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One-pot, multicomponent synthesis of symmetrical Hantzsch 1,4-dihydropyridine derivatives using glycerol as clean and green solvent

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ABSTRACT

Multi component, one pot synthesis of symmetrical 1,4-dihydropyridine derivatives from the condensation of ethyl/methyl acetoacetate, aromatic/aliphatic aldehyde and ammonium acetate has been described using glycerol, as economical, easily available and environmentally benign reagent. The targeted molecules were obtained in high purity and excellent yield without use of any additional catalyst and methodology from readily available starting materials.

1. Introduction

The chemistry of 1,4-dihydropyridines (1,4-DHP's) found birth in 1882 with Hantzsch condensation [1]. After Hantzsch, multifarious new methods have been nurtured for the synthesis of original molecule. 1,4-DHP's attracted more attention, thanks to its presence in the coenzyme, diphospho pyridine nucleotide (DPNH) [2] and identification as bio-active material. In the present scenario many representatives have been commercialised such as nifedipine [3], felodipine [4], nicardipine [5], amlodipine [6] and even more have made their presence felt in the market [7] in the treatment of angina and hypertension. The activity profiles of 1,4-DHP's were further expanded as they were detected to possess anti-tumor [8], anti-inflammatory [9], anticonvulsant activity [10], antitubercular activity [11,12] cerebral antischemic activity in the treatment of Alzheimer's disease, PAF-acether antagonists [13]. Invention and execution of various new methodologies have engendered for the synthesis of symmetrical 1,4-DHP's. Off late many supported catalysts have been brought into use such as silica supported 12-tungstophosphoric acid [14]. Organo catalyst [15], $[TBA]_2[W_6O_{19}]$ [16], $Y(OTf)_3$ [17] and use of nanoparticles also provided swiftness and higher degree of efficiency to the reaction such as Silicotungstic acid dispersed in the micropores if Cr-pillared clay [18], MgO [19] and cobalt [20] nanoparticles with the use of many instruments like microwave [18,19,21-24], sonicator [25] turn out to exemplify. The above mentioned protocols have advantages over one another as they improve the Hantzsch condensation in terms of reaction time and yield [24]. However, the use of expensive catalysts and solvents does not allow the process to stay within the peripheries of a limited budget. In addition to this considering environmental and time perspective the process of combining solvent and catalysts cannot be believed to be undoubtly beneficial, the recovery of catalysts requiring a lot of solvent, time and purification based upon special methods could be termed as potent reasons. In the recent past reactions mediated with glycerol astonishing attention as glycerol is a solvent which is easily available and costs virtually nothing. In addition to this it does not distort the environmental processes. Not a long time ago, it was found that glycerol has been used for Heck and Suzuki coupling [26-28], Michael addition [29], Fridel-Crafts type addition, epoxide ring opening [30], synthesis of xanthenes [31] and very recently for the production of benzodiazepines and octahydroacridines [32,33]. Understanding the magnanimity of both 1,4-DHP's and glycerol, a new clean and green protocol has been discussed. In this effort, we synthesize 1,4-DHP's using glycerol as green solvent without amalgamatingany catalyst (Scheme 1). The present protocol is found to be much efficient over other procedure.

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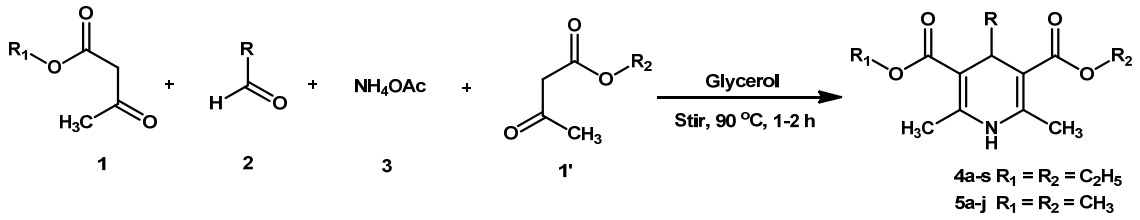
Table 1. Effect of temperature on the synthesis of compounds **4a**.

S. No.	Compound	Temperature (°C)	Time (minutes)	Yield [a] (%)
1	4a	70	110	78
2	4a	80	85	83
3	4a	90	75	94
4	4a	100	74	94
5	4a	110	74	93

[a] Yield refer to combined amounts of different crops.



Scheme 1

2. Experimental

2.1. Instrumentation

Materials were obtained from commercial suppliers and were used without further purifications. Melting points were recorded in open end capillaries and are uncorrected. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker Avance II 400 MHz spectrometer; chemical shifts (delta) are reported in ppm relative to TMS as internal standard. The mass spectrum and IR spectra were recorded at LC-MS Spectrometer Model Q-ToF Micro Waters and Perkin-Elmer Spectrum II infra-red spectrophotometer, respectively. Elemental analyses (C, H, and N) were performed using a Thermo Scientific elemental analyser.

2.2. Synthesis

2.2.1. Synthesis of diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

In a conical flask benzaldehyde (0.01 mol), ethyl acetoacetate (0.02 mol) and ammonium acetate (0.02 mol) were taken in a pre-heated glycerol (10 mL) and stirred at 90 °C for the stipulated time Table 1. After the completion of reaction (*vide* TLC), reaction mixture was cooled to room temperature and added 50 mL ice-cold water, solid separated out. Filtered and dried, recrystallized from ethanol to afford compound **4a**, 94% yield, m.p.: 159-160 °C (Entry 1, Table 2). Similarly, other aldehydes **2b-k** were reacted with ethyl/methyl acetoacetate and ammonium acetate to afford various 1,4-dihydropyridines derivatives **4b-q** and **5a-k** (Table 2). Data obtained using advanced spectral techniques for some selected compounds have been summarized.

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**): Yield: 94%. M.p.: 159-160 °C. FT-IR (KBr, ν, cm^{-1}): 3340 ν(N-H Str.), 1695 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.21 (t, 6H, 2 x CH_3), 2.36 (s, 6H, 2 x CH_3), 4.11 (q, 4H, 2 x CH_2CH_3), 4.98 (s, 1H, C-H), 6.01 (br s, 1H, N-H), 7.16-7.33 (m, 5H, Ar-H). MS (EI, *m/z,* (%)): 330 (M$^+$, 24). Anal. calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.25; H, 7.00; N, 4.24%.

Diethyl 2,6-dimethyl-4-(4-methoxyphenyl)-1,4-dihydro pyridine-3,5-dicarboxylate (**4c**): Yield: 93%. M. p.: 158-160 °C. FT-IR (KBr, ν, cm^{-1}):3327 ν(N-H Str.), 1699 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.23 (t, 6H, 2 x CH_3), 2.32 (s, 6H, 2 x CH_3), 3.57 (s, 3H, OCH_3), 4.15 (q, 4H, 2 x CH_2CH_3), 4.95 (s, 1H, C-H), 6.11 (br s, 1H, N-H), 7.01-7.22 (m, 4H, Ar-H). MS (EI, *m/z,* (%)): 360 (M$^+$, 25). Anal. calcd. for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.81; H, 6.99; N, 3.89%.

Diethyl 2,6-dimethyl-4-(3,4-dimethoxyphenyl)-1,4-dihydro pyridine-3,5-dicarboxylate (**4d**): Yield: 95%. M.p.: 148-150 °C. FT-IR (KBr, ν, cm^{-1}): 3341ν(N-H Str.), 1689 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.24 (t, 6H, 2 x CH_3), 2.31 (s, 6H, 2 x CH_3), 3.79 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3) , 4.12 (q, 4H, 2 x CH_2CH_3), 4.90 (s, 1H, C-H), 5.80 (br s, 1H, N-H), 6.73-6.89 (m, 3H, Ar-H). MS (EI, *m/z,* (%)): 390 (M$^+$, 25). Anal. calcd. for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.75; H, 6.97; N, 3.58%.

Diethyl 2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydro pyridine-3,5-dicarboxylate (**4e**): Yield: 91%. M.p.: 184-186 °C. FT-IR (KBr, ν, cm^{-1}): 3356 ν(N-H Str.), 1704 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.21 (t, 6H, 2 x CH_3), 2.30 (s, 6H, 2 x CH_3), 3.78 (s, 3H, OCH_3), 3.82 (s, 6H, 2 x OCH_3) 4.11 (q, 4H, 2 x CH_2CH_3), 4.93 (s, 1H, C-H), 5.91 (br s, 1H, N-H), 6.52 (s, 2H, Ar-H). MS (EI, *m/z,* (%)): 420 (M$^+$, 26). Anal. Calcd. for $C_{22}H_{29}NO_7$: C, 62.99; H, 6.97; N, 3.34. Found: C, 62.96; H, 6.94; N, 3.31%.

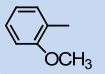
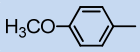
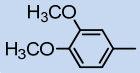
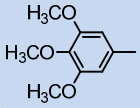
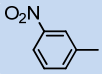
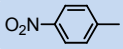
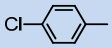
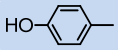
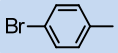
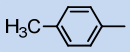
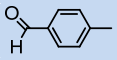
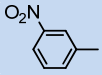
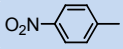
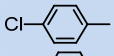
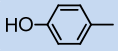
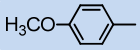
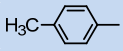
Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**4g**): Yield: 93%. M.p.: 155-166 °C. FT-IR (KBr, ν, cm^{-1}): 3343 ν(N-H Str.), 1703 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.25 (t, 6H, 2 x CH_3), 2.36 (s, 6H, 2 x CH_3), 4.11 (q, 4H, 2 x CH_2CH_3), 5.01 (s, 1H, C-H), 6.08 (br s, 1H, N-H), 7.10-7.57 (m, 4H, Ar-H). MS (EI, *m/z,* (%)): 375 (M$^+$, 26). Anal. calcd. for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.93; H, 5.90; N, 7.47%.

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**4h**): Yield: 92%. M.p.: 159-160 °C. FT-IR (KBr, ν, cm^{-1}): 3350 ν(N-H Str.), 1699 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm):1.27 (t, 6H, 2 x CH_3), 2.33 (s, 6H, 2 x CH_3), 4.13 (q, 4H, 2 x CH_2CH_3), 5.09 (s, 1H, C-H), 6.09 (br s, 1H, N-H), 7.16-7.44 (m, 4H, Ar-H). MS (EI, *m/z,* (%)): 375 (M$^+$, 25). Anal. calcd. for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.92; H, 5.91; N, 7.44%.

Diethyl 2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**4i**): Yield: 90%. M.p.: 138-139 °C. FT-IR (KBr, ν, cm^{-1}): 3339 ν(N-H Str.), 1699 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm):1.19 (t, 6H, 2 x CH_3), 2.31 (s, 6H, 2 x CH_3), 4.07 (q, 4H, 2 x CH_2CH_3), 5.08 (s, 1H, C-H), 5.97 (br s, 1H, N-H), 7.29-7.58 (m, 4H, Ar-H). MS (EI, *m/z,* (%)): 364 (M$^+$, 23). Anal. calcd. for $C_{19}H_{22}ClNO_4$: C, 62.72; H, 6.09; N, 3.85. Found: C, 62.71; H, 6.05; N, 3.84%.

Diethyl 2,6-dimethyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**4j**): Yield: 93%. M.p.: 147 °C. FT-IR (KBr, ν, cm^{-1}): 3332 ν(N-H Str.), 1693 ν(C=O Str.).

Table 2. Synthesis of symmetrical 1,4-dihydropyridine derivative.

S. No.	Product [a]	R	R^1	R^2	Yield [b] (%)	Melting point (°C)	Lit. melting point (°C)	Reference
1	4a		C_2H_5	C_2H_5	94	159-160	158-160	[37]
2	4b		C_2H_5	C_2H_5	91	139-141	138-143	[35]
3	4c		C_2H_5	C_2H_5	93	158-160	158-160	[37]
4	4d		C_2H_5	C_2H_5	95	148-150	147	[38]
5	4e		C_2H_5	C_2H_5	91	184-186	182-84	[38]
6	4f		C_2H_5	C_2H_5	85	120-123	118	[38]
7	4g		C_2H_5	C_2H_5	93	165-166	163	[37]
8	4h		C_2H_5	C_2H_5	92	134-135	136	[37]
9	4i		C_2H_5	C_2H_5	90	138-139	140-142	[37]
10	4j		C_2H_5	C_2H_5	93	147	144-146	[37]
11	4k		C_2H_5	C_2H_5	87	181-183	180-182	[34]
12	4l		C_2H_5	C_2H_5	89	230-231	228-230	[34]
13	4m		C_2H_5	C_2H_5	92	155-156	160-162	[37]
14	4n		C_2H_5	C_2H_5	91	138-139	135-137	[36]
15	4o		C_2H_5	C_2H_5	88	162-165	160-161	[37]
16	4p		C_2H_5	C_2H_5	89	173-175	171-173	[37]
17	4q		C_2H_5	C_2H_5	85	137-139	136-138	[38]
18	4r	H–	C_2H_5	C_2H_5	94	181-182	183	[39]
19	4s	H_3C–	C_2H_5	C_2H_5	89	132-133	130-131	[36]
20	5a		CH_3	CH_3	92	199-200	197-98	[40]
21	5b		CH_3	CH_3	87	172-174	171-172	[40]
22	5c		CH_3	CH_3	90	157-159	155-58	[40]
23	5d		CH_3	CH_3	93	152-153	152-154	[40]
24	5e		CH_3	CH_3	91	191-193	195-96	[40]
25	5f		CH_3	CH_3	89	200-201	198-199	[40]
26	5g		CH_3	CH_3	88	172-175	173-174	[40]
27	5h		CH_3	CH_3	90	177-180	175-176	[40]
28	5i		CH_3	CH_3	84	147-149	148-150	[40]
29	5j	H_3C–	CH_3	CH_3	85	220-222	224-25	[40]

[a] Products were characterized with spectral techniques and compared with authentic samples.
[b] Yield refer to combined amounts of different crops.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.23 (t, 6H, 2 x CH_3), 2.36 (s, 6H, 2 x CH_3), 4.13 (q, 4H, 2 x CH_2CH_3), 5.11 (s, 1H, C-H), 5.99 (br s, 1H, N-H), 7.30-7.57 (m, 4H, Ar-H). MS (EI, *m/z,* (%)): 364 (M^+, 24). Anal. calcd. for $C_{19}H_{22}ClNO_4$: C, 62.72; H, 6.09; N, 3.85. Found: C, 62.71; H, 6.08; N, 3.82%.

Diethyl 2,6-dimethyl-4-(3-hydroxyphenyl)-1,4-dihydro pyridine-3,5-dicarboxylate (**4k**): Yield: 87%. M.p.: 181-183 °C. FT-IR (KBr, ν, cm^{-1}): 3430 ν(O-H Str.), 3331 ν(N-H Str.), 1690 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.27 (t, 6H, 2 x CH_3), 2.21 (s, 6H, 2 x CH_3), 4.10 (q, 4H, 2 x CH_2CH_3), 4.99 (s, 1H, C-H), 5.98 (br s, 1H, N-H), 7.10-7.34 (m, 4H, Ar-H), 9.79 (br, s, 1H, O-H). MS (EI, *m/z,* (%)): 346 (M^+, 19). Anal. calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.06; H, 6.68; N, 4.03%.

Diethyl 2,6-dimethyl-4-(4-hydroxyphenyl)-1,4-dihydro pyridine-3,5-dicarboxylate (**4l**): Yield: 89%. M.p.: 181-183 °C. FT-IR (KBr, ν, cm^{-1}): 3447 ν(O-H Str.), 3338 ν(N-H Str.), 1701 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm):1.19 (t, 6H, 2 x CH_3), 2.30 (s, 6H, 2 x CH_3), 4.07 (q, 4H, 2 x CH_2CH_3), 5.01 (s, 1H, C-H), 6.08 (br s, 1H, N-H), 7.18-7.54 (m, 4H, Ar-H), 9.81 (br, s, 1H, O-H). MS (EI, *m/z,* (%)): 346 (M^+, 21). Anal. calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.02; H, 6.71; N, 4.04%.

Diethyl 2,6-dimethyl-4-(4-bromophenyl)-1,4-dihydro pyridine-3,5-dicarboxylate (**4m**): Yield: 92%. M.p.: 155-156 °C. FT-IR (KBr, ν, cm^{-1}): 3336 ν(N-H Str.), 1703 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm):1.21 (t, 6H, 2 x CH_3), 2.29 (s, 6H, 2 x CH_3), 4.09 (q, 4H, 2 x CH_2CH_3), 5.03 (s, 1H, C-H), 6.07 (br s, 1H, N-H), 7.13-7.51 (m, 4H, Ar-H). MS (EI, *m/z,* (%)): 409 (M^+, 25). Anal. calcd. for $C_{19}H_{22}BrNO_4$: C, 55.89; H, 5.43; N, 3.43. Found: C, 55.88; H, 5.41; N, 3.39%.

Diethyl 2,6-dimethyl-4-(4-methylphenyl)-1,4-dihydro pyridine-3,5-dicarboxylate (**4n**): Yield: 91%. M.p.: 138-139 °C. FT-IR (KBr, ν, cm^{-1}): 3329 ν(N-H Str.), 1695 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.20 (t, 6H, 2 x CH_3), 2.19 (s, 3H, CH_3), 2.21 (s, 6H, 2 x CH_3), 4.03 (q, 4H, 2 x CH_2CH_3), 5.07 (s, 1H, C-H), 5.98 (br s, 1H, N-H), 7.15-7.53 (m, 4H, Ar-H). MS (EI, *m/z,* (%)): 343 (M^+, 20). Anal. calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.88; H, 7.31; N, 4.02%.

Diethyl 2,6-dimethyl-4-(2-furyl)-1,4-dihydropyridine-3,5-dicarboxylate (**4o**): Yield: 88%. M.p.: 162-165 °C. FT-IR (KBr, ν, cm^{-1}): 3335 ν(N-H Str.), 1701 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm):1.27 (t, 6H, 2 x CH_3), 2.31 (s, 6H, 2 x CH_3), 4.17 (q, 4H, 2 x CH_2CH_3), 4.99 (s, 1H, C-H), 6.07 (br s, 1H, N-H), 6.33-6.42 (m, 2H, Furyl-H), 7.17 (m, 1H, Furyl-H). MS (EI, *m/z,* (%)): 320 (M^+, 16). Anal. calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.92; H, 6.62; N, 4.37%.

Diethyl 2,6-dimethyl-4-(2-theniyl)-1,4-dihydropyridine-3,5-dicarboxylate (**4p**): Yield: 89%. M.p.: 173-175 °C. FT-IR (KBr, ν, cm^{-1}): 3345 ν(N-H Str.), 1699 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.17 (t, 6H, 2 x CH_3), 2.30 (s, 6H, 2 x CH_3), 4.06 (q, 4H, 2 x CH_2CH_3), 5.01 (s, 1H, C-H), 6.06 (br s, 1H, N-H), 6.09-6.14 (m, 2H, Thienyl-H), 6.89 (m, 1H, Thienyl-H). MS (EI, *m/z,* (%)): 336 (M^+, 18). Anal. calcd. for $C_{17}H_{21}NO_4S$: C, 60.87; H, 6.31; N, 4.18. Found: C, 60.85; H, 6.29; N, 4.17%.

Diethyl 2,6-dimethyl-4-(4-formylphenyl)-1,4-dihydro pyridine-3,5-dicarboxylate (**4q**): Yield: 85%. M.p.: 137-139 °C. FT-IR (KBr, ν, cm^{-1}): 3349 ν(N-H Str.), 1706 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.19 (t, 6H, 2 x CH_3), 2.32 (s, 6H, 2 x CH_3), 4.07 (q, 4H, 2 x CH_2CH$_3$), 5.02 (s, 1H, C-H), 5.96 (br s, 1H, N-H), 7.49-7.80 (m, 4H, Ar-H), 8.92 (s, 1H, CHO). MS (EI, *m/z,* (%)): 358 (M^+, 23). Anal. calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.20; H, 6.47; N, 3.89%.

Dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**5a**): Yield: 92%. M.p.: 199-200 °C. FT-IR (KBr, ν, cm^{-1}): 3320 ν(N-H Str.), 1690 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.25 (s, 6H, 2 x CH_3), 3.68 (s, 6H, 2 x CH_3), 4.99 (s, 1H, C-H), 6.04 (br s, 1H, N-H), 6.94-7.34 (m, 5H, Ar-H). MS (EI, *m/z,* (%)): 302 (M^+, 25). Anal. calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.72; H, 6.34; N, 4.65%.

Dimethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydro pyridine-3,5-dicarboxylate (**5d**): Yield: 93%. M.p.: 152-153 °C. FT-IR (KBr, ν, cm^{-1}): 3342 ν(N-H Str.), 1707 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.28 (s, 6H, 2 x CH_3), 3.74 (s, 6H, 2 x CH_3), 5.03 (s, 1H, C-H), 6.07 (br s, 1H, N-H), 7.12-7.51 (m, 4H, Ar-H). MS (EI, *m/z,* (%)): 347 (M^+, 24). Anal. calcd. for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.94; H, 5.22; N, 8.08%.

Dimethyl 2,6-dimethyl-4-(4-chlorophenyl)-1,4-dihydro pyridine-3,5-dicarboxylate (**5e**): Yield: 91%. M.p.: 191-193 °C. FT-IR (KBr, ν, cm^{-1}): 3317 ν(N-H Str.), 1700 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.26 (s, 6H, 2 x CH_3), 3.70 (s, 6H, 2 x CH_3), 5.02 (s, 1H, C-H), 6.01 (br s, 1H, N-H), 7.01-7.37 (m, 4H, Ar-H). MS (EI, *m/z,* (%)): 336 (M^+, 25). Anal. calcd. for $C_{17}H_{18}ClNO_4$: C, 60.81; H, 5.40; N, 4.17. Found: C, 60.79; H, 5.35; N, 4.15%.

Dimethyl 2,6-dimethyl-4-(4-methoxyphenyl)-1,4-dihydro pyridine-3,5-dicarboxylate (**5g**): M.p.: 172-175 °C. FT-IR (KBr, ν, cm^{-1}): 3295 ν(N-H Str.), 1691 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.23 (s, 6H, 2 x CH_3), 3.68 (s, 6H, 2 x OCH_3), 3.92 (s, 3H, OCH_3), 4.97 (s, 1H, C-H), 5.94 (br s, 1H, N-H), 6.89-7.25 (m, 4H, Ar-H). MS (EI, *m/z,* (%)): 332 (M^+, 24). Anal. calcd. for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.22; H, 6.38; N, 4.20%.

Dimethyl 2,6-dimethyl-4-(4-methylphenyl)-1,4-dihydro pyridine-3,5-dicarboxylate (**5h**): Yield: 90%. M.p.: 177-180 °C. FT-IR (KBr, ν, cm^{-1}): 3312 ν(N-H Str.), 1689 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.18 (s, 3H, CH_3)2.24 (s, 6H, 2 x CH_3), 3.66 (s, 6H, 2 x CH_3), 4.96 (s, 1H, C-H), 5.92 (br s, 1H, N-H), 6.90-7.31 (m, 4H, Ar-H). MS (EI, *m/z,* (%)): 316 (M^+, 23). Anal. calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.54; H, 6.69; N, 4.41%.

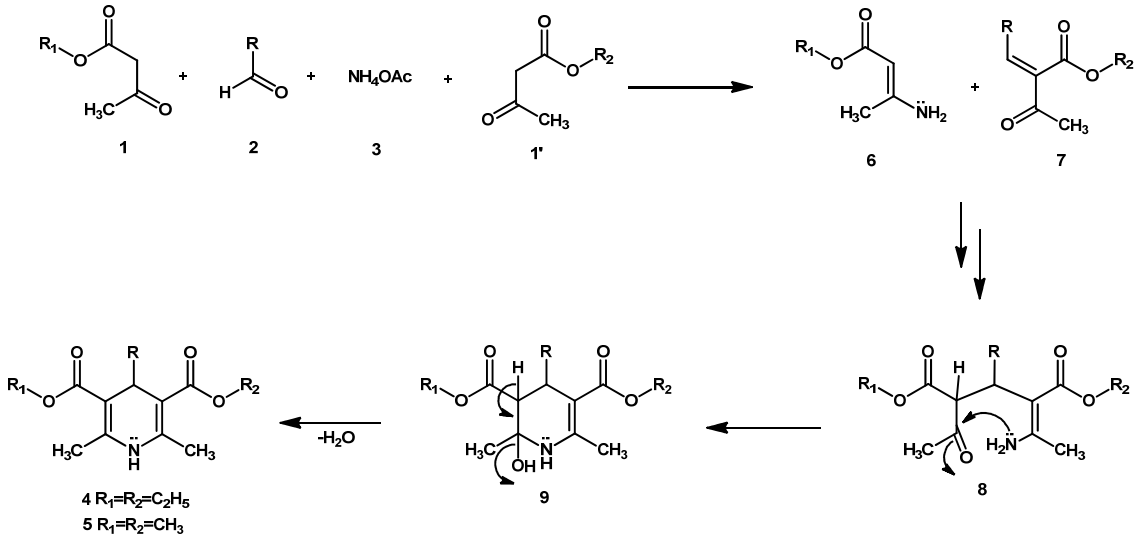
Dimethyl 2,6-dimethyl-4-(2-furyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5i**): Yield: 84%. M.p.: 147-149 °C. FT-IR (KBr, ν, cm^{-1}): 3317 ν(N-H Str.), 1700 ν(C=O Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.20 (s, 6H, 2 x CH_3), 3.65 (s, 6H, 2 x CH_3), 4.98 (s, 1H, C-H), 6.05 (br s, 1H, N-H), 6.33-6.45 (m, 2H, Furyl-H), 7.22 (m, 1H, Furyl-H). MS (EI, *m/z,* (%)): 292 (M^+, 18). Anal. calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.82; H, 5.87; N, 4.78%.

3. Results and discussion

Condensation of ethylacetoacetate (**1**), benzaldehyde (**2a**) and ammonium acetate (**3**) were carried out in glycerol at different temperatures (70-110 °C). It was observed that 90 °C is the optimal temperature for the synthesis of 1,4-dihydropyridines. Further rise in temperature had a negligible impact on rate and yield of the reaction (Table 1)

The structure of the compound **4a** was confirmed with the use of spectral techniques. In IR spectrum absorption at 3340 cm^{-1} represents the N-H stretching, a strong absorption for C=O groups was observed at 1695 cm^{-1}. In ^{1}H NMR spectra peaks for five aromatic protons are observed at δ 7.16-7.33 ppm, singlet at δ 4.98 ppm for -CH proton, singlet at δ 6.01 ppm for -NH proton and a singlet for two -CH_3groups observed at δ 2.36 ppm, a triplet for two -CH_3groups observed at δ1.21 ppm and a quartet for two -CH_2 groups was observed at δ 4.11 ppm. Spectral data of compound **4a** fully supports the structure assigned to it. Similarly, other dialkyl-2,6-dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylate **4b**-**p** and **5a**-**k** have been synthesized by the condensation of ethyl/methyl acetoacetate (**1**), aldehyde (**2**) and ammonium acetate (**3**) in glycerol. The results are summarized in Table 2.

In the proposed mechanism, for the synthesis of dihydropyridines follow the addition of compound **1** and **3** to give compound **6** by the removal of an acetic acid molecule and at the same time Knoevenagal condensation between compounds **1** and **2** to give compound **7**, which upon Michael addition with compound **6** produce compound **8** them followed



Scheme 2

by cyclization to produce **9** and rearrange to yield the 1,4-DHP molecule (**4a-s** and **5a-j**) (Scheme 2).

Reactions proceeded smoothly with aldehydes carrying electron withdrawing as well as electron donating substituents (Table 2). This method endures various functionalities like nitro, ether, halogen etc. on the aldehydes. Efficacy of this method is fairly general and affords the resultant products in excellent yield (85-95%) and products are obtained by simple work up.

4. Conclusion

The present procedure is an effective method for production of tetra substituted 1,4-dihydropyridine from readily available starting materials in a single step with inherent flexibility and diversity. This method was efficacious to reduce labor, cost, waste production and also devoid of harsh reaction conditions. The target compounds were obtained in an acceptable yield with simple recrystallization as a purification step.

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