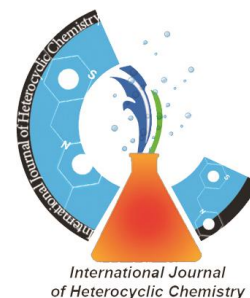

Research article

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A Novel protocol for synthesis of Hantzsch 1, 4- dihydropyridines using PEG-400 as a reaction medium and under catalyst-free condition

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Abstract - An efficient and expeditious catalyst-free procedure was developed for the one- pot synthesis of 1, 4-dihydropyridine derivatives via the three-component reaction of various aldehydes, ethyl acetoacetate, and ammonium acetate in PEG-400. The reaction was carried out at 110°C and the products were obtained in good to high yields.

Keyword: Hantzsch 1, 4 – dihydropyridines, PEG-400, three-component reaction, catalyst-free, aldehydes ,ethyl acetoacetate, ammonium acetate

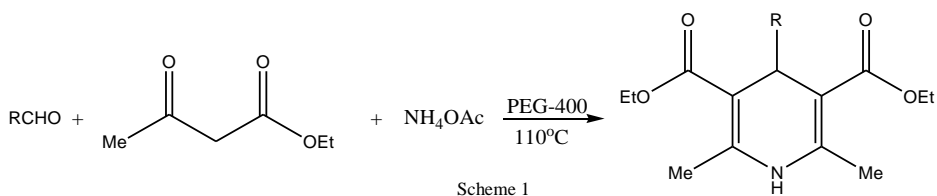
Introduction

1,4-Dihydropyridines (1,4-DHPs) are core structure of many bioactive compounds which include vasodilator, bronchodilator, anticonvulsant, antidepressive, antianxiety, analgesic, antitumoral, hypnotic and anti-inflammatory agents [1]. DHPs have found commercial utility as calcium channel blockers, for the treatment of cardiovascular diseases and hypertensive such as amlodipine, felodipe, isradipine, lacidipine and nifedipine [2]. DHPs are good precursors of the corresponding substituted pyridine derivatives [3]. Moreover, 1,4-dihydropyridine is well-known reducing agent that has found many applications in organic transformations[4]. These ubiquitous features always encourage synthetic chemist to explore improved protocol for the synthesis of DHPs.

In the literature, various procedures for the synthesis of DHPs are described [5]. However, the most frequently used procedure for the preparation of dihydropyridines is Hantzsch method which involve one-pot, three-component cyclo condensation of an aldehyde with 1,3-dicarbonyl compounds and ammonia either in acetic acid or refluxing in alcohol [6]. However, the original

method by Hantzsch had several limitations such as harsh reaction conditions, long reaction time and low yields. Therefore, many improved methods have been reported. In the improvement, several catalysts and conditions include use of microwaves [7], ionic, liquid [8], and Lewis acids such as $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ [9], $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ [10], RuCl_3 [11], HClO_4 - SiO_2 [12], SiO_2 - NaHSO_4 [13], $\text{Fe}(\text{CF}_3\text{CO}_2)_3$ or $\text{Fe}(\text{CF}_3\text{SO}_3)_3$ [14], $\text{PhB}(\text{OH})_2$ [15], 12-tungstophosphoric acid [16], montmorillonite K10 [17] and TMSI-NaI [18] were employed. Although these methods have a lot of potential, the development of green and especially catalyst-free approaches still desirable and much in demand.

PEG, (polyethylene glycol), is known to be inexpensive, thermally stable, recoverable, biological compatible, and non-toxic [19]. Their potential as reaction media and promotor for organic reaction has attracted the attention of organic chemists in recent years [20]. In present article, we wish to report the novel, catalyst-free and green synthesis of various 1,4-dihydropyridines using PEG-400 as reaction media (Scheme 1).



1. RESULTS AND DISCUSSION

Initially, for optimizing reaction condition, the effect of temperature on the rate of the reaction was examined for the preparation of diethyl-4-(2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Table 1).

Table 1. Hantzsch synthesis of 1,4-dihydropyridines ^a: Effect of temperature

Entry	Temperature (°C)	Yield (%) ^b
1	r.t	33
2	60	58
3	80	61
4	110	87

a. Reaction conditions: furfural (2mmol), ethyl acetoacetate (4mmol), ammonium acetate (3mmol), PEG-400 (2mL).

b. Isolated yields.

Based on the results shown in table 1, we concluded that 110°C is best temperature. Therefore, the protocol was extended to other aldehydes (Table 2).

Table 2. Catalyst-free synthesis of 1,4-dihydropyridines in PEG-400.

Entry	R	Time (h)	Product ^a	Yield (%) ^b
1	Ph	3:50	4a	42
2	4-BrC ₆ H ₄	5	4b	70
3	3-BrC ₆ H ₄	4:50	4c	81
4	4-MeOC ₆ H ₄	3	4d	79
5	2-MeOC ₆ H ₄	3	4e	73
6	4-HOC ₆ H ₄	4	4f	50
7	3-MeC ₆ H ₄	3	4g	58
8	2-ClC ₆ H ₄	3	4h	59
9	2-NO ₂ C ₆ H ₄	2:30	4i	68
10	3-NO ₂ C ₆ H ₄	2	4j	71
11	4-NO ₂ C ₆ H ₄	2:30	4k	69
12	fur-2-yl	4	4l	87
13	CH ₃	4	4m	73
14	CH ₂ CH ₃	3:30	4n	64
15	CH ₂ CH ₂ CH ₃	3:30	4o	52

a. All products were characterized by mp, IR and ¹HNMR.

b. Isolated yields.

As the table 2 shows, the various aromatic aldehydes with electron-donating and electron-withdrawing groups (entries 1-11), hetroaryl aldehyde (entry12) and aliphatic aldehydes (entries 13-15) afford the corresponding products in good to high yields.

2. General Procedure

In a 50ml round-bottom flask, aldehyde (2mmol), ethyl acetoacetate (4mmol), ammonium acetate (3mmol), PEG-400(2mL) was stirred at 110°C for the stipulated time. The progress of the reaction was monitored by thin-layer of chromatography (TLC). After the stipulated time (table 2), the mixture was cooled to room temperature and extracted with diethyl ether (2×10mL). The organic phase was separated and concentrated under reduced pressure to furnish the crude product, which was recrystallized from the mixture of ethanol and water or mixture of ethyl acetate and n-hexane to afford the pure products.

All compounds were fully characterized by mp, IR and ¹HNMR spectroscopy.

Data of compounds:

Diethyl-4-(Phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4a)

Mp 155-157 °C ¹HNMR (300MHz, CDCl₃): δ = 1.23 (t, J=7.2 Hz, 6H), 2.35 (s, 6H), 4.09 (m, 4H), 5.00(s, 1H), 5.5 (brs, 1H), 7.10-7.31(m, 5H). IR (KBr): 3334, 2963, 1690, 1654, 1494, 1243, 1243, 1127, 721 cm⁻¹.

Diethyl-4-(4-Bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4b)

Mp 162-164 °C ¹HNMR (300MHz,CDCl₃): δ =1.23 (t, J=7.01 Hz, 6H), 2.34(s,6H), 4.10(m,4H), 4.95(s, 1H), 5.6 (brs, 1H) 7.16 (d, J=8.4Hz, 2H), 7.33(d,J=8.4, 2H). IR (KBr): 3357, 2949, 1689, 1485, 1213, 1094, 770 cm⁻¹.

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

Mp 124-126 °C ¹HNMR (300MHz,CDCl₃): δ =1.22 (t ,J=7.2 Hz,6H), 2.33 (s,6H), 4.09 (m,4H), 4.94 (s,1H), 5,89 (brs,1H)7.06 (t, J=7.5 Hz,1 H), 7.23(m, 2H), 7.39 (t,J =1.8 Hz,1H). IR (KBr): 3327, 2918, 1695, 1640, 1482, 1213, 1105, 795 cm⁻¹.

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

Mp 154-156 °C ¹HNMR (300MHz,CDCl₃): δ =1.23 (t ,J=7.2 Hz,6H), 2.32 (s,6H),3.77 (s,3H), 4.11(m,4H), 4.99 (s,1H), 5,74 (brs,1H)6.68 (dt,1 H), 6.85(m, 2H), 7.13 (t, 1H). IR (KBr): 3315, 2986, 1673, 1610, 1482, 1210, 1114,749 cm⁻¹.

Diethyl-4-(2-Methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4e)

Mp 159-162 °C ¹HNMR (300MHz,CDCl₃): δ =1.20 (t ,J=7.0 Hz,6H), 2.30 (s,6H),3.79 (s,3H), 4.04(q,J=7.0 Hz, 4H), 5.28 (s,1H), 5,5 (brs,1H)6.79-6.85 (m,2 H), 7.12(td,J=7.5 Hz,J=1.5 Hz, 1H), 7.23 (dd,J=7.5 Hz,J=1.32 Hz,1H). IR (KBr): 3327, 2923, 1688, 1671, 1490, 1378, 1210, 1105, 746 cm⁻¹.

Diethyl-4-(4-Hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5 – dicarboxylate (4f)

Mp 231-233 °C ¹HNMR (300MHz,CDCl₃): δ =1.23 (t ,J=7.2 Hz,6H), 2.34 (s,6H),3.6 (brs,1 H), 4.09(m,4H), 4.99 (s,1H), 5,5 (brs,1H)6.8-7.4 (m,4H) .IR (KBr) :3360,1695,1651, 1487, 1212, 1122, 789 cm⁻¹.

Diethyl-4-(3-Methylphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5 - dicarboxylate (4g)

Mp 134-137 °C ¹HNMR (300MHz,CDCl₃): δ =1.24 (t ,J=7.2 Hz,6H), 2.30 (s,3H),3.34 (s,6 H), 4.10(m,4H), 4.90 (s,1H), 5,6(s,1H)6.95 (m,1H) ,7.1 (m,3H) .IR (KBr) :3355, 2924, 1708, 1648,1487, 1318,1209, 1107, 781 cm⁻¹.

Diethyl-4-(2-Chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4h)

Mp 132-133 °C ¹HNMR (300MHz,CDCl₃): δ =1.22(t ,J=7.2 Hz,6H), 2.31 (s,6H),4.08 (m,4H), 4.96(s,1H), 5,86 (brs,1H), 7.20 (m,4H). IR (KBr): 3354, 2988, 1696, 1619, 1495, 1213, 1093, 835 cm⁻¹.

Diethyl-4-(2-Nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4i)

Mp 158-160 °C ^1H NMR (300MHz,CDCl₃): δ =1.23(t ,J=7.2 Hz,6H), 2.30 (s,6H),4.0 (m,4H), 5.01 (s,1H), 5,86 (brs,1H), 7.23 (m,1 H), 7.35(m,2H), 7.72 (d, 1H). IR (KBr): 3340, 2954, 1705, 1649, 1530, 1442, 1216, 1113, 704 cm⁻¹.

Diethyl-4-(3-Nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4j)

Mp 159-161 °C ^1H NMR (300MHz,CDCl₃): δ =1.22(t ,J=7.2 Hz,6H), 2.36 (s,6H),4.08 (m,4H), 5.09(s,1H), 5,92 (brs,1H), 7.37 (t,J=7.8 Hz,1H), 7.46(dt,J=7.8 Hz,1H),8 (m,1H), 8.12(dd,1H). IR (KBr): 3343, 2983, 1706, 1647, 1520, 1485, 1213, 1111, 704 cm⁻¹.

Diethyl-4-(4-Nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4k)

Mp 134-136 °C ^1H NMR (300MHz,CDCl₃): δ =1.23(t ,J=7.2 Hz,6H), 2.35 (s,6H),4.13 (m,4H), 5.10(s,1H), 5,98 (brs,1H), 7.50 (d,J=8.4 Hz,2H), 8.14(d,J=8.4 Hz,2H). IR (KBr): 3317, 1705, 1647, 1521, 1447, 1215, 1122, 707 cm⁻¹.

Diethyl-4-(2-Furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4l)

Mp 160-162 °C ^1H NMR (300MHz,CDCl₃): δ =1.27(t ,J=6.9 Hz,6H), 2.34 (s,6H),4.17 (m,4H), 5.21(s,1H), 5,8 (brs,1H), 5.95 (d,J=3.3 Hz,1H), 6.22(dd,J=3.3 Hz,J=1.8 Hz,1H), 7.22(d,J=1.8 Hz,1H). IR (KBr): 3345, 2923,1698, 1648, 1485, 1375, 1209, 1115, 740 cm⁻¹.

Diethyl-4-(Methyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4m)

Mp 130-132 °C ^1H NMR (300MHz,CDCl₃): δ = 0.98(d, J=6.6 Hz,3H), 1.31 (t, J=6.9Hz,6H) , 2.27(s,6H), 3.84 (q,J=6.6 Hz,1H), 4.20(m,4H), 5.5 (brs,1H). IR (KBr): 3344, 2964, 1696, 1614, 1491, 1217, 1056, 781 cm⁻¹.

Diethyl-4-(Ethyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4n)

Mp 128-131 °C ^1H NMR (300MHz,CDCl₃): δ = 0.75(t, J=7.8 Hz,3H), 1.26 (t, J=7.2Hz,6H) ,1.36 (m,J=5 Hz,7,J=7.8 Hz,2H), 2.22(s,6H), 3.91 (t,J=5.7 Hz,1H), 4.72(m,4H), 5.5 (brs,1H). IR (KBr) : 3319, 2923, 1708, 1643, 1498, 1309, 1213, 1068, 795 cm⁻¹.

Diethyl-4-(n-Propyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4o)

Mp 127-130 °C ^1H NMR (300MHz,CDCl₃): δ = 0.85(t, J=6.9 Hz,3H), 1.30 (t, J=7.1Hz,6H), 1.41(m,2H), 2.29(s,6H), 2.29-2.36(m, 2H), 3.94(t,J=6.9Hz,1H),4.18 (m,4H), 5.5 (brs,1H). IR (KBr): 3349, 2953, 1698, 1646, 1487, 1303, 1213, 1083, 781 cm⁻¹.

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