Research Article

Ultrasound promoted synthesis of polyhydroquinolines using tris-(hydroxymethyl)aminomethane (THAM) as organocatalyst

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Abstract

A simple and efficient, one-pot four-component reaction has been developed for the synthesis of polyhydroquinolines by reacting an aldehyde, dimedone, ethyl acetoacetate and ammonium acetate using tris-(hydroxymethyl)aminomethane (THAM) as organocatalyst in ethanol: water solvent system under ultra sonication. In the present wok, a series of aromatic aldehydes were successfully used to prepare the targeted polyhydroquinoline derivatives with good to excellent yields (88–92%). The present protocol affords several advantages such as short reaction time, inexpensive and recyclable catalyst, easy workup, excellent yields and environment friendly procedure.

Keywords: Multicomponent reaction, Tris-(hydroxymethyl) aminomethane, THAM, Ultrasound irradiation.

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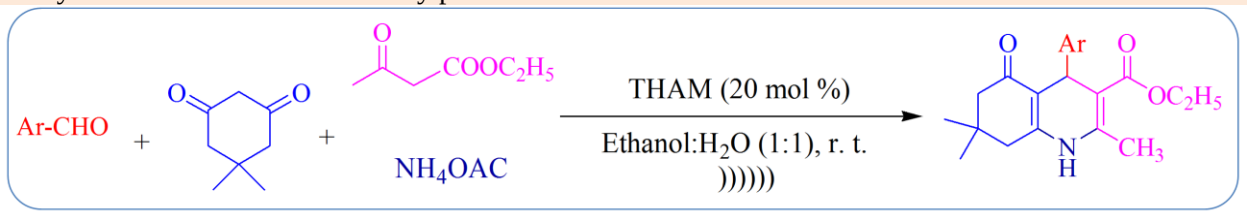


Introduction

Ultrasound promoted organic synthesis is considered as an energy conserving protocol in synthetic organic chemistry. Ultrasound assisted reactions are advantageous over the traditional thermal methods in terms of reaction rates, increased yields, purity of the products, product selectivity, minimum environmental impact of chemical synthesis etc [1].The sonochemical phenomenon is the result of the interaction of suitable field of acoustic waves with potentially reacting chemical system. This phenomenon occurs through acoustic cavitation which is a sequential process of involving the bubble formation, its growth and breakdown. Furthermore, these violent collapses of cavitation bubbles develop high temperature and pressure in the micro environment which creates turbulence and facilitates the mass transfer in the neighborhood [2]. As this technology involves energy conservation and minimal waste generation, it is widely accepted as a green chemistry approach [3].The synthesis of 1,4-dihydropyridyl compounds is an important subject of synthetic research due to their wide spectrum of biological and pharmaceutical properties such as antidiabetic, hepatoprotective, vasodilator, geroprotective, anticancer, antiatherosclerotic, bronchodilator and antitumor activities [4]. In addition, dihydropyridine skeleton containing compounds such as Amlodipine, Nifedipine, Nicardipine (**Figure 1**) are effective for the treatment of hypertension [5].

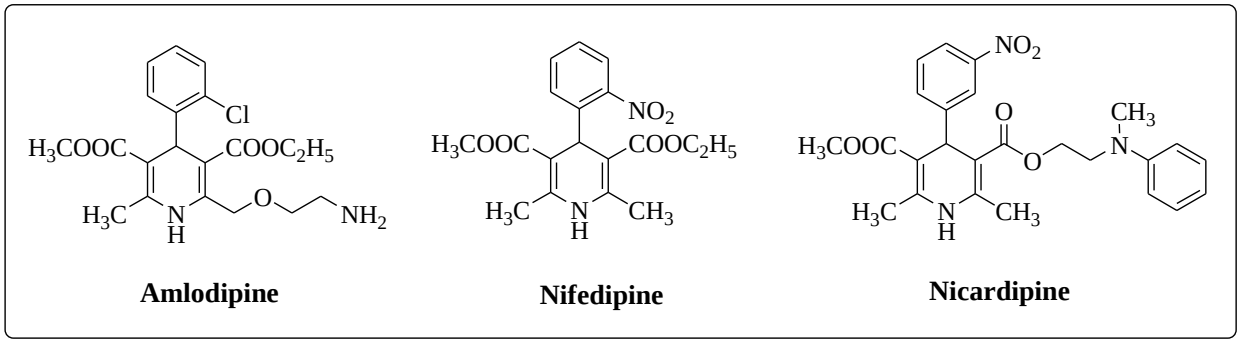
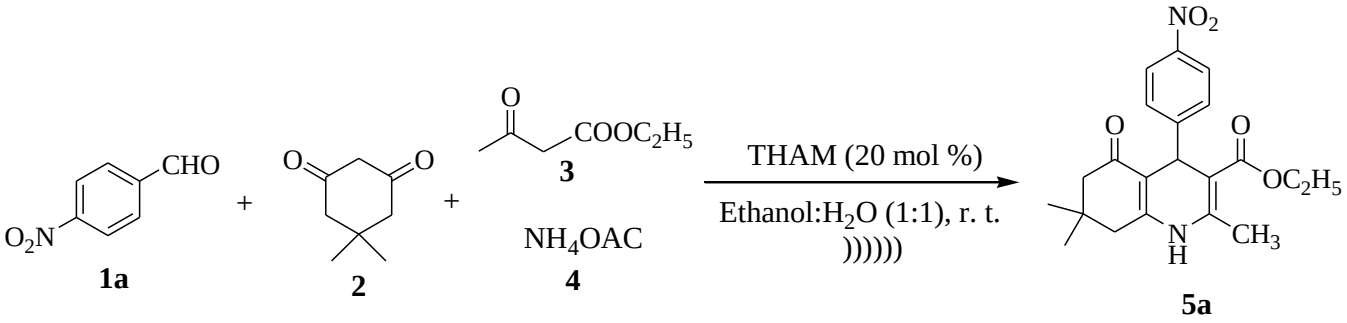


Figure 1 Biologically active compounds based on dihydropyridine skeleton

In recent years, various catalysts have been explored for the synthesis of polyhydroquinolines such as molecular iodine [6], metal triflates [7], ceric ammonium nitrate [8], baker's yeast [9], organocatalysts [10], iron(III) trifluoroacetate [11], scolecite [12], triphenyl phosphine [13], sulfamic acid [14], thiourea dioxide [15], FeF_3 [16] N-heterocyclic carbine [17], $Al_2(SO_4)_3$ [18], La_2O_3 [19], alginic acid [20] and copper complex supported on MCM-41 [21]. In addition, syntheses of polyhydroquinolines have been carried out by using ionic liquids [22], nanocatalysts [23] and under catalyst-free conditions [24]. However, some of the reported methods have disadvantages such as the use of high temperature, expensive metal precursors, catalysts that are harmful to environment, restricted scope of substrates and longer reaction times. Therefore, the search for a better catalyst for the synthesis of polyhydroquinoline derivatives using milder reaction conditions is of prime importance. Tris-(hydroxymethyl)aminomethane (THAM), an organocatalyst containing one amino and three alcoholic groups is structurally related to meglumine. It is physiologically inert, bio-degradable, non-corrosive and commercially available at low cost. THAM has been reported for the one-pot multicomponent synthesis of tetrahydrobenzo[*b*]pyrans and pyran-annulated heterocycles [25]. In continuation of our research work to develop green chemistry methodologies [26-35] and considering the importance of THAM as organocatalyst in synthetic organic chemistry, herein we wish to report an efficient synthesis of highly functionalized polyhydroquinoline derivatives *via* one-pot four-component domino Knoevenagel-Michael addition reaction in the presence of tris-(hydroxymethyl)aminomethane as catalyst under ultrasound irradiation.

Results and Discussion

In order to obtain the best experimental conditions, we have considered reaction of 4-nitrobenzaldehyde (**1a**), dimedone (**2**), ethyl acetoacetate (**3**) and ammonium acetate (**4**) in ethanol: water (1:1) solvent system in presence of THAM as catalyst to get the desired polyhydroquinoline (**5a**) (**Scheme 1**).



Scheme 1 Organocatalyzed synthesis of polyhydroquinoline

Initially the model reaction was run in water under stirring for 120 min at room temperature and noticed 20 % of product formation by TLC (**Table 1**, **entry 1**). It might be due to the insolubility of substrates in water. Then in order to increase the yield, the model reaction was run in ethanol: water (EtOH: H_2O, 1:9) solvent system under stirring for 120 min and observed 50 % product formation (**Table 1, entry 2**). When the same reaction was carried out under ultrasonication for 30 min at room temperature, the yield of product increases to 65 % (**Table 1, entry 3**). To investigate the efficiency of solvent system, we have carried out the model reaction under ultrasonication in various solvent systems of ethanol: water and results are summarized in Table 1 (**Entries 4-8**). These results clearly demonstrated that the maximum yield (92 %) of desired polyhydroquinoline derivative (**5a**) was obtained with ethanol: water (1:1) solvent system within 30 min of ultrasonication (**Table 1, entry 7**). In view of these observations we have selected ethanol: water (1:1) as the reaction medium for organocatalyst mediated synthesis of polyhydroquinolines under ultrasonic irradiation. We observed that increase in reaction time from 30 min to 40 min has no effect on the yield of desired product **5a** (**Table 1, entry 8**).

Next, we have investigated the effect of different mole % of catalyst on the reaction yield (**Table 2**, **entries 1**–**5**). Initially the model reaction was run using 5 mol % of THAM and noticed 68% product formation after 30 min of ultrasonication. Therefore the amount of catalyst was increased to 10, 15, 20, 25 mol% and observed that 20 mol% of THAM gave maximum yield (92%) of desired product. By increasing the amount of catalyst further to 25 mol % failed to increase the yield of product.

Our next task was to investigate the recyclability of THAM for the model reaction. After completion of reaction, dichloromethane (20 mL) was added to the reaction mixture to dissolve the product and insoluble THAM was separated by simple filtration. The separated THAM was washed with dichloromethane, dried at room temperature and then subjected to a new run with fresh reactants. It was noticed that the THAM could be reused for at least four runs with modest change in the product yield (**Figure 2**).

Table 1 Optimization of the reaction conditions for the synthesis of polyhydroquinoline using THAM as catalyst[a]

Entry	Reaction medium	Reaction Condition	Time (min)	Yield[b] (%)
1	H_2O	Stirring	120	20
2	EtOH:H_2O (1:9)	Stirring	120	50
3	EtOH:H_2O (1:9)	Ultrasound irradiation	30	65
4	EtOH:H_2O (2:8)	Ultrasound irradiation	30	70
5	EtOH:H_2O (3:7)	Ultrasound irradiation	30	74
6	EtOH:H_2O (4:6)	Ultrasound irradiation	30	82
7	EtOH:H_2O (1:1)	Ultrasound irradiation	30	92
8	EtOH:H_2O (1:1)	Ultrasound irradiation	40	89

[a]Reaction conditions: 4-nitrobenzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1 mmol), THAM catalyst (20 mol %) in 5 mL solvent under ultrasonication with irradiation frequency 30 kHz and ultrasonic power 100 W at room temperature 30 °C.
[b]Isolated yield.

Table 2 Study of catalyst efficiency for the synthesis of polyhydroquinoline[a]

Entry	Amount of catalyst (mol %)	Reaction Time (min)	Yield[b] (%)
1	5	30	68
2	10	30	78
3	15	30	82
4	20	30	92
5	25	30	90

[a]Reaction conditions: 4-nitrobenzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1 mmol), THAM catalyst in 5 mL of ethanol: water (1:1) as the reaction medium under sonic condition with irradiation frequency 30 kHz and ultrasonic power 100 W at room temperature 30 °C.
[b]Isolated yield.

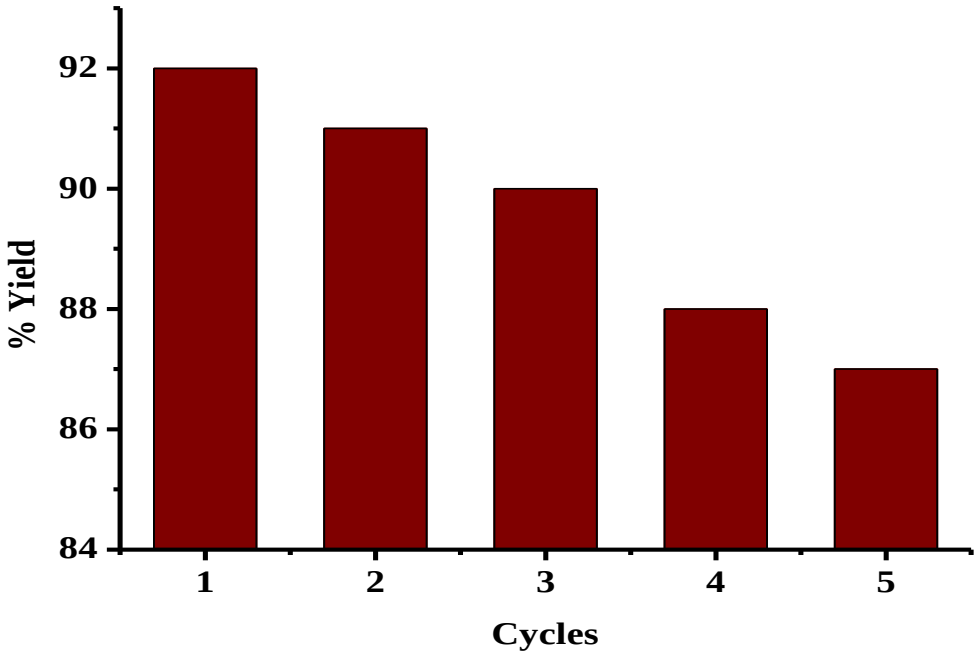
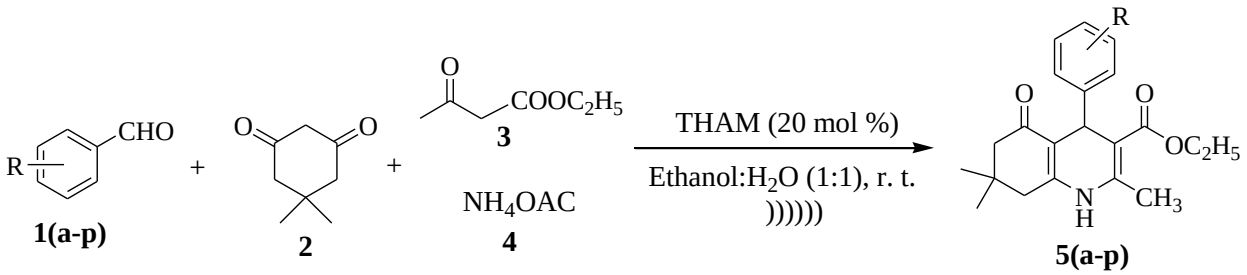
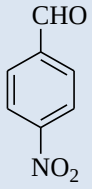
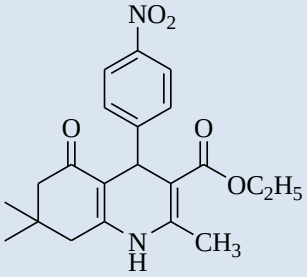
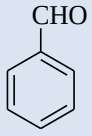
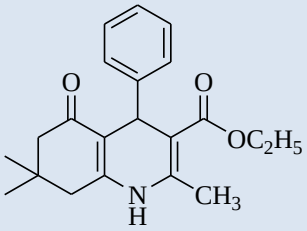
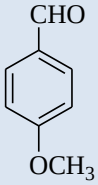
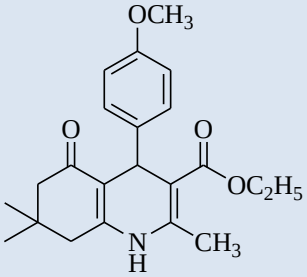
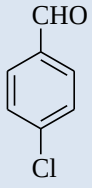
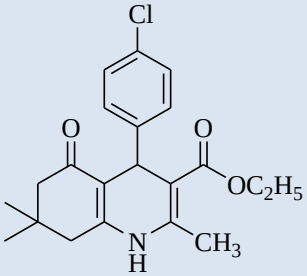
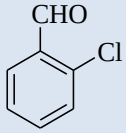
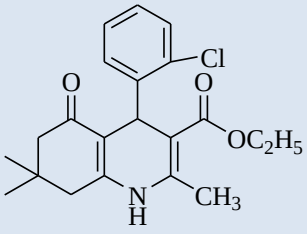


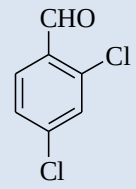
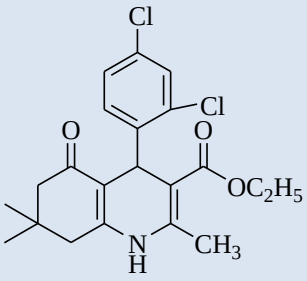
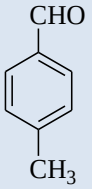
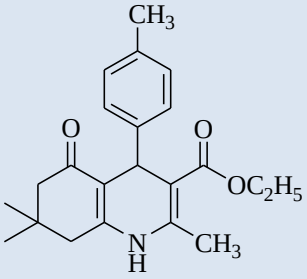
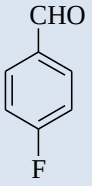
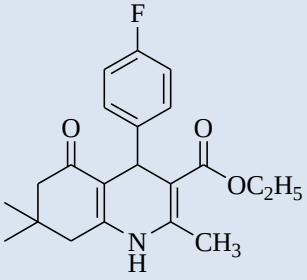
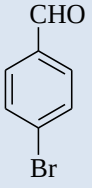
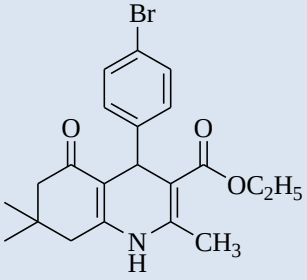
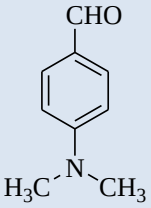
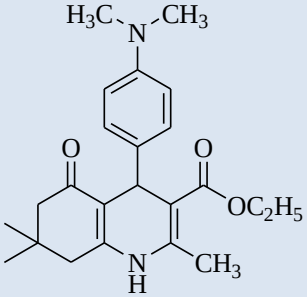
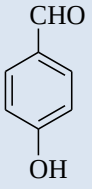
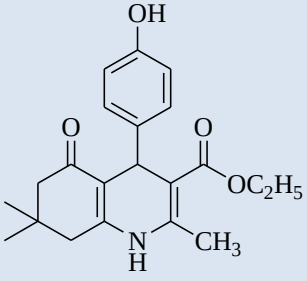
Figure 2 Reusability of the organocatalyst: Tris-hydroxymethylaminomethane

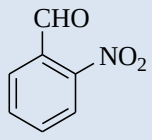
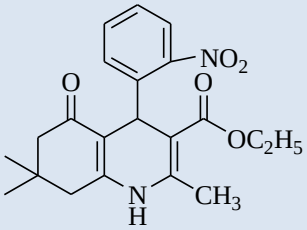
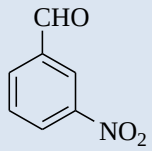
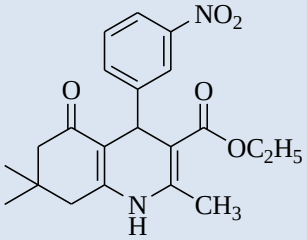
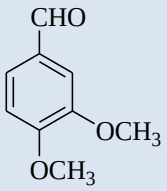
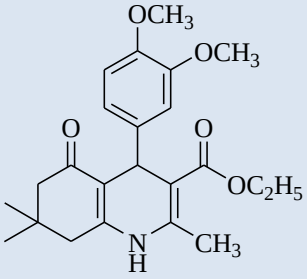
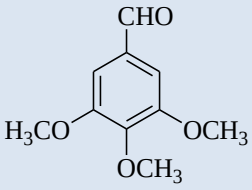
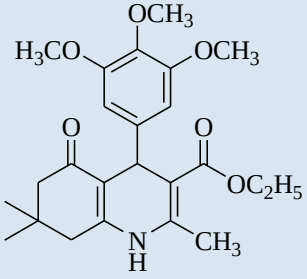
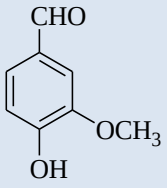
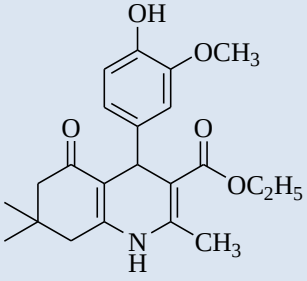
To explore the scope and generality of the developed protocol for the synthesis of functionalized polyhydroquinoline derivatives, variety of structurally diverse aldehydes possessing electron-donating as well as electron-withdrawing groups were reacted with dimedone, ethyl acetoacetate and ammonium acetate and results are summarized in **Table 3**. From these results it is amply clear that in all the cases irrespective of the presence of electron-donating or electron-withdrawing groups in an aldehyde moiety, the products were obtained in good to excellent yields.

Table 3 Organocatalyzed synthesis of polyhydroquinoline derivatives[a]



Entry	Aldehyde	Product	Time (min)	Yield (%)	Melting point (°C) Found	Melting point (°C) Reported
1	 **1a**	 **5a**	30	92	240-242	243-244[23a]
2	 **1b**	 **5b**	30	90	199-201	203-204[23a]
3	 **1c**	 **5c**	30	89	255-257	256-257[23a]
4	 **1d**	 **5d**	30	90	243-245	245-246[23a]
5	 **1e**	 **5e**	30	91	206-208	207-208[23a]

6	 **1f**	 **5f**	30	92	238-240	242-243[23a]
7	 **1g**	 **5g**	30	90	258-260	261-262[23a]
8	 **1h**	 **5h**	30	92	182-183	185-186[23a]
9	 **1i**	 **5i**	30	90	249-251	252-253[23a]
10	 **1j**	 **5j**	30	89	252-255	257-258[23a]
11	 **1k**	 **5k**	30	88	228-230	230-231[23a]

12	 **1l**	 **5l**	30	92	204-206	206-207[23a]
13	 **1m**	 **5m**	30	90	176-179	178-179[23a]
14	 **1n**	 **5n**	30	88	195-197	196-198[23a]
15	 **1o**	 **5o**	30	90	195-197	199-200[23a]
16	 **1p**	 **5p**	30	89	201-203	211-212[23a]

[a]Reaction conditions: aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1 mmol), THAM catalyst (20 mol %) in 5 mL of ethanol: water (1:1) as the reaction medium under ultrasonication with irradiation frequency 30 kHz and ultrasonic power 100 W at room temperature 30 °C.
[b]Isolated yield.

Conclusion

In conclusion, we have developed an efficient methodology for the synthesis of polyhydroquinoline derivatives under ultrasound irradiation in ethanol: water (1:1) solvent system using tris-(hydroxymethyl)aminomethane (THAM) as a mild, readily available, inexpensive and biodegradable catalyst. In addition, the developed protocol has notable features such as conversion under mild reaction conditions, tolerance of wide variety of functional groups, minimum environmental effect, no waste formation and high yield of the desired products.

Experimental Section

General Remarks

All reagents and solvent were purchased from Merck and Sigma Aldrich and used without further purification. Melting points were determined in an open capillary and are uncorrected. Infrared spectra were obtained on Alpha-Bruker FT-IR spectrometer. The samples were examined as KBr discs ~5 % w/w. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avon 300 MHz and 75 MHz spectrometer respectively using $CDCl_3$ as solvent and TMS as internal reference. Sonication was performed in SPECTRALAB-UCB-30 ultrasonic bath with a frequency of 30 kHz and a nominal power of 100 W. The reaction flask was located in the maximum energy area in the water bath. The reaction temperature was controlled at room temperature (30 °C) by addition or removal of water from ultrasonic bath.

General procedure for the synthesis of polyhydroquinoline

To the solution of an aromatic aldehyde (1mmol), ethyl acetoacetate (1mmol), dimedone (1mmol) and ammonium acetate (1mmol) in 5 mL of ethanol: water (1:1), tris-(hydroxymethyl)aminomethane (20 mol %) was added. Then the reaction mixture was sonicated at 30 kHz for stipulated time mentioned in Table 3 at 30 °C. The progress of the reaction was monitored by thin layer chromatography by using petroleum ether: ethyl acetate (7:3) as solvent system. After completion of reaction, it was extracted with dichloromethane (20 mL) and finally dried over anhydrous sodium sulphate. The resulting crude product was purified by recrystallization from ethanol to afford pure polyhydroquinoline derivatives.

Spectral data of representative compounds

2,7,7-Trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5a): m.p. = 240-242 °C. IR (KBr, cm^{-1}): 3274, 3189, 3076, 2966, 1700, 1649, 1609, 1539, 1349, 1215cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (s, 3H), 1.09 (s, 3H), 1.20 (t, 3H), 2.13-2.37 (m,4H), 2.40 (s, 3H), 4.04 (q, 2H), 5.17 (s, 1H), 6.67 (s, 1H), 7.49-7.51 (m, 2H), 8.08-8.10 (m, 2H) ppm. ^{13}CNMR (75MHz, $CDCl_3$): δ 14.2, 19.4, 27.1, 29.3, 32.7, 37.2, 40.9, 50.5, 60.1, 105.0, 110.9, 123.32, 129.00, 144.5, 146.2, 149.5, 154.4, 166.9, 195.4 ppm.

2,7,7-Trimethyl-4-(4-chlorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5d): m.p. = 243-245 °C. IR (KBr, cm^{-1}): 3288, 3198, 3076, 1683, 1606, 1492, 1225 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (s, 3H), 1.08 (s, 3H), 1.20 (t, 3H), 2.19-2.31 (m, 4H), 2.35 (s, 3H), 4.05 (q, 2H), 5.05 (s, 1H), 6.92 (s, 1H), 7.16-7.19 (m, 2H), 7.24-7.28 (m, 2H) ppm. ^{13}CNMR (75MHz, $CDCl_3$): 14.2, 19.2, 27.2, 29.4 32.7, 36.7, 40.8, 50.6, 59.9, 105.6, 111.3, 126.2, 129.1, 133.7, 144.2, 149.1, 149.5, 167.2, 195.7 ppm.

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