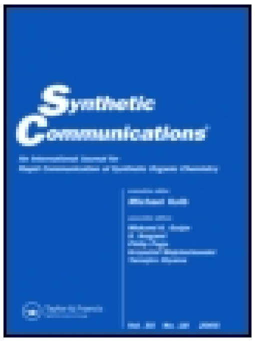

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Sulphonic acid functionalized Wang resin (Wang-OSO_3H) as polymeric acidic catalyst for the eco-friendly multi-component synthesis of polyhydroquinolines *via* Hantzsch condensation

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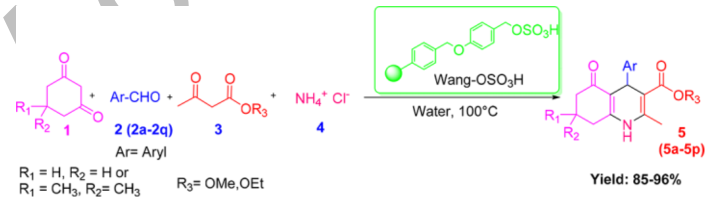
Abstract

An efficient and green approach has been developed for the synthesis of polyhydroquinoline derivatives via Hantzsch condensation reaction directly from corresponding substituted aromatic and aliphatic aldehyde, β-keto compounds, active methylene compounds and ammonium chloride using recyclable polymer supported sulphonic acid catalyst under aqueous conditions. Environmental acceptability, operational simplicity, low cost, excellent functional group compatibility and high yields are the important features of this protocol.

GRAPHICAL ABSTRACT



KEYWORDS: Reusable catalyst, Wang-SO_3H, polyhydroquinoline derivatives, Hantzsch condensation, water, green chemistry

INTRODUCTION

1,4-dihydropyridyl (DHP) skeletons constitute a class of synthetic compounds that have pharmaceutical activities, clinical applications and their significant biological activities.[1] Some representative examples of drug molecules having 1,4-dihydropyridyl (DHP) skeleton are given in **Figure 1** which are effective for the treatment of hypertension.[2] Particularly, 4-substituteted 1,4-dihydropyridines (1,4-DHPs) are well known as Ca^{2+} channel blockers and have emerged as one of the most important class of drugs for the treatment of cardiovascular diseases[3] and the heterocyclic rings are found in a variety of bioactive compounds such as bronchodilator, antiatherosclerotic, antitumour, vasodilator, antidiabetic, geroprotective, and heptaprotective activity.[4] More studies indicate that these compounds exhibit different medical functions, acting as neuroprotectants, platelet antiaggregators, cerebral antiischemic agents, and chemosensitizers.[5] Despite their importance from a pharmacological, industrial and synthetic point of view chemists have attracted the attention to synthesize polyhydroquinoline compounds.

In the past decade, a variety of synthetic methods have been employed for the preparation of functionalized 1,4-DHPs (1,4-Dihydropyridines) and the level of interest in the current domain is clearly shown by the number of publications. Recently, a number of classical methods for the synthesis of 1,4-DHPs (1,4-Dihydropyridines) have been reported in the literature involving the cyclo condensation with aldehydes, β-ketoesters, and ammonia either acetic acid or refluxing in alcohol for a longer time. However, the yields of 1,4-Dihydropyridines obtained by the Hantzsch method are generally poor. In recent years, several new methods have been reported for the synthesis of 1,4-Dihydropyridines. In the presence of various catalysts like including the use of grinding[6], thermal energy[7], ionic liquids[8,9] $Bu_4N^+HSO_4$[10], *in situ* generated HCl,[11] $K_7[PW_{11}CoO_{40}]$,[12] I_2,[13] silica-supported acids,[14,15] silica perchloric acid ($HClO_4$–SiO_2),[16] TMSCl-NaI,[17] $Sc(OTf)_3$,[18] HY-Zeolite,[19] montmorillonite K-10,[20] *p*-TSA ,[21] microwave, ultra sound[22,23], 3-nitrophenylboronic acid ,[24] L-Proline ,[25] morpholine ,[26] SBA-Pr-SO_3H,[27] silica-supported super Para magnetic Fe_3O_4 nanoparticle,[28] Fe_3O_4/SiO_2–OSO_3H,[29] Fe_3O_4/cellulose-OSO_3H,[30] and FeF_3.[31] However, the above mentioned methods have been associated with different drawbacks such as the use of hazardous organic solvents, low yields, strongly acidic conditions, expensive moisture sensitive catalysts, or tedious work-up conditions. Therefore, it is necessary to develop an efficient and versatile method for the preparation of 1, 4-Dihydropyridines.

In spite of the efficiency of homogeneous acidic catalysts, their use is associated with generation of unwanted waste and with the corrosion of process equipment. In contrast, the use of heterogeneous acid catalysis often benefits from a substantial process improvement including greater catalyst stability, recovery & regeneration and enhanced process selectivity.

The researchers continue for finding a better catalyst for the synthesis of polyhydroquinoline compounds in terms of operational simplicity, economic viability, and greater selectivity.

The objective of the present study was the development of a novel heterogeneous catalyst for efficient preparation of polyhydroquinoline compounds. A new Sulfonic acid functionalized resin (Wang-SO_3H) catalyst is an efficient, green, inexpensive, reusable, and polymeric heterogeneous solid acid catalyst[32] which can easily be handled and removed from the reaction mixture by simple filtration.

Wang resin[32] is most often used for the attachment of organic and inorganic acids. In particular, treatment of Wang resin with chlorosulfonic acid in the presence of N,N-diisopropylethylamine (DIPEA) results in the formation of a monosulfate ester.[33] (Wang-OSO_3H, **Scheme 1**).

In this work, we report an efficient procedure for the preparation of synthesis of polyhydroquinoline derivatives from four components through a reaction between variously substituted aromatic and aliphatic aldehydes, *β*-keto compound, alkyl acetoacetate, ammonium chloride under thermal condition in the presence of Wang-OSO_3H as an efficient, green, inexpensive, reusable, and polymeric catalyst[34, 35]. It is pertinent to mention that this is the first report on the synthesis of polyhydroquinoline derivatives installing Wang-OSO_3H catalyzed protocol in aqueous media (**Scheme 2**).

This process not only increases the yield of the product but also reduce the number of laboratory operations along with the quantities of solvents and chemicals used.

We found that *β*-keto compound, alkyl acetoacetate; ammonium chloride readily reacts with a variety of aldehydes **2a-2q** under the catalysis with Wang-OSO_3H resin to form polyhydroquinoline derivatives **5a-5q**.

RESULTS & DISCUSSION

The reaction conditions were optimized with respect to the quantity of catalyst (**Table 1**) , the solvent (**Table 2**), study of reusability (**Table 3**), comparison activity of different catalysts (**Table 4**) and reaction with different amines (**Table 5**) by studying the condensation of Ethyl acetoacetate (1.0 mmol), 3-Nitrobenzaldehyde (1.0 mmol), Dimedone (1.0 mmol) and ammonium chloride (1.0 mmol) and resin bound Wang-SO_3H (10 %w/w) with respect to aldehyde in water at reflux conditions. The highest isolated yields of compound **5a** were obtained by carrying out the process in water at reflux temperature for 1.0-1.6 hr.

To explore the effect of solvent on the model reaction, various solvents such as DMSO, DMF, 1,4-dioxane, ethanol, DCM, acetonitrile, methanol, toluene and water were tested at their respective reflux temperatures using 10 % w/w of Wang-OSO_3H with respect to aldehyde (**Table 2,** entries 1–9). Among the solvents tested, none of them could match the efficiency of the water as a solvent which was found superior over the other solvents in terms of both product yield and reaction time (**Table 2**, entry 9). Water is obviously the first choice of an alternative solvent. Water is clean, non-toxic, inexpensive, and the most environmentally.

The recovery and reuse of Wang-OSO_3H were examined in the reaction of 3-Nitrobenzaldehyde (1.0 mmol), Dimedone (1.0 mmol), ammonium chloride (1.0 mmol) in water at 100 °C. When the reaction was completed, methanol was added to the reaction mixture and the catalyst was recovered by filtration.

The recovered catalyst was washed with methanol, water and then acetone, dried under vacuum and reused for several times without significant loss of activity. It was found that the catalytic activities and pH of the subsequent reaction mass of the recovered catalyst were almost the same as that of fresh catalyst over four runs (**Table 3**, entries 1–5).

The experimental details captured in the table (**Table 4**, entries 1-12) clearly indicates that the yields obtained in the optimized reaction conditions using Dowex 50 and Amberlyst 15 are low compared to resin bound Wang-SO_3H. Of course, the product formation is minimal without catalyst. Previously, various catalysts reported for similar type of reactions, wherein the reaction time was more or the process involved organic solvents or lower yields. The present catalyst is capable of catalyzing the four component reaction carried under aqueous conditions. Obviously, water would be the first choice of an alternative for any solvent since it is clean, non-toxic, inexpensive, and eco-friendly.

From **Table 5**, one can see that the reaction yields of ammonium compounds (**Table 5**, entry 1 entry 2 and entry 3) are higher than for aromatic amines (**Table 5**, entry 4 and 5). This is probably due to the lower solubility of the aromatic amines in water and lower reactivity than that of the ammonium compounds. The increasing of the dosage of ammonium compound is because of the easy resolvability. (**Scheme 3**)

The scope and the utility of the suggested synthetic protocol was demonstrated by reacting compound **2** (2a-2q, **Table 6**) with a wide variety of aliphatic, aromatic and heteroaromatic aldehydes to result in the target polyhydroquinoline derivatives **5** (5a-5q, **Table 6**) in invariably high yields (85-96%).

We propose a mechanism for the Wang-SO_3H catalyzed synthesis of polyhydroquinolines[40] (**Scheme 4**). Polyhydroquinoline derivatives **5** may be formed acid-catalyzed cyclocondensation of intermediates I and II, generated respectively by Knoevenagel condensation of one equivalent of dimedone with aldehyde and reaction with one equivalent of ethyl acetoacetate with ammonia generated from ammonium chloride (**Scheme 4**).

EXPERIMENTAL

General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (100-200 mesh) using distilled hexane, ethyl acetate, dichloromethane. ^1H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ or DMSO-d_6 solution by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Melting points were determined using melting point B-540 apparatus and are uncorrected. HRMS was determined using waters LCT premier XETOF ARE-047 apparatus.

Typical Experimental Procedure For The Synthesis Of Hantzsch Polyhydroquinoline Derivatives (5) Under Aqueous Medium

In a typical experimental procedure, dimedone **1** (1 mmol), aldehyde **2** (1 mmol), acetoacetate ester **3** (1 mmol), ammonium chloride **4** (1 mmol) was dissolved in 10 ml of water and Wang-OSO_3H (10% w/w) with respect to aldehyde was added and the reaction slowly heated to reflux under stirring. Stirring was continued in for the stipulated period of time (**5a-5q**, **Table 6**). The progress of the reaction was monitored with TLC. After completion of the reaction, the reaction mixture was cooled diluted with 10volumes methanol to dissolve the precipitated product and the catalyst was removed simply by filtration. The residual catalyst was repeatedly washed with methanol (3 * 5 volumes). The combined filtrate and washings, on evaporation, gave the crude product. The pure product was obtained through crystallization from ethanol.

Analytical Data For Selected Compounds:

Ethyl 2, 7, 7-Trimethyl-5-Oxo-4-Phenyl-1, 4, 5, 6, 7, 8-Hexahydroquinoline-3-Carboxylate, 5a

Off white solid; mp: 203-206 ºC (lit.[31] 203-204 ºC); ^{1}H NMR (400 MHz, DMSO-d_6) δ : 0.84 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.14-1.10 (t, *J* = 8.00 Hz, 3H, CH_3), 1.99-1.95 (m, 1H, CH), 2.14-2.11 (m, 1H, CH), 2.30-2.26 (m, 1H, CH), 2.28 (s, 3H, =C-CH_3), 2.49-2.43 (m, 1H, CH), 3.99-3.94 (q, *J* = 8.00 Hz, 2H, CH_2), 4.85 (s, 1H, CH), 7.04 (d, *J* = 7.2 Hz, 1H, H-Ar), 7.19-7.05 (m, 4H, H-Ar), 9.04 (br s, 1H, NH).^{13}C NMR (100 MHz, DMSO-d_6);δ14.14, 18.30, 26.43, 29.15, 32.15 (2C), 35.84, 50.23, 59.03, 103.59, 109.96, 125.69, 127.47 (2C), 127.73 (2C), 145.01, 147.66, 149.52, 166.84, 194.27, HRMS (ESI): Anal.calcd for $C_{21}H_{26}NO_3$ $(M+H)^+$340.1913, Found 340.1912.

Ethyl 2, 7, 7-Trimethyl-4-(Naphthalen-2-Yl)-5-Oxo-1, 4, 5, 6, 7, 8-Hexahydroquinoline-3-Carboxylate, 5b

Light yellow solid; mp: 233-236 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.83 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.13-1.10 (t, *J* = 6.8 Hz, 3H, CH_3), 1.98-1.93 (m, 1H, CH), 2.20-2.16 (m, 1H, CH), 2.30 (s, 3H, =C-CH_3), 2.34-2.32 (m, 1H, CH),2.47-2.43 (m, 1H, CH), 3.99-3.94 (q, *J* = 6.8 Hz, 2H, CH_2), 5.03 (s, 1H,CH), 7.44-7.37 (m, 3H, H-Ar), 7.58 (s, 1H, H-Ar), 7.79-7.72 (m, 3H, H-Ar), 9.10 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 194.3, 166.85, 149.7, 145.2, 145.0, 132.7, 131.6, 127.6, 127.3, 127.2, 126.7, 125.7, 125.3, 125.1, 109.7, 130.4, 59.0, 50.2, 36.2, 32.1(2C), 29.1, 26.3, 18.3, 14.1; HRMS (ESI): Anal.calcd for $C_{25}H_{28}NO_3$ $(M+H)^+$ 390.2069, Found 390.2069.

Ethyl 4-Isobutyl-2, 7, 7-Trimethyl-5-Oxo-1, 4, 5, 6, 7, 8-Hexahydroquinoline-3-Carboxylate, 5c

Off white solid; mp: 172-174 ºC ; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 0.79-0.77 (d, *J* = 8.0 Hz, 3H, CH_3), 0.84-0.83 (d, 3H, CH_3), 0.98-0.96 (s, 3H, CH_3), 1.01-1.00 (m, 6H, 2CH_3), 1.22-1.18 (t, *J* = 8.0 Hz, 3H, CH_3), 1.39-1.33 (m, 1H, CH), 2.13-2.07 (m, 1H, CH), 2.20-2.16 (m, 1H, CH), 2.21 (s, 3H, =C-CH_3), 2.33-2.24 (m, 1H, CH), 3.82-3.79 (t, *J* = 8.0 Hz, 1H, CH), 4.09-4.02 (q, *J* = 8.0 Hz, 2H, CH_2), 8.93 (br s, 1H, NH).^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 194.6, 167.1, 150.2, 145.3, 110.1, 103.9, 58.9, 50.4, 46.9, 40.1, 31.9, 29.4, 26.8, 26.0, 23.5, 23.3, 22.8, 18.1, 14.2; HRMS (ESI): Anal.calcd for $C_{19}H_{30}NO_3$ $(M+H)^+$ 320.2226, Found 320.2235

CONCLUSION

In conclusion, we have reported a highly efficient and ecofriendly method for the synthesis of novel polyhydroquinoline derivatives products with good yield using resin bound Wang sulfonic acid as an inexpensive, biodegradable and recyclable catalyst. In this reaction Wang sulfonic acid act as a very efficient "green" promoter and prominent advantages of this method are broad scope, operational simplicity, practicability, economic viability, good yield of the products in shorter reaction time, easy work-up, and reusability of the catalyst.

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33. **Preparation of Wang-OSO_3H**: Wang-OSO_3H was prepared by adding freshly distilled $ClSO_3H$ (2.0 mmol) to wang resin (1.0 mmol), DIPEA (5.0 mmol) in DCM (10 volumes) and the resulting solution was stirred at 25-35 °C for 2 hr. The reaction mass was filtered and washed with DMF (5 x 10 volumes), DCM (5 x 10 volumes) and Isopropanol (5 x 10 volumes) and the wang catalyst was dried at 130 ^{0}C for 3 hr.

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Table 1. Optimization of catalyst loading[a]

Entry	Catalyst (% w/w)	Time (hr)	Yield[b] (%)
1	No Resin	4.0	20
2	5	1.3	88
3	10	1.2	92
4	15	1.0	91
5	20	1.0	91

[a] *Reaction and conditions*: Ethyl acetoacetate (1.0 mmol), 3-Nitrobenzaldehyde (1.0 mmol), Dimedone (1.0 mmol), Ammonium chloride (1.0 mmol) and resin bound Wang-SO_3H (10 %w/w) in water at 100 °C. [b] Yield refers to pure products after crystallization.

Table 2. Screening of solvents[a].

Entry	Solvent (Temp. °C)	Time (hr)	Yield[b] (%)
1	DMSO (100)	1.5	65
2	DMF (100)	1.5	60
3	1,4-Dioxane (100)	2.0	68
4	Ethanol (78)	1.0	85
5	DCM (38)	1.0	75
6	Acetonitrile (80)	3.0	82
7	Methanol (64)	2.5	70
8	Toluene (110)	3.0	60
9	Water (100)	1.2	92

[a] *Reaction and conditions*: Ethyl acetoacetate (1.0 mmol), 3-Nitrobenzaldehyde (1.0 mmol), Dimedone (1.0 mmol), ammonium chloride (1.0 mmol) and resin bound Wang-SO_3H (10 %w/w) wrt aldehyde in solvent at respective temperature. [b] Yield refers to pure products after crystallization.

Table 3. Recyclability of the catalyst[a]

Entry	Cycle	Time (hr)	Yield[b] (%)	pH of the reaction mass
1	Fresh	1.2	92	2.3
2	1	1.3	92	2.3
3	2	1.3	91	2.4
4	3	1.5	90	2.5
5	4	1.6	89	2.5

[a]*Reaction and conditions*: Ethyl acetoacetate (1.0 mmol), 3-Nitrobenzaldehyde (1.0 mmol), Dimedone (1.0 mmol), ammonium chloride (1.0 mmol) and resin bound Wang-SO_3H (10 %w/w) in water at 100 °C. [b]Yield refers to pure products after crystallization.

Table 4. synthesis of polyhydroquinoline derivatives in the presence of various catalysts[a]

Entry	catalyst	solvent	Temp. (^{0}C)	Time (hr)	Yield[b] (%)	Lit. Ref.
1	No catalyst	H_2O	Reflux	5.0	Traces	Present work
2	Wang-SO_3H	H_2O	Reflux	1.2	85-96	Present work
3	Dowex 50	H_2O	Reflux	4.0	78	Present work
4	Amberlyst 15	H_2O	Reflux	5.5	72	Present work
5	Cellulose sulfuric acid	H_2O	Reflux	2-5	78-92	36
6	PPh_3	C_2H_5OH	Reflux	5.0	72	37
7	$MgAl_2$/hydrotalcites	CH_3CN	25-35	6.5	32-75	38
8	$NaHSO_4/SiO_2$	CH_3CN	25-35	5-8	75-90	39
9	Fe_3O_4/SiO_2	C_2H_5OH	25-35	4.0	60	28
10	$Fe_3O_4/SiO_2/PPh_3$	C_2H_5OH	25-35	3.0	70	28
11	$Fe_3O_4/SiO_2/PPh_3/[CrO_3Br]$	C_2H_5OH	25-35	0.5	87-96	28
12	PTSA	H_2O	Reflux	6.0	28	31

[a]*Reaction and conditions:* Ethyl acetoacetate (1.0 mmol), 3-Nitrobenzaldehyde (1.0 mmol), Dimedone (1.0 mmol), ammonium chloride (1.0 mmol) and resin bound Wang-SO3H (10 %w/w) in water at 100 °C. [b]Yield refers to pure products after crystallization

Table 5. Reaction time and yield for the reaction of different amines/ammonium salts[a]

Entry	Amine (6a-e)	Time (hr)	Product	Product (R) (7a-e)	Yield[b] (%)
1	NH_4OAc	1.5	7a	H	90
2	NH_4Cl	1.2	7b	H	92
3	NH_4HCO_3	1.3	7c	H	91
4	$C_6H_5NH_2$	2.0	7d	C_6H_5	78
5	$2\text{-}CH_3\text{-}C_6H_5\text{-}NH_2$	2.5	7e	$2\text{-}CH_3\text{-}C_6H_5$	69

[a]*Reaction and conditions:* Ethyl acetoacetate (1.0 mmol), 3-Nitrobenzaldehyde (1.0 mmol), Dimedone (1.0 mmol), Amine (1.0 mmol) and resin bound Wang-SO3H (10 %w/w) in water at 100 °C. [b]Yields refers to pure products after crystallization.

Table 6. Wang-OSO_3H catalyzed synthesis of polyhydroquinoline derivatives[a]

Entry	Aldehyde (R) (2a-q)	R^1	R^2	R^3	Product (5a-q)	Time (hr)	Yield [b] (%)	M.P. (°C)	
								Observed	Reported
1	Benzaldehyde, **2a**	CH_3	CH_3	C_2H_5	5a	1.2	96	203-206	203-204[31]
2	2-Napthaldehyde, **2b**	CH_3	CH_3	C_2H_5	5b	1.3	94	233-236	…
3	Isovaleraldehyde, **2c**	CH_3	CH_3	C_2H_5	5c	1.3	85*	172-174	….
4	Furfural, **2d**	CH_3	CH_3	C_2H_5	5d	1.2	90*	245-247	…
5	4-Nitro benzaldehyde, **2e**	CH_3	CH_3	CH_3	5e	1.1	90	251-253	252-254[31]
6	4-Cyano benzaldehyde, **2f**	CH_3	CH_3	CH_3	5f	1.3	90	223-225	220-222[13]
7	5-Hydroxy-2–Nitro benzaldehyde, **2g**	CH_3	CH_3	C_2H_5	5g	1.2	89	166-168	167-169[31]
8	4-Chloro bezaldehyde, **2h**	CH_3	CH_3	CH_3	5h	1.3	91	221-224	221-223[13]
9	3-	CH	CH	C_2H	5i	1.2	92	175-178	177-178[16]

	Nitrobezaldehyde, **2i**	3	3	5					
10	3,4-Dimethoxy benzaldehyde, **2j**	CH_3	CH_3	C_2H_5	5j	1.3	90	197-201	198-199[16]
11	4-Methoxy benzaldehyde, **2k**	CH_3	CH_3	C_2H_5	5k	1.3	93	254-256	256-257[13]
12	3-Nitrobezaldehyde, **2l**	H	H	C_2H_5	5l	1.4	93	203-205	204-206[31]
13	3,4-Dimethoxy benzaldehyde, **2m**	CH_3	CH_3	CH_3	5m	1.3	94	208-210	209-211[31]
14	4-(Trifluoromethyl) benzaldehyde, **2n**	CH_3	CH_3	C_2H_5	5n	1.3	90	188-191	188-190[31]
15	4-Cyano Benzaldehyde, **2o**	CH_3	CH_3	C_2H_5	5o	1.3	93	141-143	140-142[31]
16	4-Chlorobenzaldehyde, **2p**	CH_3	CH_3	C_2H_5	5p	1.5	94	231-233	232-234[13]
17	4-Nitrobezaldehyde, **2q**	CH_3	CH_3	C_2H_5	5q	1.6	95	243-245	242-244[16]

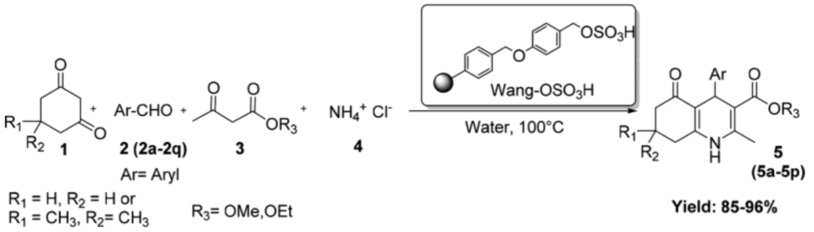
[a] All reactions were carried out in water at 100 ^{0}C using catalyst Wang-SO_3H(10 %w/w) wrt aldehyde.

[b] Yields refer to pure products after crystallization.

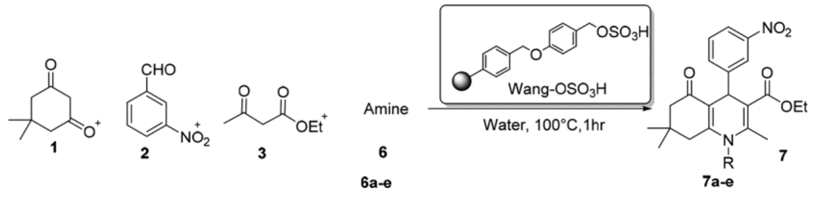
* Yields refer to pure products after column purification.

Scheme 1. Preparation of Wang-OSO_3H.

Scheme 2. Wang-SO_3H mediated synthesis of polyhydroquinoline derivatives.



Scheme 3. Wang-SO_3H mediated synthesis of polyhydroquinoline.



Scheme 4. Proposed mechanism for polyhydroquinoline derivatives catalyzed by Wang sulfonic acid.

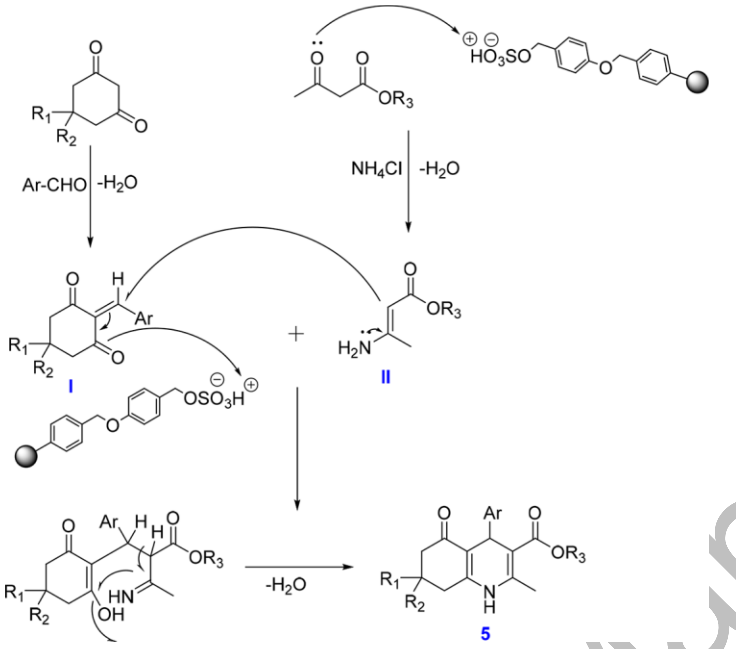


Figure 1. Structures of some biologically active natural products containing a 1,4-dihydropyridyl (DHP).