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SYNTHESIS OF NEW DERIVATIVES OF 1,4-DIHYDROPYRIDINES USING GLYCEROL AS A SUSTAINABLE REACTION MEDIA AT AMBIENT TEMPERATURE

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Abstract: An efficient Hantzsch four-component condensation reaction for the green synthesis of new 1,4-dihydropyridines was found to proceed in the presence of glycerol at room temperature. The method is really simple and environmentally benign. The keys features of this protocol are high yields of products, nontoxic solvent, and short reaction times from the principles of green chemistry point of view.

Keywords: four-components, glycerol, dihydropyridines, synthesis, aldehydes

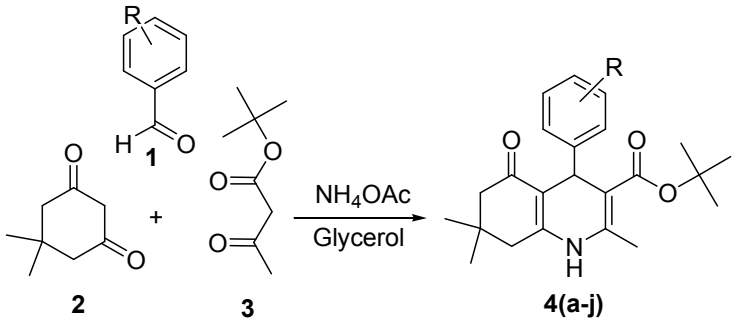
Introduction

Arthur Hantzsch 1,4- dihydropyridines, an important class of heterocyclic compounds first synthesized in 1882.[i] These compounds exhibit a wide range of biological and pharmacological actions including calcium channel blockers,[ii] antitumor[iii] anti-inflammatory [iv]and analgesic activities[v] and important drugs such as Diludine, Felodipine, Amlodipine, Nimodipin, and so are prepared and used worldwide.[vi]Very procedures for the synthesis of the mentioned compounds have been reported using various processes based on microwave assisted reaction,[vii] solar thermal energy,[viii] ultrasound irradiation,[ix] green solvents like ionic liquids or water or ethanol [x] solid support [xi] and Grignard reagent.[xii] It is noteworthy to observe that all these protocols have been accomplished under thermal reaction conditions and disposal of toxic solvents and catalysts often has a problem.

Recently, glycerin, which is easily available as a co-product in biodiesel production, has attracted attention as it is a versatile, cheap, and renewable feedstock in synthetic organic chemistry. [xiii]In addition, glycerol has also promising physical and chemical properties. It has a very high boiling point and negligible vapor pressure; it is compatible with most organic and inorganic compounds, and does not require special handling or storage.

In connection with our enduring interest for the synthesis of heterocyclic and organic compounds via green synthesis methods,[xiv - xvii]in the present investigation, to report here, for the first time, a highly efficient, rapid, and useful Hantzsch reaction for the synthesis of

unprecedented cyclic1,4-dihydropyridines using *tert*-butyl aceto acetate, dimedone, ammonium acetate and aromatic aldehydes in a one-pot four-component condensation reaction at room temperature in glycerol media (Scheme 1).



Scheme 1 Synthesis of 1,4-dihydropyridines

Results and discussion

The effect of the media on time and yield of the reaction was assessed (Table 1). The reaction does not proceed in the presence of H_2O at room temperature (Table 1, entry 1) while proceeded with low product yield in EtOH (Table 1, entry 2). Interestingly when the reaction was subjected in glycerol media (1 ml), the desired product was obtained in excellent yield and relatively short reaction time (Table 1, entry 3). Therefore, this sustainable reaction media was the optimum reaction condition for performing the reaction.

Table 1 The effect of reaction medium for the synthesis of (entry 1, Table 2)

Entry	Media (ml)	Time (h)	Yield%
1	H_2O (10)	48	-
2	EtOH (10)	24	60
3	Glycerol (1)	6	90

Reaction Condition: 4-Chlorobenzaldehyde(1 mmol), dimedone (1mmol), ammonium acetate(1mmol), *tert*-butyl acetoacetate(1mmol) in media at room temperature

To investigate the substrate scope, optimized reaction conditions were applied to various aldehydes in the presence of dimedone, ammonium acetate, *tert*-butyl acetoacetate in glycerol at ambient temperature. All the substrate variants reacted well and afforded high yields of new 1,4-dihydropyridines in relatively short reaction times (Table 2). Several electron-donating or electron-withdrawing substituents at the ortho, meta, and para position of aryl aldehydes have been examined (Table 2, entries 1–10). All products were obtained in high yields, and the reaction rate with electron-donating substituents and with electron-withdrawing ones on substrate was independent on nature of the substituent. The corresponding products were not observed using aliphatic aldehydes. On the basis of our knowledge, this 1,4-dihydropyridines did not presented using *tert*-butyl acetoacetate and all compounds were new. Therefore, the scope of the present protocol has been explored for the synthesis of new 1,4-dihydropyridines using glycerol as a sustainable reaction media at room temperature, short reaction times and high yields,

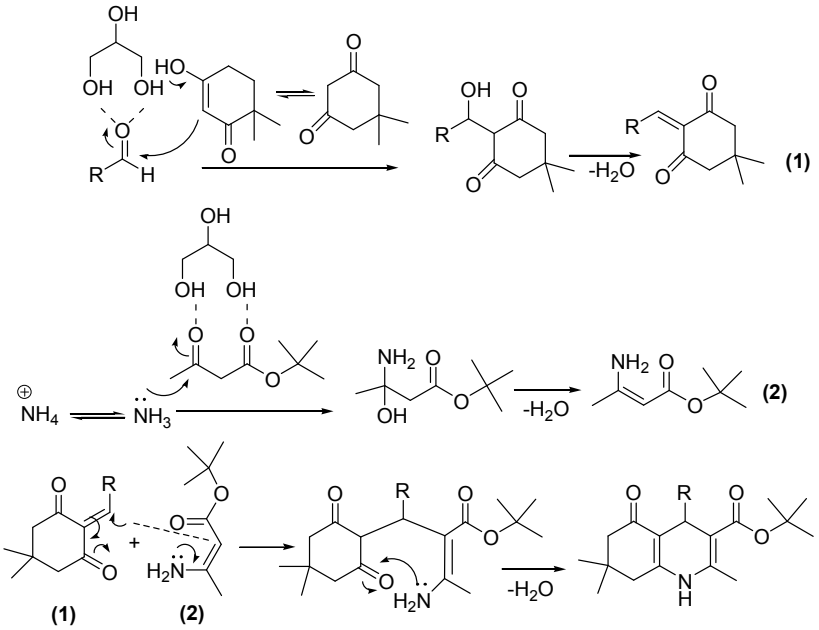
Table 2 Synthesis of new 1,4-dihydropyridines in glycerol medium

Entry	**R**	**Product**	**Yield %**[a]
1	4-Cl	**4a**	90

2	3-OH	**4b**	90
3	4-$N(CH_3)_2$	**4c**	90
4	2-OMe	**4d**	90
5	3-NO_2	**4e**	94
6	2,4-DiCl	**4f**	90
7	2-OH-OMe	**4g**	90
8	5-Br-2OH	**4h**	90
9	4-$(CH_3)_2CH$	**4i**	92
10	4-NO_2	**4j**	91

[a]Isolated yields at 6 h.

Proposed mechanism for the synthesis of 1,4- dihydropyridines has been shown in scheme 2.



Scheme 1 Suggested mechanism for the the synthesis of 1,4-dihydropyridines in glycerol medium.

Experimental

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on Perkin Elmer FT-IR spectrometer did scanning between 4000–400 cm^{-1}. ^1H NMR spectra were obtained on Bruker DRX-300MHz NMR instrument in $CDC1_3$. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60F-254 on aluminum).

General procedures. Preparation of new 1,4-dihydropyridines in glycerol: Aromatic aldehyde (1 mmol), *tert*-butyl acetoacetate (1 mmol), dimedone (1 mmol) and ammonium acetate (1 mmol) in glrcerol (1 mml) were mixed together in a round bottom flask at ambient temperature for 6 h. After completion of the reaction as indicated by TLC, water (20 ml) was added to the reaction mixture, and the obtained solid was filtered. The filtrate was washed with water (2 × 25 ml). In order to achieve highly pure 1,4-dihydropyridines the residues were recrystallized in ethanol.

Physical and spectra data for all compounds

***tert*-Butyl 4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (entry 1, Table 2):** Color yellow solid, m.p: 215 ºC, IR (KBr, cm^{-1}): 3312, 3247, 3216, 2961, 1699,1646. ^{1}HNMR ($CDCl_3$, 300 MHz): 0.89 (s, 3H, CH_3), 1.05 (s, 3H,

CH_3), 1.34 (t, 6H,C(CH_3)$_3$) 2.18- 2.23 (M, 4H, CH_2), 4.93 (s, 1H, CH), 6.16 (s, 1H, NH), 6.99-7.02 (m, 2H, CH), 7.13- 7.24 (m, 3H, Ar).

***tert*-Butyl 1,4,5,6,7,8-hexahydro-4-(3-hydroxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (entry 2, Table 2):** Color: Yellow, solid, , m.p: 130 ºC, IR (KBr) cm-1: 3329, 2963, 1698, 1598, 1485, 1381. ^{1}HNMR ($CDCl_3$, 300 MHz): 0.86 (s, 3H, CH_3), 1.002 (s, 3H, CH_3), 1.39 (s, 9H, C(CH_3)$_3$), 2.26- 2.38 (m, 4H, CH_2), 4.93 (s, 1H, CH), 6.5 (s, 1H, NH), 6.70 (s, 1H, OH), 7 (m, 4H, Ar).

***tert*-Butyl 4-(4-(dimethylamino)phenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (entry 3, Table 2):** Color: yellow, solid, , m.p: 190 ºC, IR (KBr) cm^{-1}: 3295, 2960, 1692, 1603, 1484, 1366, 1147, 810. ^{1}HNMR ($CDCl_3$, 300 MHz): 0.95 (s, 3H, CH_3) 1.06 (s, 3H, CH_3), 1.22 (s, 6H, CH_3), 1.36 (s, 9H, C(CH_3)$_3$), 2.16 -2.37(m, 4H, CH_2), 4.87(s, 1H, CH), 5.47 (s, 1H, NH), 6.58-6.74(m, 4H, CH_2), 6.92, 6.95(d, 2H, CH_2), 7.13-7.20 (d, 2H, CH_2).

***tert*-Butyl 1,4,5,6,7,8-hexahydro-4-(2-methoxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (entry 4, Table 2):** Color: yellow, solid, , m.p: 210 ºC, IR (KBr) cm^{-1}:3376,3299, 2929, 1690, 1609, 1488,1139,752. ^{1}HNMR ($CDCl_3$, 300 MHz): 0.89 (s, 3H, CH_3),1.02 (s, 3H, CH_3), 1.29 (s, 9H, C(CH_3)$_3$), 2.03-2.33 (m, 4H, CH_2),3.59 (s, 3H, CH_3),5.15 (s, 1H, CH), 6.21 (s, 1H, NH), 6.74-6.90 (m, 4H, Ar).

***tert*-Butyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-4-(3-nitrophenyl)-5-oxoquinoline-3-carboxylate (entry 5, Table 2):** Color: yellow, solid, m.p: 180 ºC IR (KBr) cm^{-1}: 3444, 3206, 30747, 2926, 1737,1698, 1600, 1529,1349, 1144. ^{1}HNMR ($CDCl_3$, 300 MHz): 0.90 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.34 (s, 9H, C(CH_3)$_3$), 2.30- 2.42 (m, 4H, CH_2), 5.06 (s, 1H, CH), 6.05 (s, 1H, NH), 7.26-7.99 (m, 4H, Ar).

***tert*-Butyl 4-(2,6-dichlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (entry 6, Table 2):** Color: Yellow, solid, m.p: 250 ºC IR (KBr) cm-1:3445, 3277, 2922, 1732, 1703, 1604, 1368, 111, 851. ^{1}HNMR ($CDCl_3$, 300 MHz): 0.99(s, 3H, CH_3), 1.04(s, 3H, CH_3), 1.29(s, 9H, C(CH_3)$_3$), 2.09-2.14(m, 4H, CH_2), 5.82(s, 1H, CH),5.99(s, 1H, NH),7.20-7.26 (m, 4H, Ar).

***tert*-Butyl 1,4,5,6,7,8-hexahydro-4-(2-hydroxy-3-methoxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (entry 7, Table 2):** Color: Yellow, solid, m.p: 110 ºC IR (KBr) cm-1: 3423, 3301, 3088, 2957, 2871, 1734, 1698, 1647, 1484, 1382,732. ^{1}HNMR ($CDCl_3$, 300 MHz): 0.87 (s, 3H, CH_3),0.98 (s, 3H, CH_3),1.20 (s, 9H, C(CH_3)$_3$), 2.23-2.26 (m, 4H, CH_2), 3.83 (s, 3H, CH_3), 4.66 (s, 1H, CH), 5.07 (s, 1H, NH), 6.59-6.64 (s, 1H, NH), 6.69-6.75 (m, 2H, CH_2), 6.86-6.96. (m, 4H, Ar).

***tert*-Butyl 4-(5-bromo-2-hydroxyphenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (entry 8, Table 2):** Color: Yellow, solid, m.p: 210 ºC IR (KBr) cm^{-1}: 3444, 3105, 2928, 2867, 1737, 1623, 1477, 1376, 1115, 819. ^{1}HNMR ($CDCl_3$, 300 MHz): 0.92(s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.01 (s, 9H, C(CH_3)$_3$), 1.98(s, 4H, CH_2), 2.32 (s, 4H, CH_2), 2.54, 3.66 (s, H, CH), 5.34 (s, H, NH), 6.88- 6.91 (m, 2H, CH_2), 7.12- 7.15 (m, 2H, CH_2), 10.38(s, H, OH)

***tert*-Butyl 1,4,5,6,7,8-hexahydro-4-(4-isopropylphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (entry 9, Table 2):** Color: Yellow, solid, m.p: 100 ºC IR (KBr) cm^{-1}: 3294, 3085, 2928, 2870, 1697, 1607, 1380, 1311, 1163, 855. ^{1}HNMR ($CDCl_3$, 300 MHz): 0.87(s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.19 (s , 3H, CH_3), 1.34(s, 9H, C(CH_3)$_3$), 1.62 (s, 2H, CH_2), 2.15-2.33 (m, 4H, CH_2), 4.92 (s, H, CH), 6.57 (s, H, NH), 7.20-7.26 (m, 4H, Ar).

***tert*-Butyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxoquinoline-3-carboxylate (entry 10, Table 2):** Color: Yellow, solid, m.p: 190 ºC IR (KBr) cm-1:3211, 3087, 2929, 1733, 1677, 1524, 1343, 1110, 852. ^{1}HNMR ($CDCl_3$, 300 MHz): 0.87 (s, 3H,

CH_3), 1.06(s, 3H, CH_3), 1.32 (t, 9H, C(CH_3)$_3$), 2.29-2.38 (m, 4H, CH_2), 3.63 (d, 3H, CH_2), 5.07 (s, H, CH), 5.54 (s, H, NH), 7.22 -8.26 (m, 4H, Ar).

Conclusions

In conclusion, synthesis of some new 1,4-dihydropyridines with simple and efficient procedure, easy work-up, and high yield was described. We also believe that the applying methodology addresses the current devise toward green chemistry due to high yields and atomic economy, fewer reagents and the use of sustainable reaction media at room temperature.

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