Bannimath, G. (2025). Updates on intrinsic medicinal chemistry of 1,4-dihydropyridines, perspectives on synthesis and pharmacokinetics of novel 1,4-dihydropyrimidines as calcium channel blockers: Clinical pharmacology. *Current Topics in Medicinal Chemistry*, *25*(11), 1351–1376. DOI: 10.2174/0115680266323908241114064318.

[28] Soni, A., Sharma, M. & Singh, R. K. (2025). A decade of catalytic progress in 1,4-dihydropyridines (1,4-DHPs) synthesis (2016–2024). *Current Organic Synthesis*, *22*(6), 703–720. DOI: 10.2174/0115701794374153250307065611.

[29] Rahimi, J., Niksefat, M., Heidari, M., Naderi, M., Abbasi, H., Ijdani, M. T. & Maleki, A. (2022). Ammonium metavanadate (NH_4VO_3): A highly efficient and eco-friendly catalyst for one-pot synthesis of pyridines and 1,4-dihydropyridines. *Scientific Reports*, *12*(1), 13687. DOI: 10.1038/s41598-022-17378-7.

[30] Avudaiappan, G., Unnikrishnan, V. & Sreekumar, K. (2020). Convenient synthesis of dihydropyridine and dihydropyrimidinethione derivatives using a porphyrin cored G1 PAMAM dendrimer as a homogeneous catalyst. *ChemistrySelect*, *5*, 506–514. DOI: 10.1002/slct.201903597.

[31] Sohal, H. S. (2022). A review on recent trends in synthesis and applications of 1,4-dihydropyridines. *Materials Today: Proceedings*, *48*(5), 1163–1170. DOI: 10.1016/j.matpr.2021.08.209.

[32] Koduri, R. G., Pagadala, R., Varala, R. & Boodida, S. (2021). An effective process for the synthesis of dihydropyridines via SO_4^{-2}/SnO_2-catalyzed Hantzsch reaction. *Journal of the Chinese Chemical Society*, *68*(2), 333–337. DOI: 10.1002/jccs.202000264.

[33] Mishra, A. P., Bajpai, A. & Rai, A. K. (2019). 1,4-Dihydropyridine: A dependable heterocyclic ring with the promising and the most anticipable therapeutic effects. *Mini Reviews in Medicinal Chemistry*, *19*(15), 1219–1254. DOI: 10.2174/1389557519666190425184749.

[34] Sharma, V. K., Singh, S. K. (2017). Synthesis, utility and medicinal importance of 1,2- & 1,4-dihydropyridines. *RSC Advances*, *7*, 2682–2732. DOI: 10.1039/C6RA24823C.

[35] Rucins, M., Plotniece, A., Bernotiene, E., Tsai, W.-B. & Sobolev, A. (2020). Recent approaches to chiral 1,4-dihydropyridines and their fused analogues. *Catalysts*, *10*(9), 1019. DOI: 10.3390/catal10091019.

[36] Mathur, R., Negi, K. S., Shrivastava, R. & Nair, R. (2021). Recent developments in the nanomaterial-catalyzed green synthesis of structurally diverse 1,4-dihydropyridines. *RSC Advances*, *11*, 1376–1393. DOI: 10.1039/D0RA07807G.

[37] Gawade, R., Jadhav, P., Shinde, S. & Kulkarni, P. S. (2022). $DBUHI_3$-catalyzed synthesis of arylidenepyrazoles. *Heterocyclic Letters*, *12*(4), 767–773.

[38] Gawade, R. & Kulkarni, P. S. (2023). $DBUHI_3$ complex as an efficient catalyst for 2-phenylbenzimidazole and benzothiazole derivatives. *Journal of the Serbian Chemical Society*, *88*(10), 959–974. DOI: 10.2298/JSC220526007G.

[39] Gawade, R., Varala, R. & Kulkarni, P. (2025). $DBUHI_3$-catalyzed efficient synthesis 2,4,5-triaryl substituted imidazoles. *Current Chemistry Letters*, *14*(4), 843–850. DOI: 10.5267/j.ccl.2025.7.004.