An efficient one-pot synthesis of polyhydroquinoline derivatives via Hantzsch condensation using a heterogeneous catalyst under solvent-free conditions

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Abstract

An efficient Hantzsch condensation of polyhydroquinoline derivatives was reported via a four-component coupling reaction of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of $HClO_4$-SiO_2 under solvent-free conditions. Operational simplicity, use of an economically convenient catalyst, high yield, short reaction times are the key features of this protocol.

Keywords: $HClO_4$-SiO_2, Hantzsch condensation, one-pot synthesis, polyhydroquinoline derivatives

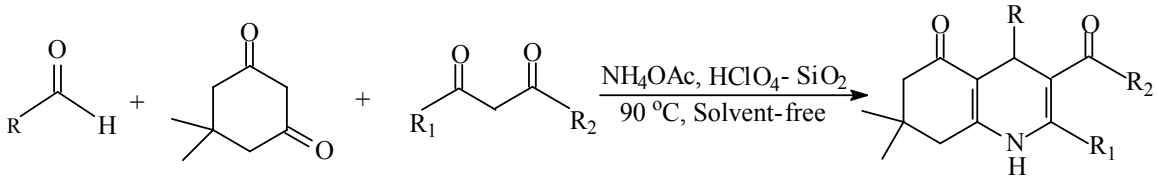
Introduction

4-Substituted 1,4-dihydropyridines (1,4-DHPs) are well known as Ca^{2+} channel blockers and emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases, including hypertension.[1] 1,4-Dihydropyridines possess a variety of biological activities, such as, vasodilator, bronchodilator, anti-atherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agent.[2a-d] Recent studies have revealed that 1,4-DHPs exhibit several medicinal applications which include neuroprotectant[3a] and platelet anti-aggregatory activity,[3b] in addition cerebral antiischemic activity in the treatment of Alzheimer's disease[3c] and as chemo sensitizer in tumor therapy.[3d] These examples clearly demonstrate the remarkable potential of novel DHP derivatives as a source of valuable drug candidates. A recent computational analysis of the comprehensive medicinal chemistry database showed the DHP framework to be among the most prolific chemo-types found. Development of drug resistance, both intrinsic drug resistance and acquired drug resistance, remains a clinical obstacle in the chemotherapy of many cancers.[4-5] Among the possible resistance modifiers, the dihydropyridines, calcium antagonists, have been studied extensively as the analogue of

verapamil.[6] Furthermore, the photocatalytic oxidation of these compounds to pyridines has been intensively investigated.[7] Relatively speaking 1,4-dihydropyridine derivatives combined with a single ring have been mostly reported. Thus, the synthesis of the heterocyclic nucleus is of continuing interest.

In view of the importance of polyhydroquinoline derivatives, many classical methods for their synthesis were reported[8-13] using conventional heating and refluxing approaches in the presence of an organic solvent. These methods, however, involves long reaction times, harsh reaction conditions, the use of a large quantity of volatile organic solvents and generally leading to low yields. Therefore, it is necessary to develop an efficient and versatile method for the preparation of 1,4-dihydropyridines and the progress in this field is remarkable including recently the promotion of microwave,[14] TMSCl,[15] ionic liquids,[16,17] polymers[18,19] and $Yb(OTf)_3$.[20] Moreover, to the best of our knowledge no report has been made so far about the use of $HClO_4$-SiO_2 as catalyst in the Hantzsch condensation. Recently $HClO_4$-SiO_2 has been used to catalyze the acetylation of alcohols and phenols using acetic acid.[21] The multi-component reactions are powerful tools in the modern drug discovery process and allow fast, automated and high throughput generation of organic compounds.[22] The possibility of performing multi-component reactions under solvent-free conditions with a heterogeneous catalyst could enhance their efficiency from an economic as well as an ecological point of view. In recent years heterogeneous catalysts are gaining more importance due to environmental-economic factors. The catalyst is generally of low cost and can be easily handled or removed.

Herein, we would like to report a facile Hantzsch condensation in the presence of a heterogeneous catalyst under solvent-free conditions, using substituted aldehydes (**1**), dimedone (**2**), ethyl acetoacetate (**3**) and ammonium acetate to produce the polyhydroquinoline derivatives (**4**) in excellent yields.



1 **2** **3** **4**

Scheme 1

Results and Discussion

The experimental procedure is very simple, convenient, and has the ability to tolerate a variety of other functional groups such as methoxy, nitro, hydroxyl, halides and olefins under the reaction conditions. Thus, we have selected the optimized reaction conditions to examine the generality of this catalyst application. Various aromatic, aliphatic, unsaturated and heterocyclic aldehydes were selected to undergo the Hantzsch condensation in the presence of this heterogeneous

catalyst ($HClO_4$-SiO_2). The results of this study are summarized in (Table-1). It was indicated that both electron rich and electron deficient aldehydes as well as heterocyclic ones such as furfural, thiophene-2-carboxaldehyde, thiophene-3-carboxaldehyde and pyridine-3-carboxaldehyde worked well, mostly leading to high yields of products.

Table 1. $HClO_4$-SiO_2 Catalyzed Hantzsch condensation of polyhydroquinoline derivatives under solvent-free conditions

Entry	R	R_1	R_2	Time (min)	Pro-duct	Yield (%)	MP (^oC) Found	MP (^oC) Reported
1	C_6H_5	CH_3	OEt	8	**4a**	95	203-204	202-204[20]
2	4-CH_3-C_6H_4	CH_3	OEt	12	**4b**	92	261-262	260-261[20]
3	4-CH_3O-C_6H_4	CH_3	OEt	10	**4c**	96	256-257	257-259[20]
4	4-Cl-C_6H_4	CH_3	OEt	10	**4d**	95	245-246	245-246[16]
5	4-NO_2-C_6H_4	CH_3	OEt	14	**4e**	90	243-244	242-244[16]
6	2,4-Cl_2-C_6H_3	CH_3	OEt	15	**4f**	92	242-243	241-243[20]
7	2-Cl-C_6H_4	CH_3	OEt	13	**4g**	94	207-208	208-210[16]
8	3,4,5-$(OCH_3)_3$-C_6H_2	CH_3	OEt	20	**4h**	89	199-200	198-199[9]
9	C_6H_5CH=CH	CH_3	OEt	16	**4i**	90	204-205	204-206[20]
10	2-NO_2-C_6H_4	CH_3	OEt	12	**4j**	89	206-207	206-208[9]
11	3-NO_2-C_6H_4	CH_3	OEt	14	**4k**	86	178-179	177-178[9]
12	4-F-C_6H_4	CH_3	OEt	10	**4l**	92	185-186	184-186[20]
13	3,4,-$(OCH_3)_2$-C_6H_3	CH_3	OEt	20	**4m**	95	198-199	-
14	4-$N(CH_3)_2$-C_6H_4	CH_3	OEt	15	**4n**	90	262-263	263-264[13]
15	2- furyl	CH_3	OEt	12	**4o**	92	247-248	246-248[20]
16	2-thienyl	CH_3	OEt	15	**4p**	96	239-240	238-240[20]
17	3-thienyl	CH_3	OEt	16	**4q**	91	246-247	248-250[16]
18	3-pyridyl	CH_3	OEt	20	**4r**	94	66-67	66-67[20]
19	4-OH-3-CH_3O-C_6H_3	CH_3	OEt	14	**4s**	89	211-212	210-212[16]
20	4-OH-C_6H_4	CH_3	OEt	18	**4t**	90	230-231	232-234[20]
21	4-Br-C_6H_4	CH_3	OEt	16	**4u**	92	252-253	253-255[20]
22	C_2H_5	CH_3	OEt	15	**4v**	83	145-146	145-146[20]
23	n-C_3H_7	CH_3	OEt	13	**4w**	81	146-147	147-148[20]
24	3,4,5-$(OCH_3)_3$-C_6H_2	CH_3	OMe	20	**4x**	87	220-221	220-224[9]
25	4-$N(CH_3)_2$-C_6H_4	CH_3	OMe	16	**4y**	85	257-258	258[9]

The structures of the products were determined from their spectroscopic (IR, 1H NMR and MS) data.

However, aliphatic aldehydes afforded relevant lower yields (entry 22-23). All the products were identified by comparison of analytical data (IR, NMR and MS) with those reported of authentic samples.

Conclusions

In conclusion, we have developed a simple and efficient method for the synthesis of polyhydroquinoline derivatives via Hantzsch condensation using a $HClO_4$-SiO_2 catalyst under solvent-free conditions. The mildness of the conversion, the experimental simplicity, the compatibility with various functional groups, the inexpensive reagents, the high yields and regioselectivity, the short reaction times and the easy workup procedure employed, makes this procedure very attractive to synthesize a variety of these derivatives.

Experimental Section

General Procedures. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded in KBr discs on a Bio-Rad win FT-IR spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian Gemini 400 & 200 spectrometer. LCMS was recorded on a Agilent-1100 periods LC/ MSD (VL). Elemental analyses were performed on a Vario EL-III. TLC was carried out on GF_{254} silica gel plates.

General experimental procedure. A mixture of aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1.5 mmol) and $HClO_4$-SiO_2 (50 mg) was heated at 90 ^{o}C with stirring for 8-20 min. and the solid product gradually formed. After completion of the reaction as indicated by TLC, the resulting solid product was treated with EtOAc followed by water and a brine solution and dried with anhydrous Na_2SO_4. The solution was concentrated in vacuum to afford the crude product. The pure product was obtained by further recrystallization using absolute alcohol. The spectral and analytical data for selected compounds are presented below.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-fluorophenyl)-5(6*H*)-oxoquinolin-3-carboxylate (4l). Yellow solid, mp 185-186 ^{o}C. IR (KBr): 3292, 2959, 1696, 1649, 1608, 1487, 1380, 1219, 1025, 764 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.18 (t, *J* = 7.3 Hz, 3H, CH_3), 2.13-2.25 (m, 4H, 2 ×CH_2), 2.38 (s, 3H, CH_3), 4.05 (q, *J* = 7.33 Hz, 2H, CH_2), 5.02 (s, 1H, CH), 5.8 (s, 1H, NH), 6.85-6.89 (m, 2H, ArH), 7.23-7.27 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.2, 26.4, 29.0, 32.1, 35.2, 50.1, 50.3, 59.0, 103.4, 110.0, 114.2, 114.3, 114.4, 129.0, 129.1, 144.1, 145.1, 149.4, 169.8, 194.2. LCMS: *m*/*z* = 356 $(M-H)^-$. Anal. Calcd for $C_{21}H_{24}NO_3F$: C, 70.58; H, 6.72; N, 3.92; F, 5.32. Found: C, 70.52; H, 6.79; N, 3.87; F, 5.28.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(3,4-dimethoxylphenyl)-5(6*H*)-oxoquinolin-3-carboxylate (4m). Yellow solid, mp 198-199 ^{o}C. IR (KBr): 3239, 2956, 1694, 1644, 1609, 1488, 1379, 1217, 1027, 753 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 0.95 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.21 (t, *J* = 7.3 Hz, 3H, CH_3), 2.19-2.35 (m, 4H, 2 ×CH_2), 2.38 (s, 3H, CH_3), 3.83 (s, 3H OCH_3), 3.81 (s, 3H OCH_3) 4.07 (q, *J* = 7.3 Hz, 2H, CH_2), 5.02 (s, 1H, CH), 5.92 (s, 1H, NH), 6.70 (d, *J* = 8.30 Hz,1H, ArH), 6.78 (dd, *J* = 8.30 and 1.96 Hz, 1H, ArH), 6.92 (d, *J* = 1.96 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 18.2, 26.4, 29.1, 32.0, 35.0, 50.2, 50.5, 55.2, 55.3, 59.0, 103.8, 110.1, 111.4, 111.7, 119.2, 140.4, 144.5, 146.9, 147.9, 149.4, 166.9, 194.3. LCMS: *m*/*z* = 398 (M-H)$^{-}$. Anal. Calcd for $C_{23}H_{29}NO_5$: C, 69.17; H, 7.26; N, 3.50; Found: C, 68.91, H, 7.30 N, 3.46.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-methoxylphenyl)-5(6*H*)-oxoquinolin-3-carboxylate (4c). Yellow solid, mp 256-257 ^{o}C. IR (KBr): 3276, 2956, 1703, 1648, 1606, 1496, 1381, 1215, 1031, 765 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ = 0.95 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.21 (t, *J* = 7.2 Hz, 3H, CH_3), 2.01-2.10 (m, 4H, 2 ×CH_2), 2.30 (s, 3H, CH_3), 3.70 (s, 3H OCH_3), 4.00 (q, *J* = 7.2 Hz, 2H, CH_2), 4.80 (s, 1H, CH), 6.65 (d, *J* = 7.3 Hz, 2H, ArH), 7.10 (d, *J* = 7.3 Hz, 2H, ArH), 8.65 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.1, 18.2, 26.4, 29.1, 32.1, 34.7, 50.2, 50.5, 54.8, 58.9, 103.2, 110.1, 113.0, 113.1, 128.2, 128.3, 139.8, 144.6, 149.1, 157.2, 166.9, 194.2. LCMS: *m*/*z* = 368 (M-H)$^{-}$. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.54; H, 7.31; N, 3.79; Found: C, 71.59; H, 7.35; N, 3.84.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-hydroxy-3-methoxylphenyl)-5(6*H*)-oxoquinolin-3-carboxylate (4s). Yellow solid, mp 211-212 ^{o}C. IR (KBr): 3388, 2953, 1700, 1643, 1589, 1482, 1385, 1218, 1029, 782 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ = 0.95 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.25 (t, *J* = 7.2 Hz, 3H, CH_3), 2.02-2.20 (m, 4H, 2 ×CH_2), 2.30 (s, 3H, CH_3), 3.80 (s, 3H OCH_3), 4.05 (q, *J* = 7.2 Hz, 2H, CH_2), 4.80 (s, 1H, CH), 6.60 (s 2H, ArH), 6.82 (s, 1H, ArH), 7.69 (s, OH), 8.49 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.2, 18.2, 26.3, 29.2, 32.1, 35.0, 50.2, 55.4, 58.9, 104.0, 110.1, 112.0, 114.9, 119.3, 119.5, 139.0, 144.3, 144.5, 146.7, 149.2, 167.0, 194.3. LCMS: *m*/*z* = 384 (M-H)$^{-}$. Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.57; H, 7.06; N, 3.64; Found: C, 68.52; H, 7.10; N, 3.60

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(2-chlorolphenyl)-5(6*H*)-oxoquinolin-3-carboxylate (4g). Yellow solid, mp 207-208 ^{o}C. IR (KBr): 3063, 2956, 1721, 1640, 1611, 1467, 1384, 1227, 1021, 745 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ = 0.95 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.20 (t, *J* = 7.2 Hz, 3H, CH_3), 2.01-2.21 (m, 4H, 2 ×CH_2), 2.40 (s, 3H, CH_3), 4.05 (q, *J* = 7.2 Hz, 2H, CH_2), 4.60 (s, 1H, CH), 7.10-7.30 (m 4H, ArH), 7.60 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.5, 29.1, 31.2, 32.3, 42.4, 46.8, 48.9, 50.5, 52.9, 55.1, 101.3, 109.2, 114.2, 125.9, 127.1, 128.7, 131.1, 132.3, 141.0, 167.5, 195.7. LCMS: *m*/*z* = 372 (M-H)$^{-}$. $C_{21}H_{24}NO_3Cl$: Anal. Calcd for C, 67.56; H, 6.43; N, 3.75; Cl, 9.38; Found: C, 67.52; H, 6.48; N, 3.72; Cl, 9.42

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