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Facile and Efficient One-Pot Synthesis of Polyhydroquinoline Derivatives via Unsymmeterical Hantzsch Condensation under Solvent-Free Conditions

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Abstract

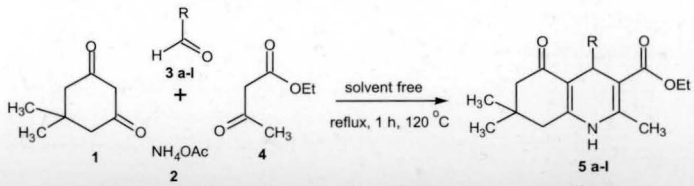
An efficient, one-pot synthesis of polyhydroquinolines has been achieved via four-component reaction of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate under solvent free conditions. The present protocol is catalyst-free and affords the desired polyhydroquinolines in excellent yield. Further advantages of the present study are short reaction time, simple workup procedures, and purification of products by simple recrystallization.

Keywords: One-pot, polyhydroquinoline, solvent free, dimedone, Hantzsch condensation

Introduction

The dihydropyridine (DHPs) ring system is of considerable interest because of its presence in the coenzyme, diphosphopyridine nucleotide (DPNH) [1]. 1, 4-dihydropyridines(1, 4-DHPs) are the important class of Ca^{2+} channel blockers and are also known to be effective cardiovascular agents for the treatment of hypertension apart from these activities DHPs are found to be as PAF-acether antagonists [2], calcium antagonists [3], antihypertensives [4], cerebral antischemic activity in the treatment of Alzheimer's disease and chemosensitizer acting in tumor therapy.

Being precursor of many drug molecules, the synthesis and evaluation of this class of compounds is of considerable interest for chemists and biologists. As a result preparation of these molecules have been reported using various catalysts such as trimethylsilyl chloride (TMSCl) [5], ionic liquid [6,7], silica supported perchloric acid ($HClO_4$-SiO_2) [8], HY-Zeolite [9], montmorillonite K-10 [10], cerium (IV) ammonium nitrate [11], iron(III) trifluoroacetate [12], heteropoly acid [13], $Sc(OTf)_3$ [14], *p*-TSA [15], TiO_2 [16] and FeF_3 [17] under varied reaction conditions like conventional heating [18], light or microwave irradiation and ultrasounds [19-21]. The already reported methods have few advantages like improvisation in product yield, minimizing the wastage of chemicals and recyclisation of the catalyst. But these protocols have one or another disadvantage like, collection and purification of catalyst that may cause harmful effects, harsh reaction conditions, use of harmful solvents, etc. Therefore, development of a clean, green and efficient procedure is still timely and hence, in continuation of our work on nitrogen heterocycles [22-23] we here by present one-pot, solvent free synthesis of polyhydroquinolines (Scheme 1).



Scheme 1. Synthesis of polyhydroquinolines

Results and Discussion

In a pilot experiment dimedone 1, benzaldehyde 3a, ammonium acetate 2 and ethyl acetoacetate 4 heated to synthesize Ethyl-2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate 5a under solvent free conditions. In course of reaction optimisation, 120°C is found to be the optimum temperature for the smooth progress of the reaction. Decrease in the temperature, decreases the rate of reaction while increase in temperature resulted into decomposition (entry 5-6) of the product (Table 1).

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Table 1. Effect of reaction temperature on the synthesis of 5a

S. No.	Temperature	Yield (%)	Time
1	60	72	7
2	80	81	4
3	100	88	3
4	120	90	1
5	140	84	1
6	160	77	1

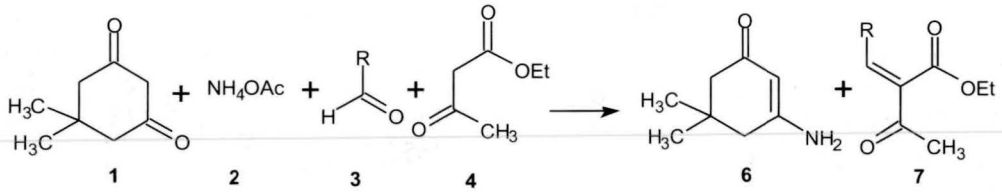
The structure of the compound 5a was confirmed by the advanced spectral techniques. In IR spectrum absorption at 3287 cm^{-1} represent the N-H stretching, while absorption at 3078 and 2963 cm^{-1} represent the sp^2 and sp^3 hybridised C-H stretching, respectively. Strong absorptionpeaks for C=O are observed at 1718 and 1740 cm^{-1}. In ^1H NMR spectra peaks for five aromatic protons are observed at □7.08-7.33, peak at □ 6.64 for -NH proton and three singlet for CH_3 groups are observed at □ 0.94 and □ 1.07, □2.35. Spectral data of 5a fully supports the structure assigned to it. After optimizing the conditions, we next examined the generality of this procedure to other substrates using dimedone, ethyl acetoacetate, ammonium acetate with different aromatic aldehydes (3b-l) using the similar procedure to obtain 5b-l in excellent yield and with high purity. The results are summarised in table 2.

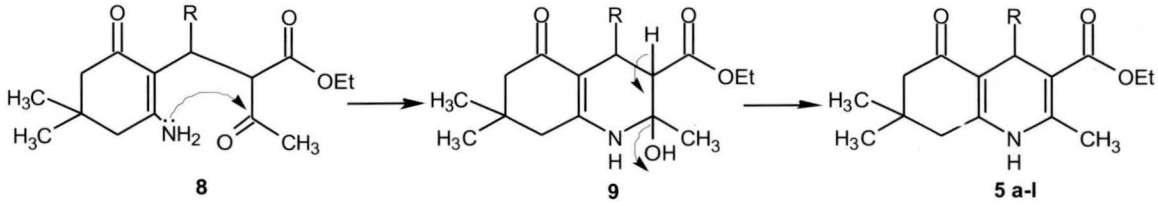
Table 2. Synthesis of polyhydroquinoline derivatives 5a-l.

S.No.	Product#	R	Yield(%)	Melting point(°C)	Lit. melting point(°C)
1	5a	C_6H_5	90	203-204	204-205[8]
2	5b	4-Cl C_6H_4	92	243-245	245-246[7]
3	5c	2-Cl C_6H_4	93	208-209	208-210[16]
4	5d	4-$NO_2C_6H_4$	91	240-242	242-244[7]
5	5e	2-$NO_2C_6H_4$	90	207-209	206-208[8]
6	5f	3-$NO_2C_6H_4$	92	177-179	177-178[16]
7	5g	4-OHC_6H_4	89	232-233	232-234[7]
8	5h	4-$OMeC_6H_4$	87	260-261	258-259[8]
9	5i	C_6H_5CH=CH	83	207-209	206-207[8]
10	5j	2-furyl	88	247-248	248-249[8]
11	5k	4-MeC_6H_4	92	261-262	260-262[8]
12	5l	4-$N(CH_3)_2C_6H_4$	91	230-232	233-234[5]

#All products were characterized from their spectroscopic (IR, ^1H NMR, ^{13}C-NMR, and MS) data and compared with authentic samples.

In the proposed mechanism for the synthesis of polyhydroquinoline (Scheme 2), the addition of 1 and 2 give 6 with the loss of an acetic acid molecule and Knoevenagal condensation between 3 and 4 give enone 7.Then Michael addition of 6 to 7 followed by cyclization generate 9 and





Scheme 2. Plausible mechanism for the synthesis of polyhydroquinolines

finally undergoes dehydration to yield the target molecule 5. In this study, aldehydes carrying different electron donating and electron withdrawing functional groups were employed. The reactions of aldehydes having electron withdrawing groups were completed in shorter time in comparison to those carrying electron donating groups. In all cases the desired product were obtained in high yield (83-93%) without the formation of any side product.

Experimental

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 $CDCl_3$ solution on a Bruker Avance II 400 MHz spectrometer; chemical shifts (delta) are reported in ppm relative to TMS as internal standard. The IR spectra were obtained on a Perkin-Elmer 237B spectrometer.

Synthesis of Ethyl-2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate 5a

In a conical flask, benzaldehyde (0.01 mol), dimedone (0.01 mol), ethyl acetoacetate (0.01 mol) and ammonium acetate (0.02 mol) were mixed and heated at 120°C for the stipulated time (Table 2) After the completion of reaction (vide TLC), reaction mixture was cooled to room temperature and added 10 ml EtOH then pour the content of the flask in ice-cold water, solid separated out. Solid thus obtained was filtered, dried and recrystallized from ethanol to afford colourless compound 5a, 90 % yield, mp 203-204°C (lit.[8] 204-205°C) (entry 1, Table 2). Similarly, other aldehydes 3b-l were reacted with dimedone, ethyl acetoacetate and ammonium acetate to afford various polyhydroquinoline derivatives 5b-l (Table 2).

Characterization And Spectral Data For Some Selected Compounds

1. Ethyl-2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5a

Mp = 203-204°C. ^{1}H NMR (400 MHz, DMSO-d6): □ = 0.94 (s, 3H), 1.07 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H), 2.13-2.29 (m, 4H), 2.35 (s, 3H), 4.06 (q, J = 7.1 Hz, 2H), 5.07 (s, 1H), 6.64 (br s, 1 H, NH), 7.08-7.33 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d6): □ = 12.9, 17.9, 25.8, 28.1, 31.3, 35.3, 39.6, 49.5, 58.5, 104.7, 110.7, 124.7, 126.5, 126.7, 142.4, 145.8, 147.4, 166.2, 194.4. IR (KBr): 3287, 3078, 2963, 1718, 1740 cm^{-1}. MS (EI)m/z 340 (M+).

2. Ethyl-4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5b

Mp = 243-245°C. ^{1}H NMR (400 MHz, DMSO-d6): □ = 0.94 (s, 3H), 1.08 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H), 2.12-2.34 (m, 4H), 2.37 (s, 3H), 4.04 (q, J = 7.1 Hz, 2H), 5.04 (s, 1H), 6.46 (br s, 1 H, NH), 7.15-7.19 (d, J = 8.1 Hz, 2 H), 7.24-7.26 (d, J = 8.1 Hz, 2 H). ^{13}CNMR(100 MHz, DMSO-d6): □ = 12.9, 18.0, 25.8, 28.1, 31.3, 34.9, 39.6, 49.4, 58.6, 104.4, 110.4, 126.4, 128.1, 130.3, 142.4, 144.3, 147.2, 165.9, 194.3. IR (KBr): 3276, 3199, 3077, 2964, 1716, 1738 cm^{-1}. MS (EI)m/z 374 (M+).

3. Ethyl-4-(4-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5d

Mp = 240- 242°C. ^{1}H NMR (400 MHz, DMSO-d6):□ = 0.89 (s, 3H), 1.09 (s, 3H), 1.08 (t, J = 7.3 Hz, 3H), 2.05-2.25 (m, 4H,), 2.37 (s, 3H), 4.00 (q, J = 7.3 Hz, 2H), 5.05 (s, 1H), 6.01 (br s, 1 H, NH) 7.42 (d, J = 9.2 Hz, 2H), 8.05 (d, J = 9.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d6): □ = 12.9, 18.1, 25.7, 28.1, 31.4, 35.7, 39.5, 49.3, 58.7, 103.7, 109.7, 119.9, 121.5, 127.3, 133.5, 143.4, 146.9, 148.1, 165.7, 194.3. IR (KBr): 3506, 3285, 3193, 2447, 1720, 1740 1518, 1484, 1306, 1284, 1166, 870, 755 cm^{-1}. MS (EI)m/z 385 (M+).

4. Ethyl-4-(3-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5f

Mp 177-179°C.^{1}H NMR (400MHz, DMSO-d6) □□ 0.93 (s, 3H), 1.07 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H), 2.12-2.41 (m, 7H), 3.69 (q, J = 7.1 Hz, 2H), 5.15 (s, 1H), 6.86 (s, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.96 (m, 1H), 7.98 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d6): □ = 12.9, 18.1, 25.7, 28.1, 31.4, 35.7, 39.5, 49.3, 58.7, 103.7, 109.7, 119.9, 121.5, 127.3, 133.5, 143.4, 146.9, 148.1, 165.7, 194.3. IR (KBr): 3506, 3285, 3193, 2447, 1719, 1740, 1484, 1306, 1284, 1166, 870, 755 cm^{-1}. MS (EI)m/z 385 (M+).

5. Ethyl-4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5g

Mp = 232-233°C. ^{1}H NMR (400 MHz, DMSO-d6): □ = 0.94 (s, 3H), 1.08 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H), 2.08-2.18 (m, 3H), 2.20-2.35 (m, 4H), 4.07 (q, J = 7.6 Hz, 2H), 4.98 (s, 1H), 5.62 (br s, 1 H, NH), 6.65 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d6): □ = 15.1, 19.1, 19.1, 27.4, 33.4, 36.7, 41.1, 51.7, 54.9, 60.2, 106.2, 112.6, 115.5, 130.1, 131.3, 140.4, 145.3, 149.7, 156.6, 168.4, 195.3. IR (KBr): 3331, 3122, 1718, 1737, 1495, 1234, 730 cm^{-1}. MS (EI)m/z 356 (M+).

6. Ethyl-4-(4-methoxyhenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5h

Mp = 260-261°C. ^{1}H NMR (400 MHz, DMSO-d6): □ = 0.94 (s, 3H), 1.07 (s, 3H), 1.21 (t, J = 7.2 Hz,3H), 2.13-2.36 (m, 7H), 3.74 (s, 3H), 4.06 (q, J = 7.2 Hz, 2H), 5.00 (s, 1H), 6.01 (br s, 1 H, NH), 6.74 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d6): □ = 14.2, 19.4, 27.1, 29.4, 32.6, 35.6, 41.1, 50.7, 55.1, 59.7, 106.3, 112.4, 113.2, 128.9, 139.5, 139.5, 143.1, 147.7, 157.7, 167.4, 195.5. IR (KBr): 3292, 3224, 3087, 2958, 1716, 1735, 1491 cm^{-1}. MS (EI)m/z 370 (M+).

7. Ethyl-4-styryl-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5i

Mp = 207-209°C. ^{1}H NMR (500 MHz, DMSO-d6): □ = 1.09 (s, 3H), 1.12 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 2.19-2.33 (m, 4H), 2.37 (s, 3H), 4.18 (q, J = 7.1 Hz, 2H), 4.71 (d, J = 6.1 Hz, 1H), 6.16 (dd, J = 16.2, and 6.1 Hz, 1H), 6.58 (d, J = 16.2 Hz, 1H), 6.23 (d, J = 7 Hz, 2H), 7.21-7.32 (m, 5H), 9.03 (br s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d6): □ = 13.1, 18.1, 25.8, 28.3, 31.3, 32.1, 39.7, 49.5, 54.1, 58.5, 102.7, 108.6, 109.5, 119.1, 121.8, 124.9, 125.4, 126.5, 130.8, 143.1, 147.2, 148.1, 166.3, 194.44. IR (KBr): 3335, 3180, 2949, 1719, 1741, 1432 cm^{-1}. MS (EI)m/z 366 (M+).

8. Ethyl-4-(furan-2-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5j

Mp = 247-248°C. ^{1}H NMR (400 MHz, DMSO-d6): □ = 1.01 (s, 3H), 1.10 (s, 3H), 1.25 (t, J = 7 Hz, 3H), 2.21-2.28 (m, 3H), 2.34-2.38 (m, 4H), 4.13 (q, J = 7 Hz, 2H), 5.20 (s, 1H), 5.81 (br s, 1 H, NH), 6.04-7.19 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d6): □ = 14.2, 19.3, 21.1, 27.5, 30.2, 36.9, 59.8, 103.1, 104.7, 110.1, 140.8, 144.2, 150.5, 157.9, 167.2, 195.5. IR (KBr): 3342, 3122, 1717, 1738, 1480, 1361, 1211, 1132 cm^{-1}. MS (EI)m/z 334 (M+).

9. Ethyl-4-(4-methylphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, 5k

Mp 261-262°C. ^{1}H NMR (400 MHz, DMSO-d6) □□ 0.94 (s, 3H), 1.08 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H), 2.10-2.24 (m, 4H), 2.26 (s, 3H), 2.37 (s, 3H), 4.06 (q, J = 7.1 Hz, 2H), 5.03 (s, 1H), 5.96 (s, 1H), 7.02 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d6): □ = 14.2, 19.4, 27.1, 29.4, 32.6, 35.6, 41.1, 50.7, 55.1, 59.7, 106.3, 112.4, 113.2, 128.9, 139.5, 139.5, 143.1, 147.7, 157.7, 167.4, 195.5. IR (KBr): 3292, 3224, 3087, 2958, 1715, 1740, 1491 cm^{-1}. MS (EI) m/z 354 (M+).

Conclusion

The present procedure is an effective method for the production of highly functionalized polyhydroquinolines from readily available starting materials in a single step with inherent flexibility and diversity. The target compounds were obtained in good to excellent yield (83-93%) with simple recrystallization as purification step. The present study have an edge over the previous reported methods of production of polyhydroquinolines in terms of minimization of cost, waste production, time and devoid of harsh reaction conditions.

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