CHAPTER 5

Montmorillonite K-10 Catalyzed Synthesis of Hantzsch Dihydropyridine Derivatives from Methyl Arenes via *in situ* Generated Ammonia under Microwave Irradiation in Neat Conditions

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5.1 Introduction

Heterocyclic compounds with six members are integral in organic chemistry [1]. Among the *N*-heterocyclic molecules, the 1,4-dihydropyridine (1,4-DHP) skeleton and its derivatives have gained additional significance due to various pharmacological activities [2, 3]. The 1,4-Dihydropyridine core structure finds extensive use in various biological and therapeutic realms, including as inhibitors of cyclooxygenase-2 and α-glucosidase, as well as agents with anti-tumor, anti-anginal, anti-hypertensive, anti-diabetic, and anti-microbial properties. It also exhibits anti-inflammatory and myorelaxant activities in the gastric fundus [4]. The 1,4-DHP nucleus is a constituent of various drugs like Nifedipine, Nicardipine, Levamoldipine, Isradipine, and Amlodipine [5, 6] (**Figure 5.1**). Amlodipine drug, known as calcium channel blockers, is employed in managing hypertension. Additionally [7], it serves as an active intermediate in significant organic transformations.

Currently, green chemistry principles present significant opportunities for enhancing the synthesis of biologically and pharmacologically active heterocyclic frameworks through multicomponent reactions (MCRs) [8, 9].

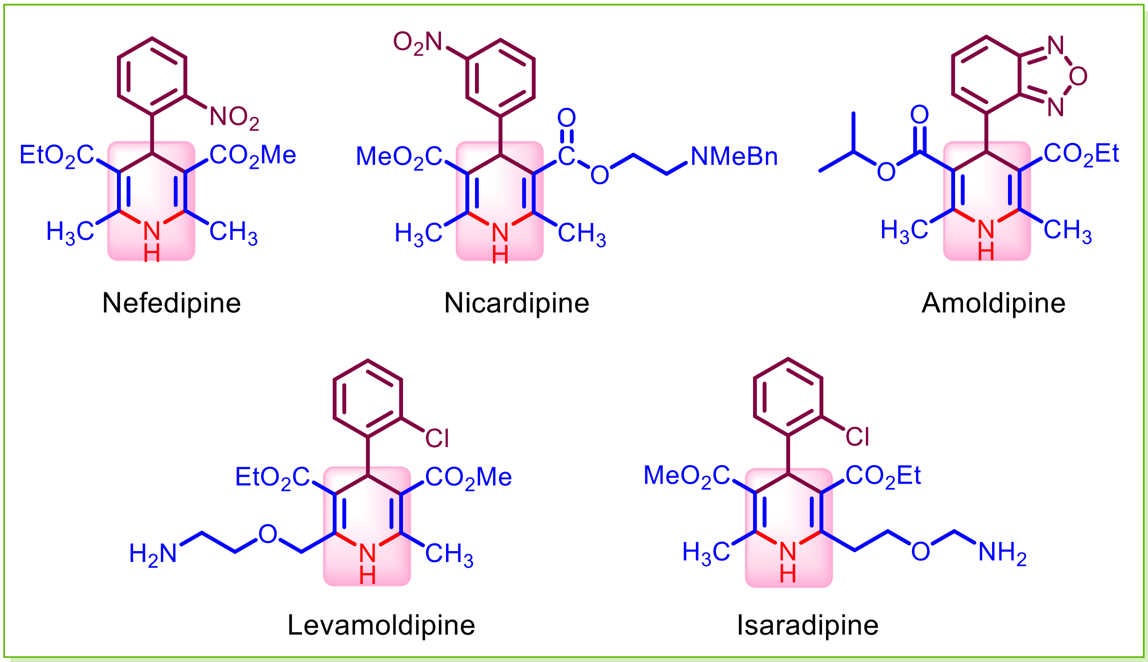


Figure 5.1 Biologically active 1,4-dihydropyridines as a key functional moiety.

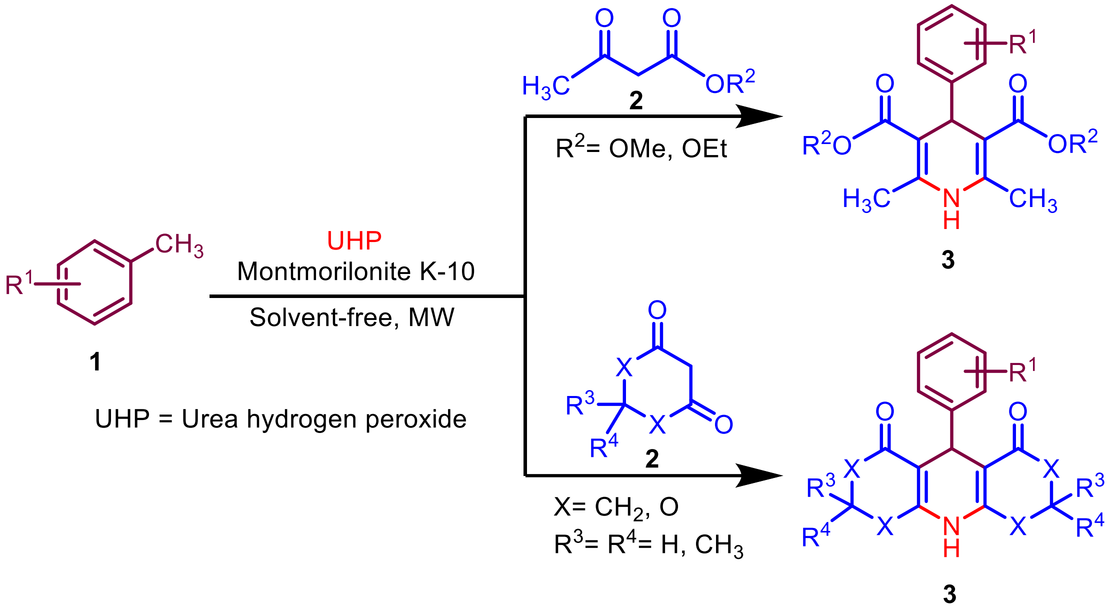
Multi-component reactions are particularly advantageous as they generally afford good yields and offer rapid access to a wide range of heterocyclic frameworks for their diverse applications [10]. In this context, the advancement of solvent-free conditions for one-pot multicomponent coupling reactions has garnered significant attention. The solvent-free multi-component reaction technique is an environmentally conscious approach, which opens several possibilities for conducting quick organic synthesis, functional group conversions, and also either reduction or elimination of solvents thereby preventing pollution in organic synthesis [11–13]. Traditionally, the synthesis of 1, 4-dihydropyridine (1, 4-DHP) and its derivatives typically involved the conventional Hantzsch reaction [14].

This process encompasses a one-pot multicomponent synthesis, where two molecules of β-ketoester, an aldehyde, and an N-donor ligand (such as ammonia, ammonium salts, or derivatives of ammonia) undergo cyclo-condensation in EtOH under refluxing conditions [15].

Due to the significant importance of the 1,4-dihydropyridine motif, a wide array of catalysts including homogeneous, heterogeneous, and diverse nanomaterials are utilized in its synthesis via the MCR such as 2-hydroxyethyl ammonium acetate [16], Cd metal-organic framework [17], cerium (IV) ammonium nitrate [18], scandium triflates [19], *p*-TSA [20], sulfamic acid [21], Fe_3O_4/KCC- 1/BPAT [22], NiO/ZrO_2 as a recyclable catalyst [23], magnetic Fe_3O_4 as an efficient heterogeneous [24], V_2O_5/ ZrO_2 [25], USY-zeolite, [26], and Fe_3O_4@SiO_2 molecular sieves supported iron catalyst [27], Ni–Zn–Fe LDH mesoporous silica [28], Fe_3O_4@SiO_2 nanoparticles [29], and the use of citric acid as an organo-catalyst [30].

Despite several advantages of these reported methods, there are some limitations such as harsh reaction conditions, non-ecofriendly solvents, high reaction temperature, longer reaction times and low to moderate yields. Therefore, the development of simple, efficient, and environmentally friendly methods is still in demand for the synthesis of 1,4 DHPs containing molecules. The current research focused on employing eco-friendly and environmentally conscious chemical methods for the synthesis of Hantzsch 1,4-dihydropyridines, utilizing methyl arenes as a sustainable alternative to acyl precursors [31, 32]. Urea hydrogen peroxide (UHP) is a solid oxidizing agent, and it offers a significant benefit in oxidation processes by generating non-toxic commercial urea as a byproduct [33, 34]. Montmorillonite K-10 (MK-10) as an efficient, versatile, solid, inexpensive, non-toxic, and odourless organo-heterogeneous catalyst [35]. MK-10 has been documented as a catalyst for conducting a variety of chemical conversions [36–38]. The use of MK-10 as heterogeneous catalysts is preferred over homogeneous catalysts due to the easy isolation and disposal off from the reaction mixture. In green chemistry, using environmentally benign reaction conditions and safe chemicals is essential for synthesizing important organic compounds.

The employment of microwave (MW) technology primarily aligns with environmentally friendly green methods [39, 40], and MW in solvent-free reactions has emerged as a vital aspect of synthetic organic chemistry [41–43]. Moreover, microwave techniques have gained significant attention in organic synthesis due to their ability to accelerate chemical reactions, enhance selectivity, improve product yields, and promote atom economy, thereby minimizing by-product generation compared to conventional heating methods [44, 45]. In continuation of our affords in developing greener approaches towards the synthesis of biologically relevant molecules herein, we disclose a novel and efficient MK-10 catalyzed synthesis of 1,4-dihydropyridine derivatives from methyl arenes *via in situ* generated ammonia in neat conditions under microwave irradiation (**Scheme 5.1**). This method provides a straightforward experimental setup with swift reaction times, excellent yields and distinctive selectivity, the use of a reusable heterogeneous acid catalyst and a filtration-only work-up. To, the best of our knowledge, there is no report available for the synthesis of 1, 4-dihydropyridines using methyl arenes as a sustainable surrogate of aldehyde precursor and UHP as an oxidant as well as a source of ammonia.



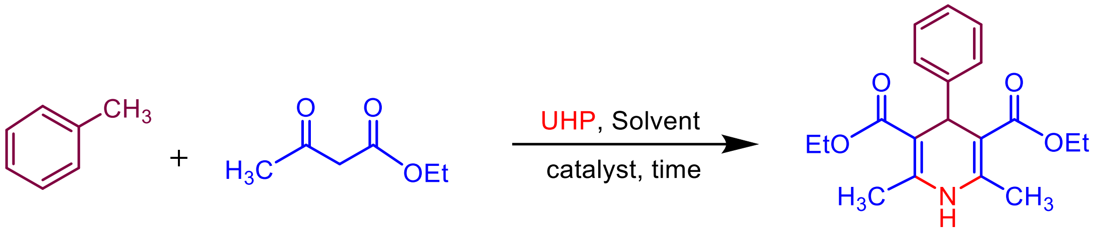
Scheme 5.1 Synthesis of 1,4-dihydropyridines.

5.2 Results and discussion

5.2.1 Optimsation of reaction conditions

In our initial trial, for the optimization of reaction conditions, toluene **1a** (1.0 mmol), ethyl acetoacetate **2a** (3.0 mmol) and UHP (2.0 mmol) were selected as starting materials and using MK-10 (10 mg) as catalyst under microwave irradiation to synthesize specifically the of model compound **3a.** The model reaction was subjected to various parameters at a randomly fixed temperature of 50 °C. The outcomes of the screening studies are presented in **Table 5.1**.

Table 5.1 Screening of different parameters for the synthesis of dihydropyridine **3a**[a]



1a **2a** **3a**

Entry	Solvent	UHP (mmol)	MK10 (mg)	Microwave power (W)	Temp. (°C)	Time (min)	yield (%)b
1	Water	2	10	200	50	60	40
2	Ethanol	2	10	200	50	60	45
3	Methanol	2	10	200	50	60	40
4	DMF	2	10	200	50	60	50
5	1,4-dioxane	2	10	200	50	60	38
6	-	2	10	200	50	30	60
7	-	2	10	250	50	30	68
8	-	2	10	300	50	30	75
9	-	2	10	350	50	30	75
10	-	2	10	300	60	20	80
11	-	2	10	300	80	20	80
12	-	3	10	300	60	15	85
13	-	4	10	300	60	15	90
14	-	5	10	300	60	15	90
15		4	15	300	60	15	92
16	**-**	**4**	**20**	**300**	**60**	**15**	**95**

17	-	4	30	300	60	15	95
18		4	-	300	60	15	NR

[a] **Reaction conditions**: Toluene **1a** (1.0 mmol), methyl acetoacetate **2a** (3.0 mmol) and UHP with MK-10 as a catalyst in solvent (2ml) under microwave-irradiation. [b] Isolated yield.

The polar protic solvents namely water, ethanol, and methanol gave 40-45% yield of the desired product **3a** at 200 W in 60 min, while the polar aprotic solvents such as DMF, 1,4 dioxane gave 38-50% yields in 60 min. To improve the greener context of the synthesis, the reaction was performed under solvent-free conditions surprisingly, it gave a 60 % yield in 30 min (**Entry 6, Table 5.1**). Next, we have optimised the microwave power by increasing the microwave power from 200 MW to 350 MW. The maximum yield 75 % of the product **3a** was obtained at 300 MW power in 20 min. Further increase in microwave power no significant change in the yield was observed. Subsequently, the influence of temperature on the desired product 3a was examined at different temperature ranges of 60-80 ^{o}C **(Entry 10, 11, Table 5.1)**. The temperature rise had a direct effect on the product yield, with 80% yield achieved at 60°C within 15 minutes. However, further elevation of the temperature did not lead to an enhancement in the yield. The variation in catalyst loading, ranging from 10 to 30 mg, resulted in a notable increase in yield, indicating that 20 mg of catalyst was adequate to achieve the maximum yield (85%). Subsequently, in the ongoing optimization of solvent, temperature, and catalyst loading, the quantity of UHP was investigated. By increasing the amount of UHP from 2 to 5 mmol, a 95% yield of the desired product **3a** was obtained with 4 mmol of UHP within 15 minutes.

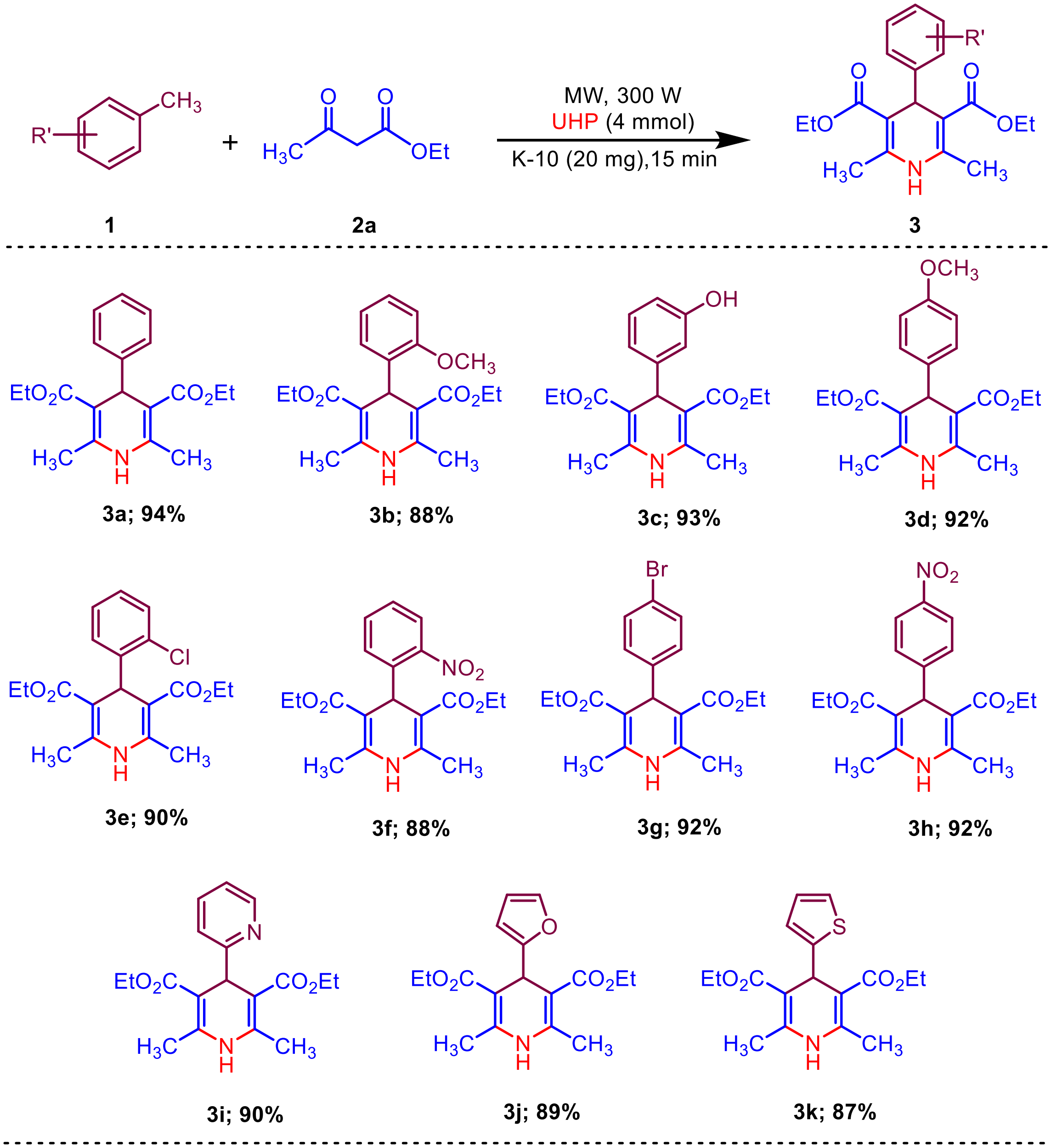
5.2.2. Substrate Scope

Afterwards, to broaden the range of substrates, a variety of methyl arenes such as toluene (**1a**), 1-methoxy-2-methylbenzene (**1b**), m-cresol (**1c**), 1-methoxy-4-methylbenzene (**1d**), 1-chloro-2-methylbenzene (**1e**), 1-methyl-2-nitrobenzene (**1f**), 1-bromo-4-methylbenzene (**1g**) , 1-methyl-4-nitrobenzene (**1h**), 2-methylpyridine (**1i**), 2-methylfuran (**1j**), 2-methylthiophene (**1k**), o-cresol (**1l**), 1-bromo-2-methylbenzene (**1m**), 1-chloro-4-methylbenzene (**1n**), 1-chloro-3-methylbenzene (**1o**), 1-fluoro-4-methylbenzene (**1p**), 2-methoxy-6-methylphenol (**1q**), 1-methylnaphthalene (**1r**) were treated with acyclic active methylene compounds (e.g. ethyl acetoacetate, methyl acetoacetate) and cyclic active methylene compounds (e.g. 1,3 cyclohexanedione, dimedone and meldrum acid) with UHP and catalytic amount MK-10 for the synthesis of dihydropyridines under the obtained optimal condition (**Table 5.1**).

Toluene and various substituted methyl arenes, incorporating electron-donating or electron-withdrawing groups at ortho, para and meta, positions, were subjected to the reaction conditions. This yielded the desired product *viz* diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**3a**), diethyl 4-(2-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3b**), diethyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3c**), diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-

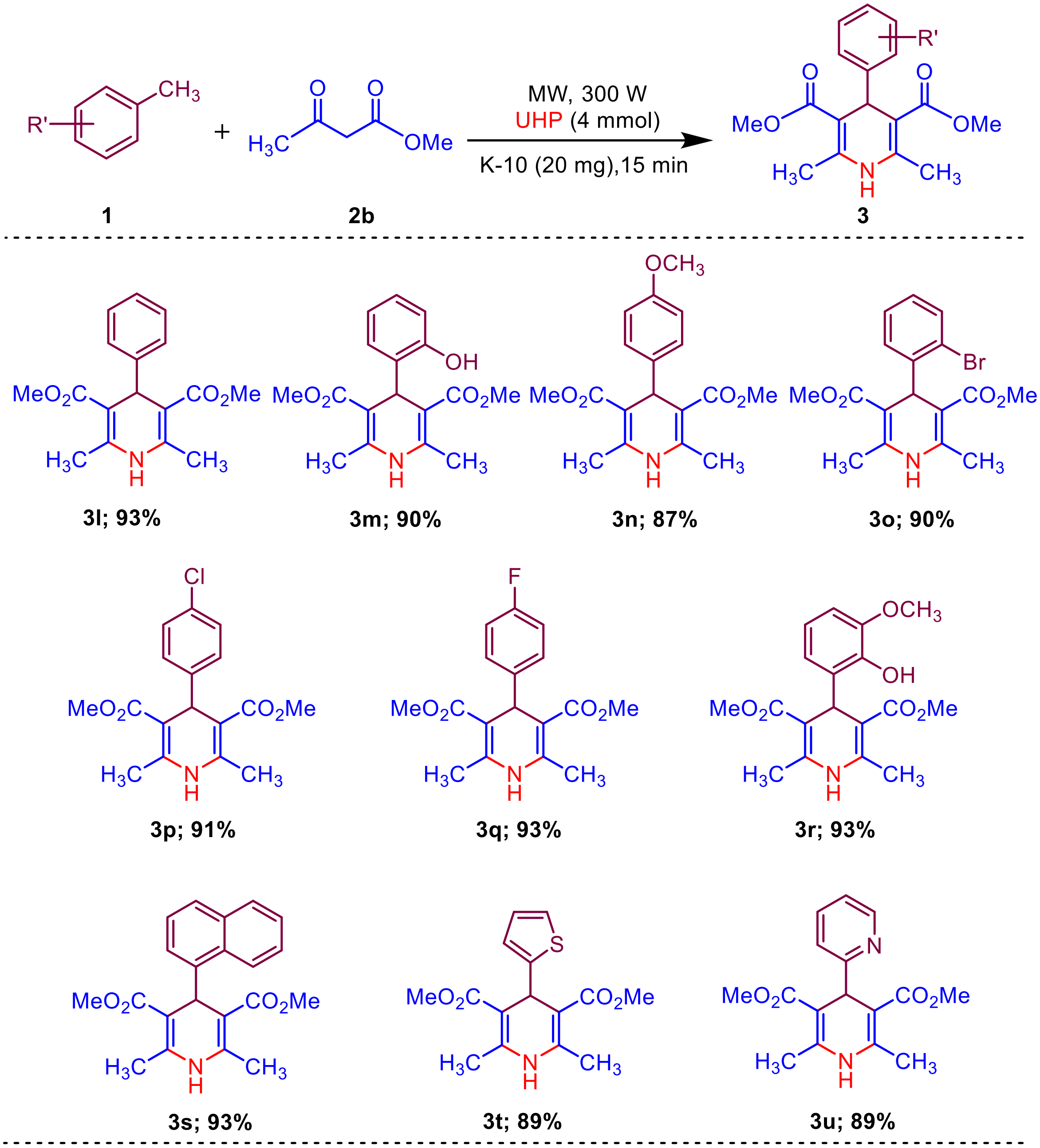
dihydropyridine-3,5-dicarboxylate (**3d**), diethyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3e**), diethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3f**), diethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3g**), diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3h**), diethyl 2',6'-dimethyl-1',4'-dihydro-[2,4'-bipyridine]-3',5'-dicarboxylate (**3i**), diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3j**), diethyl 2,6-dimethyl-4-(thiophen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (**3k**), dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**3l**), dimethyl 4-(2-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3m**), dimethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3n**), dimethyl 4-(2-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3o**), dimethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3p**), dimethyl 4-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3q**), dimethyl 4-(2-hydroxy-3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3r**), dimethyl 2,6-dimethyl-4-(naphthalen-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate (**3s**), dimethyl 2,6-dimethyl-4-(thiophen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (**3t**), dimethyl 2',6'-dimethyl-1',4'-dihydro-[2,4'-bipyridine]-3',5'-dicarboxylate (**3u**), 9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**3v**), 9-(4-methoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**3w**), 9-(3-chlorophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**3x**), 9-(4-bromophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**3y**), 3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**3z**), 9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**3aa**), 9-(3-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**3ab**), 3,3,6,6-tetramethyl-9-(pyridin-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**3ac**), 2,2,8,8-tetramethyl-5-phenyl-5,10-dihydro-4H,6H-bis([1,3]dioxino)[4,5-b:5',4'-e]pyridine-4,6-dione (**3ad**), 5-(4-methoxyphenyl)-2,2,8,8-tetramethyl-5,10-dihydro-4H,6H-bis([1,3]dioxino)[4,5-b:5',4' e]pyridine-4,6-dione (**3ae**), 2,2,8,8-tetramethyl-5-(4-nitrophenyl)-5,10-dihydro-4H,6H-bis([1,3]dioxino)[4,5-b:5',4'-e]pyridine-4,6-dione (**3af**), 5-(4-bromophenyl)-2,2,8,8-tetramethyl-5,10-dihydro-4H,6H-bis([1,3]dioxino)[4,5-b:5',4'-e]pyridine-4,6-dione (**3ag**) in high to excellent yields under optimized reaction conditions. Heterocyclic methyl arenes have also adopted this transformation, which proceeded well and the cyclocondensation products were obtained with good yields (**Scheme 5.2-5.4**).

Scheme 5.2 Substrate scope of MK-10 catalysed synthesis of 1,4-dihydropyridines from acyclic ethyl b- ketoester under microwave irradiation **(3a-k)**[a]



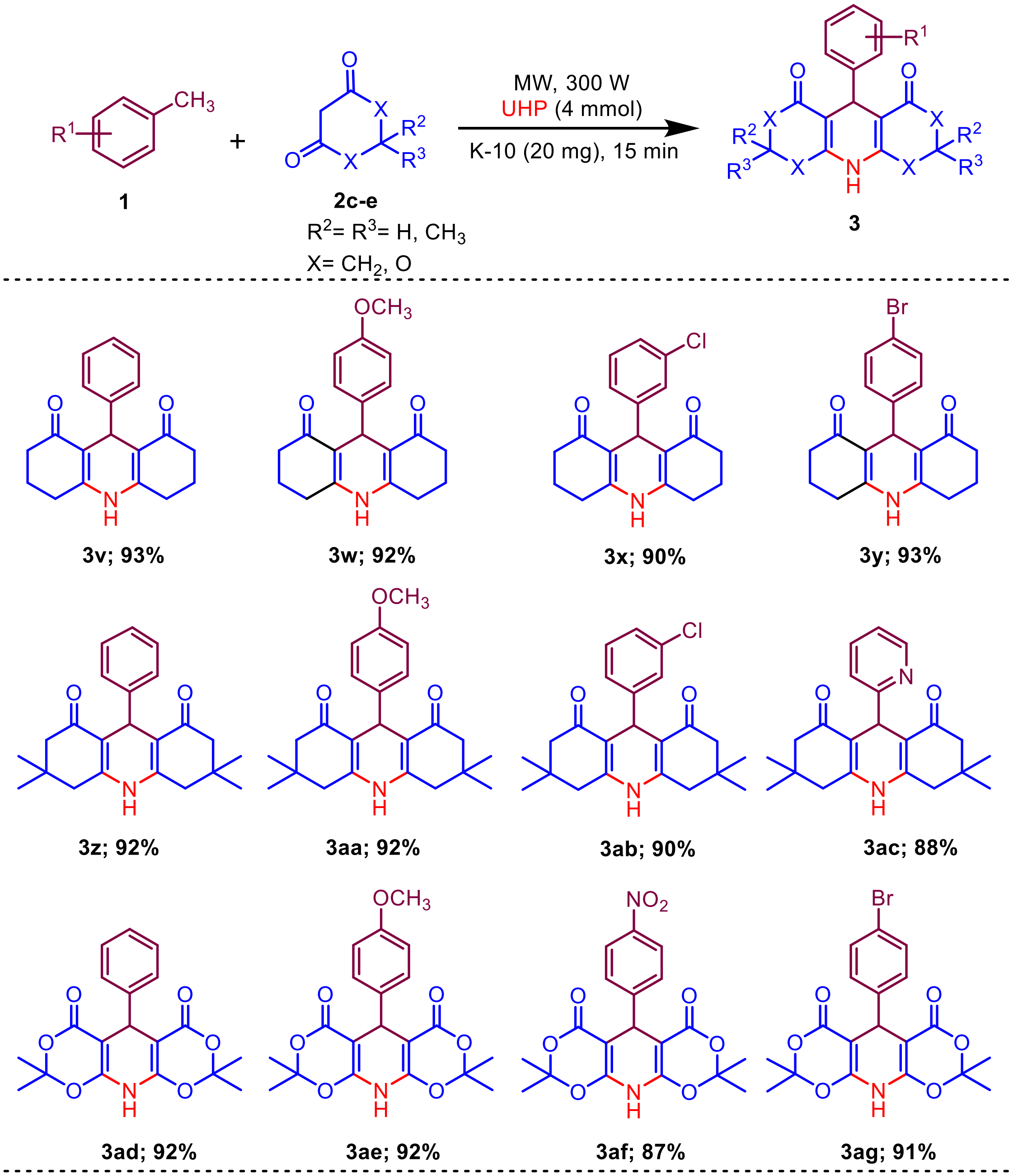
[a]**Reaction conditions**: Methyl arenes (1.0 mmol), ethyl acetoacetate (3.0 mmol) and UHP (4.0 mmol) with MK-10 (20 mg) in solvent-free condition under MW irradiation.

Scheme 5.3 Substrate scope of MK-10 catalysed synthesis of 1,4-dihydropyridines from acyclic methyl β- ketoester under Microwave irradiation **(3l-u)**[a]



[a] **Reaction conditions**: Methyl arenes (1.0 mmol), methyl acetoacetate (3.0 mmol) and UHP (4.0 mmol) with MK-10 (20 mg) in solvent-free condition under MW irradiation.

Scheme 5.4 Substrate scope of MK-10 catalysed synthesis of 1,4-dihydropyridines from cyclic active methylene compounds under microwave irradiation **(3v-ag)**[a]



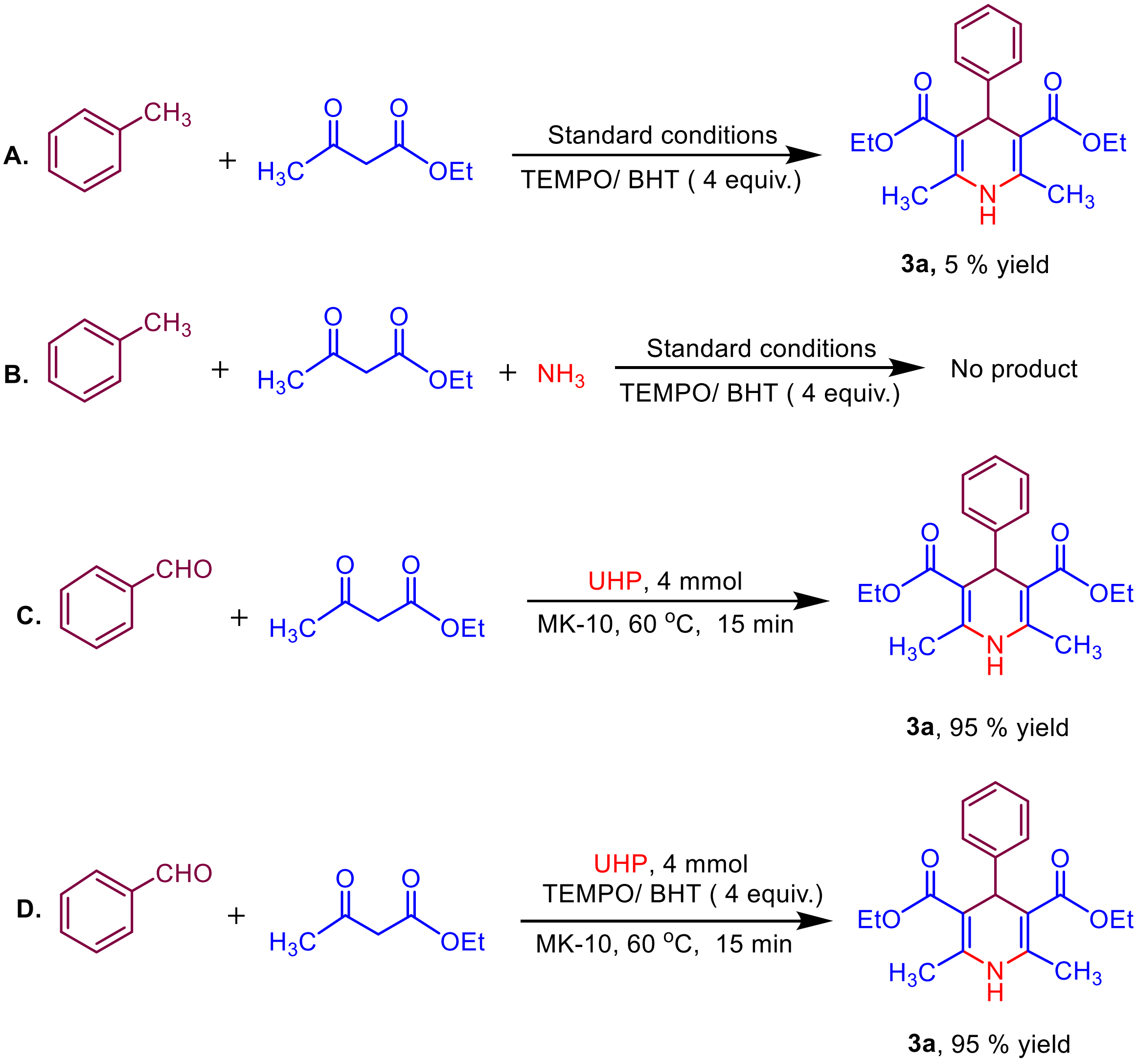
[a]**Reaction conditions**: Methyl arenes (1.0 mmol), cyclic active methylene compounds (3.0 mmol) and UHP (4.0 mmol) with MK-10 (20 mg) in solvent-free condition.

5.3 Mechanistic studies

5.3.1 Control experiments

To elucidate the likely reaction mechanism, few controlled experiments were performed under optimized reaction conditions, as shown in (**Scheme 5.5**). In this study, conducting the reaction in the presence of radical scavengers BHT (butylated hydroxytoluene) (4 equiv) and TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxy and (**Scheme 5.5, A**) resulted in less than 5% yield o df the product **3a**. This suggests that the formation of 1,4-dihydropyridine likely proceeds through a radical mechanistic pathway. Subsequently, the control reaction proceeded with toluene, ethyl acetoacetate, and urea in the absence of UHP, resulting in failure to yield the desired product. This outcome suggests that toluene cannot undergo oxidation to benzaldehyde without the presence of UHP, highlighting the indispensability of UHP for the initial step (**Scheme 5.5, B**). Following this, the control reaction was conducted using benzaldehyde, ethyl acetoacetate, and UHP under optimized conditions, resulting in a highly successful reaction with a yield of 95% (**Scheme 5.5, C**). This suggests that the breakdown of UHP produced hydrogen peroxide (H_2O_2) and urea.

Afterwards, H_2O_2 serves as an oxidant that converts toluene into benzaldehyde. while the remaining urea served as a supplier of ammonia in the cyclocondensation reaction The aforementioned findings elucidated the dual function of UHP in both the oxidation of methyl arene to aldehyde and as a source of ammonia. Interestingly, when the experiment was repeated with radical scavengers such as BHT and TEMPO (**Scheme 5.5, D**), no notable alteration in the yield was observed.



Scheme 5.5 Control experiments in support of the mechanism

This suggests the formation of 1,4-tetrahydropyridines through a non-radical mechanistic pathway subsequent to the oxidation of methyl arenes. To identify the stages at which MK-10 functions as a catalyst, each synthesis step was scrutinized both with and without MK-

10. It was determined that MK-10 did not influence the initial oxidation of toluene to benzaldehyde in the presence of urea hydrogen peroxide. However, all subsequent steps were catalyzed by MK-10.

5.3.2 Reaction mechanism

On the basis of control experiments along with previously reported literature [5, 46], a plausible mechanism for the reaction is anticipated, as depicted in (**Figure 5.2**). The reaction is initiated by the oxidation of methyl arenes (1) with UHP that selectively aldehyde produces derivative intermediate (**I**) [47]. Montmorillonite K-10 serves as a potent solid acid catalyst, featuring both Lewis and Brønsted acid sites [35, 48]. The catalyst MK-10 polarised the carbonyl group of the aldehyde, which subsequently condenses with one molecule of active methylene compound (**2**) via Knoevenagel condensation reaction and form an intermediate (**II**). The ammonia which is generated during oxidation of toluene from UHP combines with the second molecule of active methylene compound and gives intermediate ester enamine (**III**). In the subsequent step, intermediate (II) and intermediate (III) combine through Michael's addition to generate intermediate (IV), which then undergoes intramolecular cyclization. This is followed by the elimination of a water molecule to yield the target molecule (**3**).

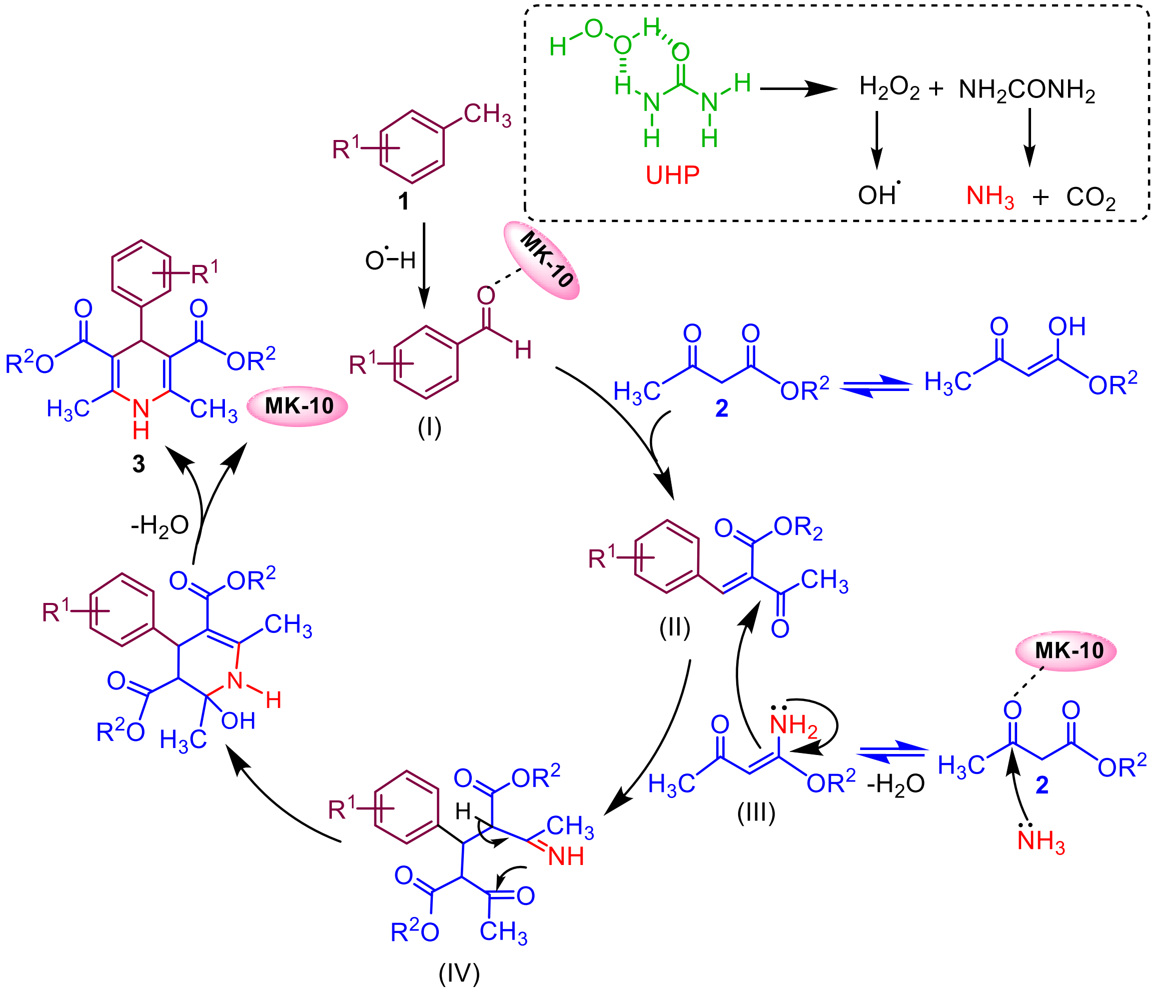
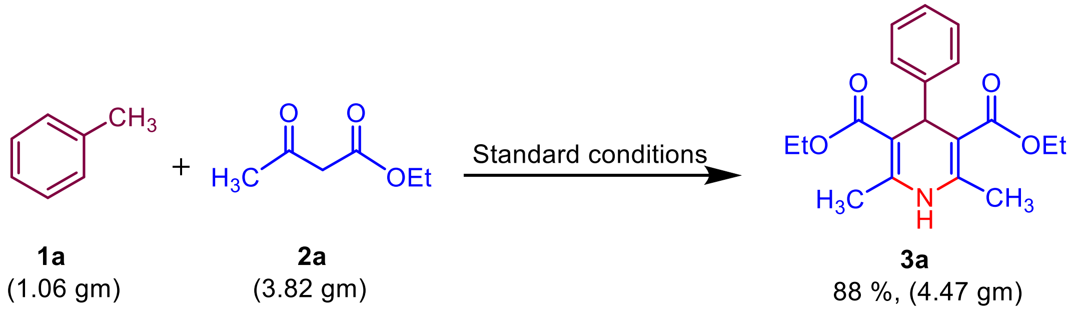


Figure 5.2 Proposed reaction mechanism.

5.4 Gram-scale synthesis of 1,4-dihydropyridine (3a)

To verify the potential synthetic use of the proven methodology for 1,4-dihydropyridine **3a**, we experimented at the gramme level (**Scheme 5.6**). Toluene **1a** (10.0 mmol, 1.06 g), ethyl acetoacetate **2a** (30.0 mmol, 3.82 g), UHP (40 mmol, 4.47 gm) and MK-10 (200 mg) were utilised in the process. The experiment proceeded at 300 W without solvent at 60 °C, with

TLC used to monitor progress. After the reaction was completed (15 min), the resulting mixture was allowed to cool to ambient temperature, diluted with the solvent ethyl acetate, and the catalyst was removed by filtration. The organic layer underwent drying over Na_2SO_4, followed by filtration and concentration under vacuum. The crude product was subsequently purified via recrystallization using ethanol as the solvent, yielding the pure product **3a** with 88 % yield.



Scheme 5.6 Gram-scale procedure for synthesis of 1,4-dihydropyridine **3a**

5.5 Catalyst recycling

The reusability the MK-10 catalyst was also investigated using the optimized reaction conditions for up to five cycles (**Figure 5.3**). After the completion of the reaction, the catalyst was separated by filtration and washed with ethyl acetate (3x5 mL) then it was dried at 100 °C for 10 h, shows that the clay can be recycled several times without any appreciable loss in activity and selectivity.

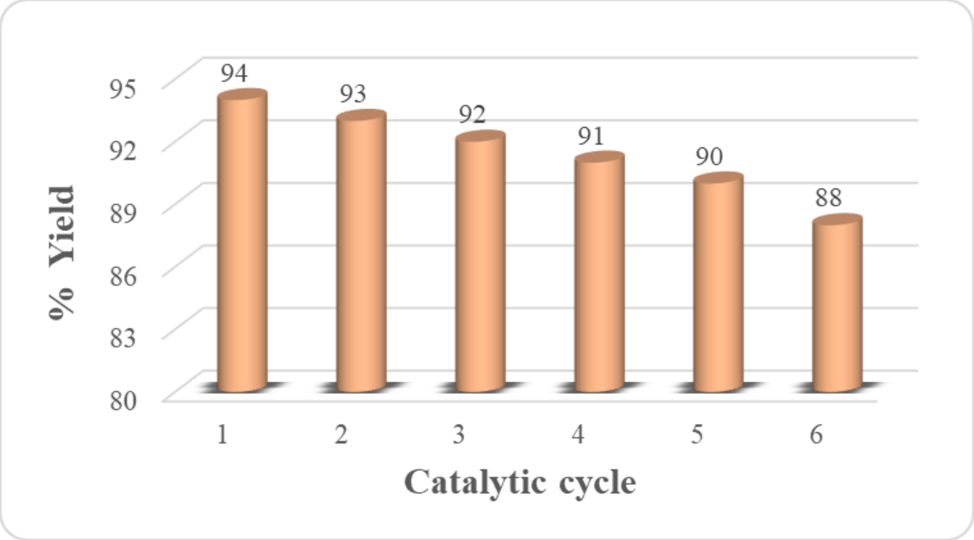


Figure 5.3 Reusability of MK-10 catalyst for the synthesis of 1,4-DHP derivative **3a.**

5.6 Experimental section

5.6.1 General procedure for the synthesis of 1,4-dihydropyridines

A mixture of appropriate methyl arene (1.0 mmol) active methylene compound (3.0 mmol) UHP (4 mmol) and MK-10 (20 mg) were placed in a 20-mL pressurised vials with ‘‘snap-on’’ cap and irradiated in the microwave using 300 W power at 60 °C for 15 min. The completion of the reaction was monitored with TLC, after completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate to dissolve the product and the catalyst was removed by filtration. The organic layer underwent washing with water, dried over Na_2SO_4 and subsequent concentrated under vacuum. The resulting crude product underwent further purification via recrystallization using ethanol to obtain the pure product **(3)**.

5.7 Analytical data for [3a-3ag]

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (3a) Light yellow solid; yield 94%; m.p. 155−157 °C; **^{1}H NMR** (500 MHz, DMSO-*d₆*): δ 8.91 (s, 1H), 7.47 (d, 2H), 7.32 (t, 3H), 4.61 (s, 1H), 4.23 (q, 4H), 2.25 (s, 6H), 1.40 (t, 6H) **^{13}C NMR** (126 MHz, DMSO-d_6): δ 169.9, 145.6, 140.7, 128.8, 128.4 127.6, 89.7, 61.1, 34.4, 16.2, 14,7; **HR-MS** (ESI) for $C_{19}H_{23}NO_4$ (m/z) $[M + H]^+$ calcd: 330.1627, found: 330.1645.

Diethyl 4-(2-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3b) Yellow solid; yield 88%; m.p. 150-153 °C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.94 (s, 1H, NH), 7.36 (d, 1H), 7.27 (t, 2H), 6.96 (d, 1H), 4.80 (s, 1H), 4.19 (q, 4H), 3.82 (s, 3H, OCH_3), 2.24 (s, 6H, CH_3), 1.32 (t, 6H); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 170.1, 156.2, 144.5, 133.9, 130.6, 129.3, 120.6, 111.3, 89.0, 61.4, 56.7, 28.6, 16.3, 14.6; **HR-MS** (ESI) for $C_{20}H_{25}NO_5$ (m/z) $[M + H]^+$ calcd: 360.1733, found: 360.1738.

Diethyl 4-(3-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3c) Yellow solid; yield 93%; m.p. 135-137 °C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.96 (s, 1H, NH), 7.17 (t, 1H), 7.09 (d, 1H), 6.84 (d, 1H), 4.58 (s, 1H), 4.24 (q, 4H), 3.65 (s, 1H), 2.27 (s, 6H, CH_3), 1.37 (t, 6H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 169.2, 150.2, 143.9, 140.2, 130.2, 120.4, 117.6, 116.0, 89.3, 35.7, 16.1, 14.7; **HR-MS** (ESI) for $C_{19}H_{23}NO_5$ (m/z) $[M + H]^+$ calcd : 346.1576, found: 346.1567.

Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3d) Yellow solid; yield 92 %; m.p. 165 °C; **^{1}H NMR** (500 MHz, DMSO- d_6): δ 8.89 (s, 1H, NH), 7.37 (d, 2H), 6.92 (d, 2H), 4.53 (s, 1H), 4.20 (q, 4H), 3.75 (s, 3H), 2.24 (s, 6H, CH_3), 1.38 (t, 6H, CH_3); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 170.1, 159.2, 144.9, 130.2, 129.5, 113.1, 117.6, 89.4, 61.5, 56.0, 34.7, 16.3, 14.4; **HR-MS** (ESI) for $C_{20}H_{25}NO_5$ (m/z) $[M + H]^+$ calcd: 360.1733, found: 360.1719

Diethyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3e) Yellow solid; yield 90%; m.p. 120-122 °C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.95 (s, 1H, NH), 7.67 (d, 1H), 7.32-7.27 (m, 2H), 7.13 (t, 1H), 4.67 (s, 1H), 4.29 (q, 4H), 3.80 (s, 3H), 2.31 (s, 6H, CH_3), 1.46 (t, 6H); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 171.7, 145.9, 138.6, 133.4, 131.3, 130.2, 126.4, 87.9, 61.5, 30.7, 16.3, 14.4; **HR-MS** (ESI) for $C_{19}H_{22}ClNO_4$ (m/z) $[M + H]^+$ calcd: 364.1237, found: 364.1223.

Diethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3f) Brown solid; yield 88%; m.p. 170 ^{o}C; **^{1}H NMR** (500 MHz, DMSO-d_6): 8.98 (s, 1H, NH), 8.07 (d, 1H), 7.58 (t, 1H), 7.47-7.52 (m, 2H), 4.69 (s, 1H), 4.33 (q, 4H), 2.37 (s, 6H, CH_3), 1.49 (t, 6H); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 172.4, 149.7, 144.6, 134.5, 131.2, 131.0, 130.7, 123.2, 88.3, 61.8, 30.7, 14.7; **HR-MS** (ESI) for $C_{19}H_{22}N_2O_6$ (m/z) $[M + H]^+$ calcd: 375.1478, found: 375.1491.

Diethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3g) Yellow solid; yield 92%; m.p. 164 -166 °C; **^{1}H NMR** (500 MHz, DMSO-*d*$_6$): *δ* 8.77 (s, 1H, NH), 7.44 (d, 2H), 7.32 (d, 2H), 4.63 (s, 1H), 4.30 (q, 4H), 2.32 (s, 6H), 1.42 (t, 6H); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$): δ 171.4, 143.7, 138.5, 131.9, 129.6, 127.6, 88.8, 61.3, 33.2, 16.7, 14.1 **HR-MS** (ESI) for $C_{19}H_{22}BrNO_4$ (m/z) $[M + H]^+$ calcd: 408.0732, found: 408.0735.

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3h) Brown solid; yield 92%; m.p. 116-118 °C; **^{1}H NMR** (500 MHz, DMSO-*d*$_6$): *δ* 8.87 (d, 2H), 8.70 (s, 1H, NH), 7.80 (d, 2H), 4.50 (s, 1H), 4.41 (q, 4H), 2.26 (s, 6H), 1.43 (t, 6H); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$): δ 174.6, 151.3, 148.5, 145.9, 129.0, 123.1, 90.3, 63.0, 34.8, 17.0, 14.6; **HR-MS** (ESI) for $C_{19}H_{22}N2O_6$ (m/z) $[M + H]^+$ calcd: 375.1478, found: 375.1469.

Diethyl 2',6'-dimethyl-1',4'-dihydro-[2,4'-bipyridine]-3',5'-dicarboxylate (3i) Brown solid; yield 90%; m.p.194 °C; **^{1}H NMR** (500 MHz, DMSO-*d*$_6$): δ 8.50 (d, 2H), 8.43 (s, 1H, NH), 7.90 (t, 1H), 7.20 (d, , 2H), 4.52 (s, 1H, CH), 4.28 (q, 4H), 2.29 (s, 6H, CH_3), 1.39 (t, 6H, CH_3); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$): δ 171.0, 157.2, 146.1, 144.2, 140.6, 129.5, 119.3, 94.5, 62.0, 35.3, 16.3, 14.7; **HR-MS** (ESI) for $C_{18}H_{22}N_2O_4$ (m/z) $[M + H]^+$ calcd: 331.1579, found: 331.1587

Diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3j) Yellow solid; yield 89%; m.p. 236-238 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.45 (s, 1H, NH), 7.31 (d, 1H), 6.20 (t, 1H), 5.62 (d, , 1H), 4.92 (s, 1H), 4.38 (q, 4H), 2.28 (s, 6H), 1.37 (t, 6H); **^{13}C NMR** (126 MHz, DMSO-*d$_6$*): δ 171.4, 154.2, 146.6, 140.5, 115.8, 110.9, 86.3, 61.5, 36.0, 16.1, 14.2; HR-MS (ESI) for $C_{17}H_{21}NO_5$ (m/z) $[M + H]^+$ calcd: 320.1420, found: 320.1425.

Diethyl 2,6-dimethyl-4-(thiophen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (3k) Light yellow; Yield 87%; m.p. 170-172 °C; **^{1}H NMR** (500 MHz, DMSO-*d$_6$*): δ 8.43 (s, 1H, NH), 7.28 (d, 1H), 6.19 (t, 1H), 5.62 (d, , 1H), 4.87 (s, 1H), 4.34 (q, 4H), 2.27 (s, 6H), 1.37 (t, 6H); **^{13}C NMR** (126 MHz, DMSO-*d$_6$*): δ 171.1, 154.0, 146.3, 140.4, 115.7, 110.8, 86.2, 61.4, 36.0, 16.0, 14.1; **HR-MS** (ESI) for $C_{17}H_{21}NO_4S$ (m/z) $[M + H]^+$ calcd: 336.1191, found: 336.1178.

Dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (3l) yellow solid; yield 93%; m.p. 188-190 °C; **^{1}H NMR** (500 MHz, DMSO-*d$_6$*): δ 8.72 (s, 1H), 7.39 (d, 2H), 7.32-7.25 (m, 3H), 4.67 (s, 1H), 3.85 (s, 6H), 2.24 (s, 6H) **^{13}C NMR** (126 MHz, DMSO-*d$_6$*): δ 170.2, 143.7, 140.5, 128.6, 128.3 127.9, 88.1, 52.1, 34.3, 16.3, 14,7; **HR-MS** (ESI) for $C_{17}H_{19}NO_4$ (m/z) $[M + H]^+$ calcd: 302.1314, found: 302.1325.

Dimethyl 4-(2-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5 dicarboxylate (3m) Yellow solid; yield 90%; m.p. 198-200 °C; **^{1}H NMR** (500 MHz, DMSO-*d$_6$*): δ 8.67 (s, 1H), 7.19 (d, 1H), 7.12 (t, 1H), 6.87 (t, 1H), 6.80 (d, 1H), 6.38 (s, 1H), 4.50 (s, 1H), 3.84 (s, 6H), 2.34 (s, 6H) **^{13}C NMR** (126 MHz, DMSO-*d$_6$*): δ 169.,8 151.7, 143.5, 130.3, 130.0 129.9, 119.8, 116.4, 86.1, 52.0, 27.9, 16.1; **HR-MS** (ESI) for $C_{17}H_{19}NO_5$ (m/z) $[M + H]^+$ calcd: 318.1263, found: 318.1254.

Dimethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3n) Yellow solid; yield 87%; m.p. 181-183 °C; **^{1}H NMR** (500 MHz, DMSO-*d₆*): δ 8.63 (s, 1H, NH), 7.47 (d, 2H), 7.04 (d, *2*H), 4.64 (s, 1H), 3.90 (s, 3H), 3.60 (s, 6H), 3.81 (s, 6H); **^{13}C NMR** (126 MHz, DMSO-*d₆*): δ 170.3, 159.1, 143.3, 130.1, 129.5, 113.1, 88.1, 56.6, 52.3, 34.4, 17.1; **HR-MS** (ESI) for $C_{18}H_{21}NO_5$ (m/z) $[M + H]^+$ calcd:332.1420, found: 332.1417.

Dimethyl 4-(2-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3o) Yellow solid; yield 90%; m.p. 205-207 °C; **^{1}H NMR** (500 MHz, DMSO-*d₆*): δ 8.81 (s, 1H), 7.46 (d, 1H), 7.17-7.12 (m, 3H), 4.75 (s, 1H), 3.87 (s, 6H), 2.37(s, 6H) **^{13}C NMR** (126 MHz, DMSO-*d₆*): δ 172.5 143.0, 138.7, 133.2, 132.5 130.9, 127.9, 126.8, 86.5, 52.3, 34.3, 16.3; **HR-MS** (ESI) for $C_{17}H_{18}BrNO_4$ (m/z) $[M + H]^+$ calcd: 380.0419, found: 380.0431.

Dimethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3p) Yellow solid; yield 91%; m.p. 198 °C; **^{1}H NMR** (500 MHz, DMSO-*d₆*): δ 8.92 (s, 1H), 7.31-7.27 (m, 4H), 4.80 (s, 1H), 3.88 (s, 6H), 2.40 (s, 6H) **^{13}C NMR** (126 MHz, DMSO-*d₆*): δ 173.6 143.3, 139.5, 132.5, 130.2 129.9, 88.3, 52.0, 35.0, 16.8; HR-MS (ESI) for $C_{17}H_{18}ClNO_4$ (m/z) $[M + H]^+$ calcd:336.0924, found: 336.0915.

Dimethyl 4-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3q) White solid; yield 93%; m.p. 173 °C; **^{1}H NMR** (500 MHz, DMSO-*d$_6$*): δ 8.90 (s, 1H), 7.35 (d, 2H), 6.99 (d, 2H), 4.83(s, 1H), 3.87 (s, 6H), 2.41 (s, 6H) **^{13}C NMR** (126 MHz, DMSO-*d$_6$*): δ 173.6 163.3, 143.3, 136.6, 129.7, 114.4, 88.1, 52.0, 34.8, 16.8; **HR-MS** (ESI) for $C_{17}H_{18}FNO_4$ (m/z) $[M + H]^+$ calcd: 320.1220, found: 320.1228.

Dimethyl 4-(2-hydroxy-3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3r) Yellowish solid; yield 93%; m.p. 195-197 °C; **^{1}H NMR** (500 MHz, DMSO-*d$_6$*): *δ* 8.80 (s, 1H), 7.16 (d, 1H), 6.87 (t, H), 6.81 (d, 1H), 4.47 (s, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.49 (s, 6H), 2.23(s, 6H) **^{13}C NMR** (126 MHz, DMSO-*d$_6$*): δ 169.7 148.4, 146.7, 143.0, 130.0 123.6, 118.9, 116.4, 86.5, 56.7, 52.1, 27.2, 16.3; **HR-MS** (ESI) for $C_{18}H_{21}NO_6$ (m/z) $[M + H]^+$ calcd: 348.1369, found: 348.1354.

Dimethyl 2,6-dimethyl-4-(naphthalen-1-yl)-1,4-dihydropyridine-3,5-dicarboxylate (3s) Yellow solid; yield 93%; m.p. 204-206 °C; **^{1}H-NMR** (500 MHz, DMSO-*d$_6$*): δ 8.73 (s, 1H, NH), 8.02 (d, 1H), 7.81 (d, 1H,), 7.70, (d, 1H), 7.51-7.46 (m, 2H), 7.30 (t, 1H), 7.07 (d, 1H), 4.96 (s, 1H), 3.84 (s. 6H), 2.29 (s, 6H); **^{13}C-NMR** (126 MHz, DMSO-*d$_6$*): δ 170.0, 142.9, 134.3, 132.1, 131.6, 129.7, 127.1, 126.6, 125.9, 3 87.5, 52.0, 53.8, 16.3; **HR-MS** (ESI) for $C_{21}H_{21}NO_4$ (m/z) $[M + H]^+$ calcd: 352.1470, found: 352.1475.

Dimethyl 2,6-dimethyl-4-(thiophen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (3t) Brown solid; yield 89%; m.p. 212-214; °C; **^{1}H NMR** (500 MHz, DMSO-*d$_6$*): δ 8.36 (s, 1H, NH), 7.08 (d, 1H), 6.80-6.77 (m, 2H), 4.79 (s, 1H), 4.84 (s, 6H), 2.37 (s, 6H); **^{13}C NMR**

(126 MHz, DMSO-d_6): δ 171.3, 153.1, 142.9, 135.1, 125.2, 89.2, 52.4, 39.2, 16.3; **HR-MS** (ESI) for $C_{15}H_{17}NO_4S$ (m/z) $[M + H]^+$ calcd: 308.0878, found: 308.0875.

Dimethyl 2',6'-dimethyl-1',4'-dihydro-[2,4'-bipyridine]-3',5'-dicarboxylate (3u) Brown solid; yield 89%; m.p. 248-250 ^oC; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.57 (d, 2H), 8.43 (s, 1H, NH), 7.69 (t, 1H), 7.17 (t, 1H), 7.07 (d, 1H) 4.82 (s, 1H), 3.88 (s, 6H), 2.27 (s, 6H); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 172.2, 157.5, 146.0, 142.7, 140.5, 129.5, 119.5, 92.4, 52.0, 35.9, 16.5; **HR-MS** (ESI) for $C_{16}H_{18}N_2O_4$ (m/z) $[M + H]^+$ calcd: 303.1266, found: 303.1254.

9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3v) Yellowish solid; yield 93%; m.p. 281 °C; **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.80 (s, 1H, NH), 7.57 (d, 2H), 7.29 (t, 3H), 4.72 (s, 1H), 2.48 (t, 4H), 2.27 (t, 4H), 1.67 (m, 4H); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 192.6, 150.6, 140.3, 128.5, 128.3, 127.7, 105.2, 37.2, 32.0, 28.6, 20.4; **HR-MS** (ESI) for $C_{19}H_{19}NO_2$ (m/z) $[M + H]^+$ calcd: 294.1416, found: 294.1424.

9-(4-methoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3w) Yellow solid; yield 92%; m.p. 190-192 °C; **^{1}H NMR** (500 MHz, DMSO-d_6): 9.81 (s, 1H, NH), 7.43 (d, 2H), 6.98 (d, 2H), 4.69 (s, 1H), 3.78 (s, 1H), 2.56 (t, 4H), 2.19 (t, 4H), 1.73 (m, 4H); **^{13}C NMR** (126 MHz, DMSO-d_6): δ 193.6, 159.4, 150.1, 130.3, 129.5, 113.1, 105.6, 56.0, 37.4, 32.8, 28.5, 20.6; **HR-MS** (ESI) for $C_{20}H_{21}NO_3$ (m/z) $[M + H]^+$ calcd: 324.1521, found: 324.1518.

9-(3-chlorophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3x) Light yellow solid; yield 90%; m.p. 202-204 °C; **^{1}H NMR** (500 MHz, DMSO-*d_6*): *δ* 9.71 (s, 1H, NH), 7.51 (s, 1H), 7.29 (d, 2H), 7.26 (d, 2H), 7.18 (t, 1H) 4.62 (s, 1H), 2.46 (t, 4H), 2.29 (t, 4H), 1.63 (m, 4H); **^{13}C NMR** (126 MHz, DMSO-*d_6*): δ 195.0, 150.6, 143.2, 134.0, 129.7, 128.8, 127.4, 126.8, 105.2, 37.2, 33.8, 28.4, 20.7; **HR-MS** (ESI) for $C_{19}H_{18}ClNO_2$ (m/z) $[M + H]^+$ calcd: 328.1026, found: 328.1022.

9-(4-bromophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3y) Yellow solid; yield 93%; m.p. 295 °C; **^{1}H NMR** (500 MHz, DMSO-*d_6*): 7.52 (d, 2H), 7.41 (s, 1H, NH), 7.20 (d, 2H), 7.26 (d, 2H), 7.18 (t, 1H) 4.83 (s, 1H), 2.37 (t, 4H), 2.21 (t, 4H), 1.73 (m, 4H); **^{13}C NMR** (126 MHz, DMSO-*d_6*): δ 194.9, 150.3, 138.5, 131.9, 129.6, 124.0, 105.7, 37.3, 32.8, 28.9, 21.0; **HR-MS** (ESI) for $C_{19}H_{18}BrNO_2$ (m/z) $[M + H]^+$ calcd: 372.0521, found: 372.0511.

3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3z) Yellow solid; yield 92%; m.p. 277 °C; **^{1}H NMR** (500 MHz, DMSO-*d_6*): δ 7.42 (d, 2H), 7.31 (s, 1H, NH), 7.25 (t, 3H), 4.71 (s, 1H), 2.57 (s, 4H), 2.17 (s, 4H), 1.13 (s, 12H); **^{13}C NMR** (126 MHz, DMSO-*d_6*): δ 194.6, 159.7, 140.2, 128.6, 128.4, 127.3, 113.7, 51.0, 36.3, 32.8, 28.9, 21.0; **HR-MS** (ESI) for $C_{23}H_{27}NO_2$ (m/z) $[M + H]^+$ calcd: 350.2042, found: 350.2063.

9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3aa) Brown solid; yield 92%; m.p. 268-270 °C; **^{1}H NMR** (500 MHz, DMSO-*d_6*):

7.44 (d, 2H), 7.37 (s, 1H, NH), 6.98 (d, 2H), 4.67 (s, 1H), 3.77 (s, 3H), 2.49 (s, 4H), 2.04 (s, 4H), 1.09 (s, 12H); **^{13}C NMR** (126 MHz, DMSO-*d_6*): δ 194.9, 159.9, 159.2, 130.3, 129.5, 113.1, 112.5, 56.0, 51.4 36.7, 33.8, 32.7, 28.8; **HR-MS** (ESI) for $C_{24}H_{29}NO_3$ (m/z) $[M + H]^+$ calcd: 380.2147 found: 380.2141.

9-(3-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3ab) Yellow solid; yield 90%; m.p. 295-297 °C; **^{1}H NMR** (500 MHz, DMSO-*d_6*): *δ* 7.54 (s, 1H, NH), 7.47 (s, 1H), 7.29 (dt, 2H), 7.13 (d, 1H), 4.74 (s, 1H), 2.54 (s, 4H), 2.14 (s, 4H), 1.11 (s, 12H); **^{13}C NMR** (126 MHz, DMSO-*d_6*): δ 194.6, 159.3, 143.2, 134.0, 129.1, 128.4, 127.4, 126.8, 112.5, 51.7, 36.3, 33.1, 32.3, 28.2; **HR-MS** (ESI) for $C_{23}H_{26}ClNO_2$ (m/z) $[M + H]^+$ calcd: 384.1652, found: 384.1643.

3,3,6,6-tetramethyl-9-(pyridin-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (3ac) Light orange solid; yield 88%; m.p. 298 °C; **^{1}H NMR** (500 MHz, DMSO-*d_6*): δ 8.64 (d, 1H), 7.67 (t, 1H), 7.37 (s, 1H), 7.23 (t, 1H), 7.12 (d, 1H), 4.76 (s, 1H), 2.60 (s, 4H), 2.07 (s, 4H), 1.13 (s, 12H); **^{13}C NMR** (126 MHz, DMSO-*d_6*): δ 194.8, 157.5, 156.2, 146.0, 140.5, 129.4, 119.5, 112.7, 51.4, 36.6, 34.4, 32.7, 28.8; **HR-MS** (ESI) for $C_{22}H_{26}N_2O_2$ (m/z) $[M + H]^+$ calcd: 351.1994, found: 351.1998.

2,2,8,8-tetramethyl-5-phenyl-5,10-dihydro-4H,6H-bis([1,3]dioxino)[4,5-b:5',4' e]pyridine-4,6-dione (3ad) White solid; yield 92%; m.p. 172-174 °C; **^{1}H NMR** (500 MHz, DMSO-*d_6*): δ 8.94 (s, 1H), 7.47 (d, 2H), 7.27 (t, 3H), 4.76 (s, 1H), 1.73 (s, 12H); **^{13}C NMR**

(126 MHz, DMSO-*d*$_6$): δ 164.4, 149.1, 140.5, 128.6, 128.4, 127.6, 100.9, 84.2, 38.2, 26.1; **HR-MS** (ESI) for $C_{19}H_{19}NO_6$ (m/z) $[M + H]^+$ calcd: 358.1212, found: 3581225.

5-(4-methoxyphenyl)-2,2,8,8-tetramethyl-5,10-dihydro-4H,6H-bis([1,3]dioxino) [4,5-b:5',4' e] pyridine-4,6-dione (3ae) Yellow solid; yield 92%; m.p. 171 °C; **^{1}H NMR** (500 MHz, DMSO-*d*$_6$): δ 8.95 (s, 1H), 7.37 (d, 2H), 6.87 (d, 2H), 4.68 (s, 1H), 3.78 (s, 1H), 1.71 (s, 12H); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$): δ 164.7, 159.1, 149.3, 140.5, 130.3, 129.5, 113.1, 100.8, 84.2, 56.0 38.3, 26.2; **HR-MS** (ESI) for $C_{20}H_{21}NO_7$ (m/z) $[M + H]^+$ calcd: 388.1318, found: 388.1328.

2,2,8,8-tetramethyl-5-(4-nitrophenyl)-5,10-dihydro-4H,6H-bis([1,3]dioxino)[4,5-b:5',4'-e]pyridine-4,6-dione (3af) Brown solid; yield 87%; m.p. 191-193 °C; **^{1}H NMR** (500 MHz, DMSO-*d*$_6$): 8.90 (s, 1H), 8.17 (d, 2H), 7.67 (d, 2H), 4.80 (s, 1H), 1.77 (s, 12H); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$): δ 165.1, 149.3, 145.9, 129.0, 123.1, 100.9, 84.7, 38.6, 26.0; **HR-MS** (ESI) for $C_{19}H_{18}N_2O_8$ (m/z) $[M + H]^+$ calcd: 403.1063, found: 403.1054.

5-(4-bromophenyl)-2,2,8,8-tetramethyl-5,10-dihydro-4H,6H-bis([1,3]dioxino)[4,5-b:5',4'-e]pyridine-4,6-dione (3ag) Yellow solid; yield 91%; m.p. 187 °C; **^{1}H NMR** (500 MHz, DMSO-*d*$_6$): 8.87 (s, 1H), 7.47 (d, 2H), 7.30 (d, 2H), 4.71 (s, 1H), 3.78 (s, 1H), 1.73 (s, 12H); **^{13}C NMR** (126 MHz, DMSO-*d*$_6$): δ 164.4, 149.1, 138.7, 131.8, 129.9, 124.0, 100.9, 83.9, 38.3, 26.3; **HR-MS** (ESI) for $C_sH_{18}BrNO_6$ (m/z) $[M + H]^+$ calcd: 436.0317, found: 436.0325.

5.8 Spectrum of Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (3a)

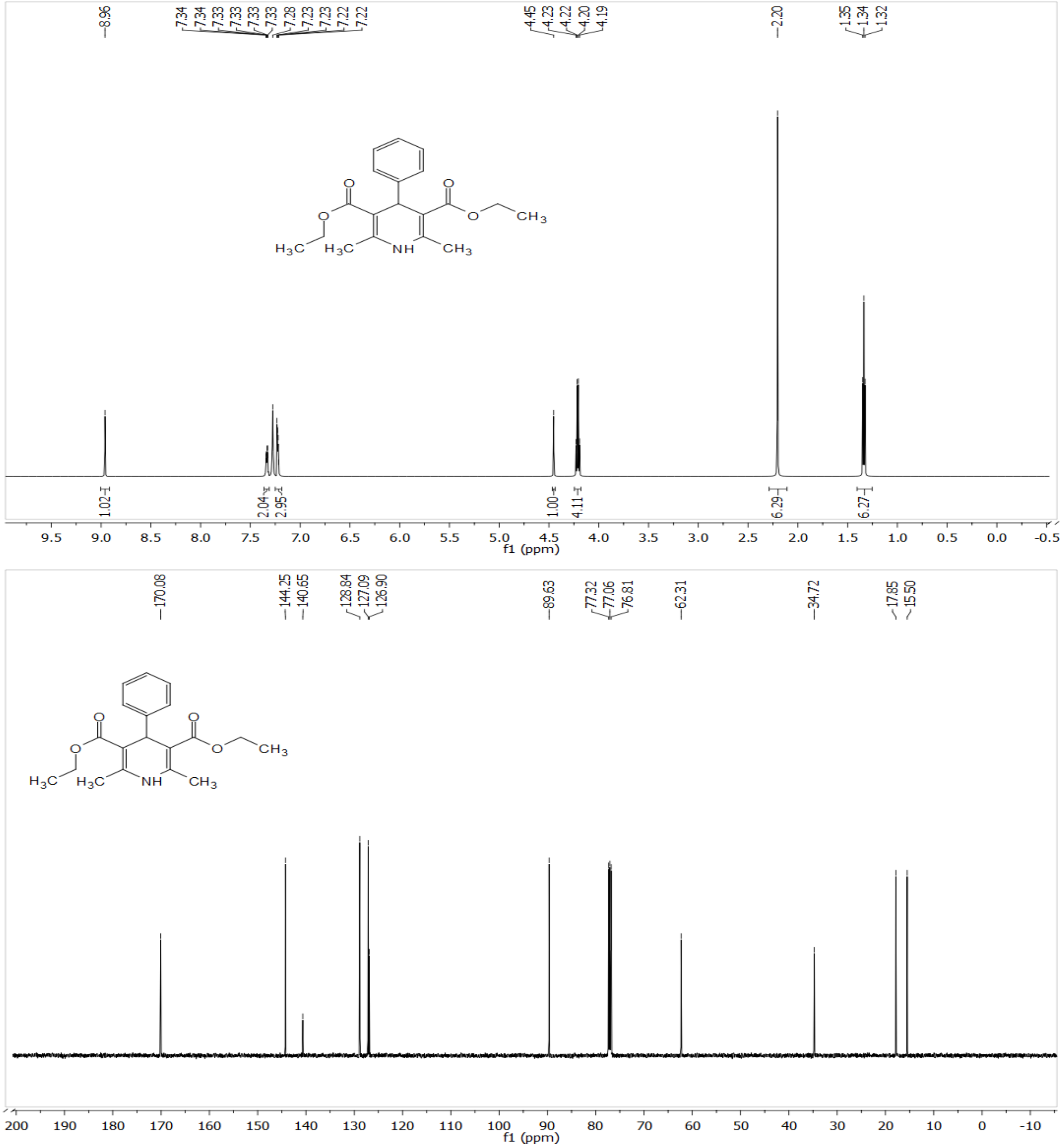


Figure 5.4 ^{1}H , ^{13}C NMR spectra of Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**3a**)

5.9 References

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