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Synthesis of Polyhydroquinolines Hantzsch Reaction Catalyzed by Starch Sulfuric Acid in Water

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Starch sulfuric acid was used as efficient catalyst of 4-components Hantzsch reaction of various aromatic aldehydes, dimedone, ammonium acetate and ethyl acetoatetate or acetylacetone in water at room temperature to afford polyhydroquinolines in high yields. The process is operationally simple, environmentally friendly and rapid. Furthermore, the catalyst is obtained easily and cheaply.

Key Words: Starch sulfuric acid, Polyhydroquinolines, Hantzsch reaction, Water.

INTRODUCTION

Recently the emphasis of science and technology is shifting more towards sustainable resources and processes. In this regard biopolymers are attractive candidates to explore for supported catalysis. Starch is a facile and biodegradable natural cheaper biopolymer. It is the cheapest natural biopolymer and totally biodegradable. To the best of our knowledge, starch have been widely used as surfactant[1]. The reports about the combinations of starch and acid such as amino acid, fatty acid, sulfuric acid for organic synthesis were also studied recently[2-4].

In addition, sulfonic acid is often used as Brønsted acid to catalyze some important reactions[5]. These applications enlightened us to synthesize starch sulfuric acid and used it as a catalyst in organic synthesis. Starch sulfuric acid has ever been used as catalyst for the preparation of quindines *via* Fridedländer reaction[6].

Hantzsch reaction of aldehydes and ammonia with β-dicarbonyl compounds is an important synthetic reaction to form the corresponding dihydropyridines. These derivatives exhibit various medicinal activities such as neuroprotectant and platelet antiaggregatory, a cerebral antiischemic in the treatment of Alzheimer's disease and as a chemosensitizer in tumor therapy[7]. Therefore the synthesis of this heterocyclic nucleus is vital to people. The classical version of the polyhydroquinoline

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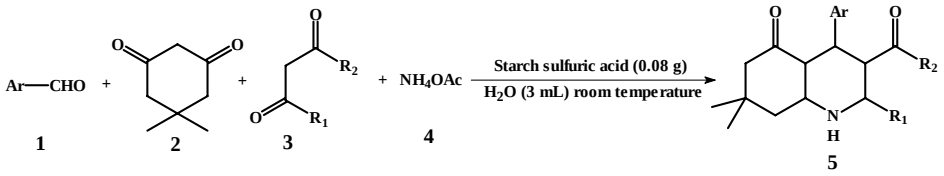
derivatives synthesis, which involves the three-component coupling of an aldehyde with ethyl acetoacetate and ammonia, was often in acetic acid or in refluxing alcohol[8,9]. Recently several methods have been reported including the use of microwaves[10], ionic liquids[11], refluxing at high temperature[12] or TMSCl-NaI[13], metal triflates[14], I_2[15], CAN[16] and L-proline as catalyst[17]. However, these methods have some drawback such as long reaction time, use of costly catalysts, use of toxic reagents and requirement of special effort for catalyst preparation.

We here developed starch sulfuric acid as an efficient catalysis of Hantzsch reaction to afford polyhydroquinolines in water at room temperature (**Scheme-I**).



Scheme-I: Hantzsch reaction catalyzed by starch sulfuric acid

EXPERIMENTAL

All reagents were purchased from commercial sources and used without purification. TLC analysis was performed with glass backed plates precoated with silica gel and examined under UV (254 nm). NMR spectra were measured in $CDCl_3$ with Me_4Si as the internal standards on a Bruker Advance DPX-400 at room temperature. IR spectra were recorded on Bruker FTIR spectrometer, absorbances are reported in cm^{-1}.

Synthesis of starch sulfuric acid: Starch (1.8 g) was charged in a 50 mL three-necked flask which was equipped with a constant-pressure dropping funnel containing chlorosulfonic acid (5.8 g) and a gas inlet tube for conducting HCl gas over aq. NaOH. Chlorosulfonic acid was added dropwise at 0-5 ºC in 2 h. After the addition was completed, the mixture was stirred for 6 h until HCl was completly removed from reaction vessel. Then, the mixture was washed with anhydrous THF (20 mL) and distilled to obtain starch sulfuric acid by removed THF under pressure evaporating apparatus.

General procedure in water with starch sulfuric acid: A mixture of aromatic aldehydes (2.0 mmol), dimedone (2.0 mmol), ethyl acetoacetate (2.2 mmol), ammonium acetate (2.5 mmol), and starch sulfuric acid (0.08 g) was stirred in water (3 mL) at room temperature for 1-7 h (monitored by TLC). The resulting solid product was washed with water, filtered and dried in vacuum to afford the crude product. A pure product was obtained by recrystallization with 95 % ethanol.

Spectral data

2,7,7-Trimethyl-5-oxo-4-(4-cyanphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5j): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.11

(s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 2.19-2.26 (m, 4H), 2.43 (s, 3H), 4.07 (q, *J* = 7.2 Hz, 2H), 5.12 (s, 1H), 5.79 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.90, 19.15, 26.80, 29.08, 32.44, 37.01, 40.75, 50.31, 59.75, 104.70, 109.31, 110.97, 128.64, 131.58, 144.02, 148.23, 152.02, 166.61, 195.06; IR (KBr, ν_{max}, cm^{-1}): 3284, 3075, 2962, 2185, 1703, 1605.

2,7,7-Trimethyl-5-oxo-4-(3,4-dimethoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5k): ^{1}H NMR (400 MHz, CDCl3) δ 0.98 (s, 3H), 1.11 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 2.18-2.24 (m, 4H), 2.41 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 4.10 (q, *J* = 6.8 Hz, 2H), 5.04 (s, 1H), 5.67 (s, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.32, 19.53, 27.12, 29.50, 32.74, 35.95, 41.24, 50.72, 55.75, 59.85, 106.80, 110.75, 112.45, 119.69, 139.96, 142.70, 147.54, 167.49, 196.21; IR (KBr, ν_{max}, cm^{-1}): 3265, 3058, 2964, 1701, 1602.

2,7,7-Trimethyl-5-oxo-4-(3,4,5-trimethoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5l): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.11 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 2.21-2.37 (m, 4H), 2.40 (s, 3H), 3.81 (s, 9H), 4.13 (q, *J* = 7.2 Hz, 2H), 5.04 (s, 1H), 5.90 (s, 1H), 6.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.38, 19.52, 27.06, 29.59, 31.13, 36.59, 41.22, 50.71, 56.02, 59.88, 60.89, 105.20, 112.08, 115.58, 142.75, 147.90, 152.67, 167.45, 195.55; IR (KBr, ν_{max}, cm^{-1}): 3276, 3071, 2956, 1687, 1602.

2,7,7-Trimethyl-5-oxo-4-(2,3-dimethoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5m): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.09 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 2.16-2.29 (m, 4H), 2.33 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 4.07 (q, *J* = 7.2 Hz, 2H), 5.24 (s, 1H), 5.74 (s, 1H), 6.73 (d, *J* = 1.2 Hz, 1H), 6.90 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.20, 19.62, 28.88, 34.37, 41.41, 50.84, 55.63, 60.18, 105.84, 110.58, 122.65, 123.87, 142.34, 148.33, 152.83, 168.21, 196.12; IR (KBr, ν_{max}, cm^{-1}): 3264, 3048, 2957, 1702, 1610.

3-Acetyl-2,7,7-trimethyl-4-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one (5o): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.09 (s, 3H), 2.18 (s, 3H), 2.22-2.24 (m, 4H), 2.29 (s, 3H), 2.41 (s, 3H), 5.06 (s, 1H), 6.02 (s, 1H), 7.05 (d, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.12, 21.04, 27.15, 29.31, 29.64, 30.98, 32.72, 36.75, 40.93, 50.84, 112.74, 113.28, 127.72, 129.04, 135.83, 142.98, 143.50, 148.19, 195.79, 199.72; IR (KBr, ν_{max}, cm^{-1}): 3259, 3042, 2961, 1668, 1607.

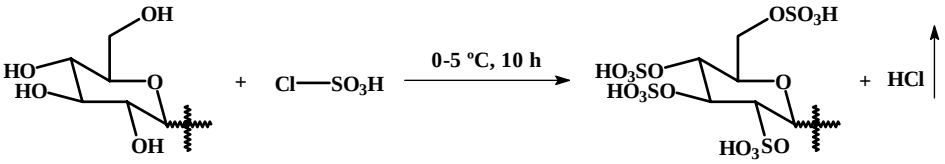
3-Acetyl-2,7,7-trimethyl-4-(4-cyanphenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one (5p): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.14 (s, 3H), 2.37-2.48 (m, 10H), 5.55 (s, 1H), 7.22 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.48, 29.56, 30.95, 31.49, 33.27, 46.43, 47.02, 109.77, 114.84, 118.93, 127.62, 132.09, 144.35, 189.52, 190.93; IR (KBr, ν_{max}, cm^{-1}): 3282, 3045, 2954, 2165, 1660, 1605.

3-Acetyl-2,7,7-trimethyl-4-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one (5q): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.08 (s, 3H), 2.16 (s, 3H), 2.21-2.33 (m, 4H), 2.40 (s, 3H), 3.76 (s, 3H), 5.04 (s, 1H), 6.06 (s, 1H), 6.78 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.26, 27.10, 29.34, 29.56, 32.76, 36.33, 41.08, 50.79, 55.18, 113.37, 113.68, 128.89, 138.22, 158.01, 195.73, 199.75; IR (KBr, í, cm-1): 3276, 3018, 2960, 1665, 1602.

3-Acetyl-2,7,7-trimethyl-4-(3,4,5-trimethoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-5-one (5r): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.27 (s, 3H), 2.38 (s, 3H), 2.43-2.45 (m, 4H), 2.54 (s, 3H), 3.78 (s, 6H), 3.84 (s, 3H), 5.52 (s, 1H), 6.37 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.83, 30.08, 31.14, 32.81, 46.36, 47.12, 55.90, 60.90, 104.15, 115.59, 133.76, 135.93, 152.86, 189.31, 190.41; IR (KBr, ν_{max}, cm^{-1}): 3272, 3036, 2959, 1669, 1605.

RESULTS AND DISCUSSION

The catalyst starch sulfuric acid (colourless oil liquid) is simply prepared by the reaction of chlorosulfonic acid and starch (**Scheme-II**).



Scheme-II

The ^{1}H NMR spectra of starch and starch sulfuric acid indicated the obviously difference. In ^{1}H NMR spectra of starch, the multiple peaks in the δ range of 3.52-4.00 ppm are signed to the tertiary hydrogen signal, the wide peak at δ 5.35 ppm is the hydroxyl signal. Compared these two spectra, it is found that proton of starch sulfuric acid moved to a lower field (5.76-5.95 ppm), which is due to the strong electron-withdrawing effect of -OSO_3H fragment. At the same time, a new strong single peak of -OSO_3H appeared at 15.44 ppm.

The reaction of 4-methoxybenzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate in water was selected as model reaction to detect whether the use of starch sulfuric acid was efficient and to optimized reaction condition (Table-1).

Interestingly, it is found that I_2, L-proline, TsOH, silica sulfuric acid could not afford good product yield. Even large amount of catalysts and longer reaction time was used, the results were still unsatisfactory (entry 1a-1d, Table-1). When starch sulfuric acid was used, the results seemed to be better. Although its reagents have low solubility in water, Hantzsch reactions were successfully catalyzed by starch sulfuric acid at room temperature (entry 1e-1i). The efficient catalytic activity of

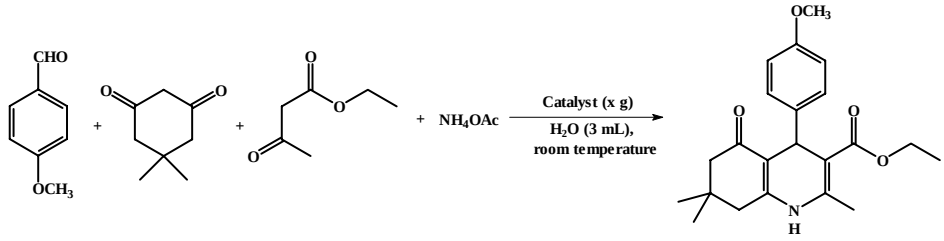


TABLE-1
THE MODEL HANTZSCH REACTION UNDER DIFFERENT CONDITIONS IN WATER[a]

Entry	Catalyst	X (g)	Time (h)	Yield (%)[b]
1a	I_2	0.08	12	NR[c]
1b	L-proline	0.08	4	60
1c	TsOH	0.08	9	46
1d	Silica sulfuric acid	0.08	6	73
1e	Starch sulfuric acid	0.02	4	41
1f	Starch sulfuric acid	0.04	4	54
1g	Starch sulfuric acid	0.06	4	75
1h	Starch sulfuric acid	0.08	4	87
1i	Starch sulfuric acid	0.10	4	72

[a]Reaction conditions: 4-methoxybenzaldehyde (2.0 mmol), dimedone (2.0 mmol), ethyl acetoacetate (2.2 mmol), ammonium acetate (2.5 mmol) and catalyst (x g) were carried at room temperature. [b]Yield of isolated product. [c]No reaction.

starch sulfuric acid was not only from its Bronsted acidity but also from its surfactancy. The giant polarity and water-solubility of starch sulfuric acid made the reaction mixture become to a homogeneous white turbid, while silica sulfuric acid, TsOH formed 2 immiscible layers. This colloidal dispersion can increase the water-solubility of 3 organic reagents in water. The optimum amount of catalyst was determined from corresponding experiments (entry 1e-1i, Table-1).

The scope of the reaction was investigated and the results are summarized in Table-2. It showed that both electron-rich and electron-deficient aldehydes worked well, leading to high yields of product (75-91 %), but the steric effect of substituted group on aldehydes had little influence on the yield (entry 12 and 13, Table-2). The substrates with electron-rich group such as Me or OMe on *p*-position gave nearly quantitative yield (entry 2 and 3, Table-2). However, with acetylacetone yields were somewhat lower than the corresponding ethyl acetoacetate due to its lower solubility in water.

In conclusion, we have found that 4-components Hantzsch reaction can be efficiently catalyzed by starch sulfuric acid in water at room temperature. The significant features of this procedure include: (1) a novel and efficient catalyst; (2) high yields; (3) mild condition; (4) non-toxic solution.

TABLE-2
SYNTHESIS OF POLYHYDROQUINOLINE DERIVATIVES CATALYZED BY STARCH SULFURIC ACID IN WATER

Entry	Ar	R_1	R_2	Time (h)	Product	Yield (%)	m.p. (°C)	
							Found	Reported
1	C_6H_5	CH_3	OC_2H_5	6	5a	84	201-203	202-204[10]
2	*p*-MeC_6H_4	CH_3	OC_2H_5	3	5b	88	259-260	260-261[10]
3	*p*-$MeOC_6H_4$	CH_3	OC_2H_5	4	5c	87	258-259	257-259[10]
4	*p*-ClC_6H_4	CH_3	OC_2H_5	4	5d	86	246-247	245-246[13]
5	*p*-BrC_6H_4	CH_3	OC_2H_5	4	5e	89	252-253	253-255[10]
6	*p*-FC_6H_4	CH_3	OC_2H_5	4	5f	89	183-184	184-186[10]
7	*p*-$NO_2C_6H_4$	CH_3	OC_2H_5	3	5g	86	240-241	242-244[7]
8	2,4-$Cl_2C_6H_3$	CH_3	OC_2H_5	5	5h	85	243-245	241-244[10]
9	*p*-$(Me)_2NC_6H_4$	CH_3	OC_2H_5	2	5i	82	230-232	229-231[10]
10	*p*-CNC_6H_4	CH_3	OC_2H_5	3	5j	83	181-182	
11	3,4-$(MeO)_2C_6H_3$	CH_3	OC_2H_5	2	5k	90	196-197	
12	3,4,5-$(MeO)_3C_6H_2$	CH_3	OC_2H_5	1	5l	91	185-186	
13	2,3-$(MeO)_2C_6H_3$	CH_3	OC_2H_5	3	5m	84	170-172	
14	3,4-$(CH_2O_2)C_6H_3$	CH_3	OC_2H_5	2	5n	89	197-199	197-199[15]
15	*p*-MeC_6H_4	CH_3	CH_3	6	5o	78	214-216	
16	*p*-CNC_6H_4	CH_3	CH_3	7	5p	75	178-180	
17	*p*-$MeOC_6H_4$	CH_3	CH_3	6	5q	76	189-190	
18	3,4,5-$(MeO)_3C_6H_2$	CH_3	CH_3	3	5r	84	176-177	

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