Journal of Molecular Catalysis A: Chemical 335 (2011) 46–50

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Cellulose sulfuric acid catalyzed multicomponent reaction for efficient synthesis of 1,4-dihydropyridines via unsymmetrical Hantzsch reaction in aqueous media

Javad Safari*, Sayed Hossein Banitaba, Shiva D. Khalili

Laboratory of Organic Chemistry Research, Department of Organic Chemistry, College of Chemistry, University of Kashan, 87317-51167 Kashan, Islamic Republic of Iran

ARTICLE INFO

Article history:
Received 1 September 2010
Received in revised form
10 November 2010
Accepted 11 November 2010
Available online 19 November 2010

Keywords:
Cellulose sulfuric acid
Biodegradable catalysts
Hantzsch reaction
One-step condensation
Aqueous media

ABSTRACT

C_5-unsubstituted 1,4-dihydropyridines were obtained in good to excellent yields by proceeding through a simple, mild and efficient procedure utilizing cellulose sulfuric acid (CSA) as a catalyst. The reaction work-up is very simple and catalyst can be easily separated from reaction mixture and reused several times in subsequent reactions.

1. Introduction

The developing of new multicomponent reactions (MCRs) and improving the known MCRs are an area of considerable current interest [1–3]. As opposed to the classical way to synthesize complex molecules by sequential synthesis, MCRs allow the assembly of complex molecules in one-pot and show a facile execution, high atom-economy and high selectivity [4–7]. As a one-pot reaction, MCRs generally afford good yields and are fundamentally different from two-component and stepwise reactions in several aspects [8] and permitted a rapid access to combinatorial libraries of complex organic molecules for an efficient lead structure identification and optimization in drug discovery.

1,4-Dihydropyridines (1,4-DHPs) are important class of compounds in the field of drugs and pharmaceuticals [9]. The DHP moiety is common to numerous bioactive compounds which include various antihypertensive, vasodilator, antimutagenic, antitumor and antidiabetic agents [10–13]. 1,4-DHPs are generally synthesised by classical Hantzsch method, which involves cyclocondensation of an aldehyde, β-ketoesters and ammonia either in acetic acid or in refluxing ethanol for long reaction times which typically leads to low yields [14–16]. However, this method cannot be applied for the synthesis of different substitiuted biologically active 1,4-DHPs. Recently, several modifications for this classical method have been reported for the facile and efficient synthesis of important dihydropyridine derivatives [17–22]. Other procedures comprise the use of microwave [23], ionic liquids [24], CAN [25], tetrabutylammonium hydrogen sulfate [26], I_2 [27] and metal triflate [28].

In recent years, the direction of science and technology has been shifting more towards eco-friendly, natural product resources and reusable catalysts. Thus, natural biopolymers are attractive candidates in the search for such solid support catalysts [29,30]. Recently, cellulose sulfuric acid (CSA) has emerged as a promising biopolymeric recyclable solid support acid catalysts for acid-catalyzed reactions, such as the synthesis of α-aminonitriles [31], imidazoazines [32], xanthenes [33] and quinolines [34]. We now report an efficient catalyzed method for the synthesis of C_5-unsubstitiuted 1,4-dihydropyridines via the three-component reaction of ethyl acetoacetate, chalcone derivatives and ammonium acetate in aqueous media (Scheme 1). To the best of our knowledge, the use of cellulose sulfuric acid as a catalyst for the synthesis of C_5-unsubstitiuted 1,4-dihydropyridines previously has not been reported.

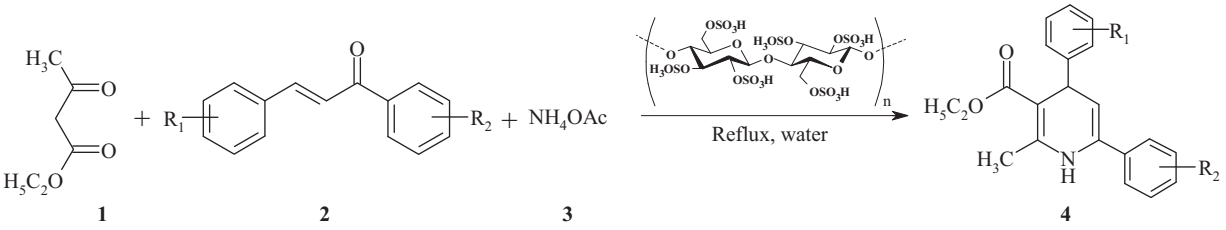
2. Experimental

2.1. General

Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Perkin-Elmer FT-IR 550 spectrom-

* Corresponding author. Fax: +98 361 5912397.
E-mail addresses: Safari_jav@yahoo.com, Safari@kashanu.ac.ir (J. Safari).

1381-1169/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2010.11.012



Scheme 1. Cellulose sulfuric acid-catalyzed unsymmetrical one-pot three-component Hantzsch reaction.

eter. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 and 100 MHz respectively. NMR spectra were obtained in DMSO-d_6 solutions. The element analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer carried out on Perkin-Elmer 240c analyzer.

2.2. Preparation of cellulose sulfuric acid

To a magnetically stirred mixture of 5.0 g of cellulose in 20 ml of *n*-hexane, 1.0 g of chlorosulfonic acid (9 mmol) was added drop wise at 0 °C during 2 h. HCl gas was removed from the reaction vessel immediately. After the addition was complete, the mixture was stirred for 2 h. Then the mixture was filtered and washed with 30 ml of acetonitrile and dried at room temperature to afford 5.25 g of cellulose sulfuric acid as a white powder. Sulfur content of the samples by conventional elemental analysis, was 0.55 for cellulose sulfuric acid. The number of H^+ sites on the cellulose-SO_3H was determined by acid–base titration was 0.50 mequiv./g [31].

2.3. General procedure for the synthesis of 2-methyl-4,6-diphenyl-1,4-dihydro-3-pyridinecarboxilate derivatives

A mixture of ethyl acetoacetate (1 mmol), 1,3-diphenyl-2-propen-1-one derivatives (1 mmol), ammonium acetate (1 mmol) and cellulose sulfuric acid (0.05 g) was stirred in H_2O (5 ml) at 100 °C for the appropriate time, as shown in Table 2. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to ambient temperature, CH_2Cl_2 was added, and the cellulose sulfuric acid was filtered off. The filtrate was concentrated to dryness, and the crude solid product was crystallized from EtOH to afford the pure ethyl 2-methyl-4,6-diphenyl-1,4-dihydro-3-pyridinecarboxilate derivatives (Table 2).

2.4. Spectral data for new compounds

2.4.1. Ethyl 2-methyl-4,6-diphenyl-1,4-dihydro-3-pyridinecarboxilate (**4a**)

IR (KBr): υ (cm^{-1}) 3341, 1688, 1726; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (t, J = 7.2 Hz, 3H), 2.23 (s, 3H), 3.91 (q, J = 7.2 Hz, 2H), 5.25 (d, J = 5.7 Hz, 1H), 5.94 (d, J = 5.7 Hz, 1H), 6.57 (s, 1H, NH), 7.0–7.50 (m, 5H), 7.60–8.0 (m, 5H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.2, 18.2, 38.4, 61.2, 102.1, 105.7, 123.8, 126.7, 127.6, 128.37, 128.7, 129.8, 134.5, 140.9, 143.9, 147.2, 171.3 ppm; Anal. Calcd. for $C_{21}H_{21}NO_2$ (%): C, 78.97; H, 6.63; N, 4.39. Found: C, 78.79; H, 6.60; N, 4.35.

2.4.2. Ethyl 2-methyl-6-(4-nitrophenyl)-4-phenyl-1,4-dihydro-3-pyridinecarboxilate (**4b**)

IR (KBr): υ (cm^{-1}) 3342, 1687, 1728, 1436, 1354; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (t, J = 7.1 Hz, 3H), 2.19 (s, 3H), 3.56 (q, J = 7.1 Hz, 2H), 5.42 (d, J = 6.1 Hz, 1H), 6.23 (d, J = 6.1 Hz, 1H), 6.65 (s, 1H, NH), 7.0–7.40 (m, 5H), 7.52 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 8.1 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.2, 18.2, 37.9, 61.1, 103.7, 105.8, 122.8, 124.7, 128.3, 130.3, 131.4, 141.4, 142.5, 143.9, 147.5, 148.1, 169.6 ppm; Anal. Calcd. for $C_{21}H_{20}N_2O_4$ (%): C, 69.22; H, 5.53; N, 7.69. Found: C, 69.15; H, 5.49; N, 7.67.

2.4.3. Ethyl 6-(4-bromophenyl)-2-methyl-4-phenyl-1,4-dihydro-3-pyridinecarboxilate (**4c**)

IR (KBr): υ (cm^{-1}) 3344, 1679, 1731; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, J = 6.9 Hz, 3H), 2.17 (s, 3H), 3.78 (q, J = 6.9 Hz, 2H), 5.70 (d, J = 6.7 Hz, 1H), 6.64 (d, J = 6.7 Hz, 1H), 6.89 (s, 1H, NH), 7.0–7.25 (m, 5H), 7.36 (d, J = 7.9 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.2, 18.2, 35.7, 60.9, 104.1, 106.1, 120.8, 123.9, 127.5, 128.2, 129.7, 130.2, 134.90, 141.3, 143.7, 146.8, 169.1 ppm; Anal. Calcd. for $C_{21}H_{20}BrNO_2$ (%): C, 63.33; H, 5.06; N, 3.52. Found: C, 63.25; H, 5.03; N, 3.51.

2.4.4. Ethyl 2-methyl-4-(4-methylphenyl)-6-phenyl-1,4-dihydro-3-pyridinecarboxilate (**4d**)

IR (KBr): υ (cm^{-1}) 3344, 1679, 1731; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.19 (t, J = 6.8 Hz, 3H), 1.98 (s, 3H), 2.20 (s, 3H), 3.87 (q, J = 6.8 Hz, 2H), 5.73 (d, J = 7.1 Hz, 1H), 6.69 (d, J = 7.1 Hz, 1H), 6.79 (s, 1H, NH), 7.0–7.50 (m, 5H), 7.66 (d, J = 8.1 Hz, 2H), 7.98 (d, J = 8.1 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.2, 18.2, 22.5, 35.6, 60.9, 104.1, 106.2, 120.7, 123.8, 127.5, 128.1, 130.2, 130.4, 134.8, 141.2, 143.7, 146.7, 170.1 ppm; Anal. Calcd. for $C_{22}H_{23}NO_2$ (%): C, 79.25; H, 6.95; N, 4.20. Found: C, 79.17; H, 6.92; N, 4.18.

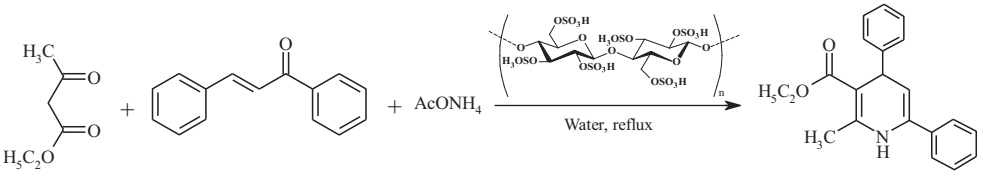
2.4.5. Ethyl 4-(4-chlorophenyl)-2-methyl-6-(4-nitrophenyl)-1,4-dihydro-3-pyridinecarboxilate (**4e**)

IR (KBr): υ (cm^{-1}) 3347, 1674, 1736; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.19 (t, J = 6.8 Hz, 3H), 2.14 (s, 3H), 3.87 (q, J = 6.8 Hz, 2H), 5.74 (d, J = 6.6 Hz, 1H), 6.62 (d, J = 6.6 Hz, 1H), 7.12 (s, 1H, NH), 7.19 (d, J = 7.8 Hz, 2H), 7.26 (d, J = 7.8 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.65 (d, J = 7.9 Hz, 2H), ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 19.1, 33.3, 61.4, 103.7, 105.8, 124.8, 128.1, 128.9, 131.6, 132.6, 140.9, 141.2, 141.3, 146.3, 147.6, 167.8 ppm; Anal. Calcd. for $C_{21}H_{19}ClN_2O_4$ (%): C, 63.24; H, 4.80; N, 7.02. Found: C, 63.14; H, 4.78; N, 7.01.

2.4.6. Ethyl 6-(4-chlorophenyl)-2-methyl-4-(3-nitrophenyl)-1,4-dihydro-3-pyridinecarboxilate (**4f**)

IR (KBr): υ (cm^{-1}) 3344, 1675, 1721; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, J = 7.1 Hz, 3H), 2.11 (s, 3H), 3.82 (q, J = 7.1 Hz, 2H), 5.62 (d, J = 6.9 Hz, 1H), 6.32 (d, J = 6.9 Hz, 1H), 7.25 (s, 1H, NH), 7.34 (d, J = 7.3 Hz, 2H), 7.43 (d, J = 7.3 Hz, 2H), 7.48 (dd, J = 8.1 Hz, J = 7.8 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 8.13 (dd, J = 8.1 Hz, J = 2 Hz, 1H), 8.32 (d, J = 2 Hz, 1H), ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 20.2, 33.9, 61.1, 104.2, 105.8, 122.4, 123.4, 124.9, 127.7, 132.5, 133.3, 134.4, 136.2, 140.1, 141.3, 143.5, 149.6, 168.3 ppm; Anal. Calcd. for

Table 1
Optimizing the reaction conditions.[a]



Entry	Cellulose sulfuric acid (g)	Time (h)	Yield (%)[b]
1	0	6	35
2	0.02	3	90
3	0.05	1.5	98
4	0.1	1	75
5	0.12	1.0	74

[a] Ethyl acetoacetate/1,3-diphenyl-2-propen-1-one/ammonium acetate = 1:1:1.
[b] Isolated yields.

$C_{21}H_{19}ClN_2O_4$ (%): C, 63.24; H, 4.80; N, 7.02. Found: C, 63.14; H, 4.78; N, 7.01.

2.4.7. Ethyl 4-(4-methoxyphenyl)-2-methyl-6-phenyl-1,4-dihydro-3-pyridinecarboxylate
(4g)

IR (KBr): υ (cm^{-1}) 3342, 1679, 1729; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.19 (t, J = 6.9 Hz, 3H), 2.20 (s, 3H), 3.53 (s, 3H, OMe), 3.77 (q, J = 6.9 Hz, 2H), 6.04 (d, J = 7.4 Hz, 1H), 6.54 (d, J = 7.4 Hz, 1H), 6.88 (s, 1H, NH), 6.99 (d, J = 7.7 Hz, 2H), 7.10–7.30 (m, 5H), 7.56 (d, J = 7.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 17.9, 36.3, 55.4, 62.3, 98.2, 106.3, 113.6, 126.4, 127.2, 128.5, 130.2, 134.5, 139.6, 140.4, 141.7, 155.8, 169.8 ppm; Anal. Calcd. for $C_{22}H_{23}NO_3$ (%): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.58; H, 6.60; N, 4.00.

2.4.8. Ethyl 4-(4-chlorophenyl)-2-methyl-6-phenyl-1,4-dihydro-3-pyridinecarboxylate
(4h)

IR (KBr): υ (cm^{-1}) 3346, 1673, 1722; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, J = 6.8 Hz, 3H), 2.14 (s, 3H), 3.52 (q, J = 6.8 Hz, 2H), 6.37 (d, J = 7.1 Hz, 1H), 6.98 (d, J = 7.1 Hz, 1H), 7.21 (s, 1H, NH), 7.32 (d, J = 7.2 Hz, 2H), 7.30–7.50 (m, 5H), 7.71 (d, J = 7.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.3, 18.7, 36.9, 63.1, 99.3, 107.8, 125.4, 127.7, 128.3, 129.3, 130.2, 132.7, 134.5, 139.6, 141.3, 141.7, 170.1 ppm; Anal. Calcd. for $C_{21}H_{20}ClNO_2$ (%): C, 71.28; H, 5.70; N, 3.96. Found: C, 71.20; H, 5.65; N, 3.93.

2.4.9. Ethyl 6-(4-chlorophenyl)-2-methyl-4-phenyl-1,4-dihydro-3-pyridinecarboxylate
(4i)

IR (KBr): υ (cm^{-1}) 3348, 1669, 1745; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.22 (t, J = 7.4 Hz, 3H), 2.11 (s, 3H), 3.44 (q, J = 7.4 Hz, 2H), 6.76 (d, J = 6.1 Hz, 1H), 7.10 (d, J = 6.1 Hz, 1H), 7.29 (s, 1H, NH), 7.0–7.3 (m, 5H), 7.34 (d, J = 7.4 Hz, 2H), 7.55 (d, J = 7.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5, 19.1, 36.1, 62.3, 100.1, 106.9, 122.3, 124.2, 127.2, 130.2, 130.9, 132.2, 133.5, 140.6, 141.4, 143.2, 170.3 ppm; Anal. Calcd. for $C_{21}H_{20}ClNO_2$ (%): C, 70.69; H, 5.35; N, 4.12. Found: C, 70.61; H, 5.32; N, 4.09.

2.4.10. Ethyl 2-methyl-6-(3-nitrophenyl)-4-(4-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate
(4j)

IR (KBr): υ (cm^{-1}) 3347, 1671, 1712; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, J = 6.9 Hz, 3H), 2.15 (s, 3H), 3.65 (q, J = 6.9 Hz, 2H), 5.80 (d, J = 7.4 Hz, 1H), 6.64 (d, J = 7.4 Hz, 1H), 7.15 (s, 1H, NH), 7.44 (d, J = 7.7 Hz, 1H), 7.53 (s, 1H), 7.89 (dd, J = 8.2 Hz, J = 7.7 Hz, 1H), 8.12 (d, J = 7.1 Hz, 2H), 8.34 (d, J = 7.2 Hz, 2H); 8,57 (d, J = 8.2 Hz, 1H); ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 21.1, 32.3, 60.5, 100.3, 105.8, 119.4, 122.4, 126.5, 129.4, 130.6, 133.3, 135.6, 140.5, 143.7, 144.5, 145.8, 148.5, 169.5 ppm; Anal. Calcd. for $C_{21}H_{19}N_3O_6$ (%): C, 60.76; H, 4.33; N, 10.63. Found: C, 60.65; H, 4.26; N, 10.59.

2.4.11. Ethyl 6-(4-hydroxyphenyl)-2-methyl-4-(4-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate
(4k)

IR (KBr): υ (cm^{-1}) 3338, 1671, 1731, 1342; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.21 (t, J = 6.5 Hz, 3H), 2.16 (s, 3H), 3.81 (q, J = 6.5 Hz, 2H), 5.61 (d, J = 6.4 Hz, 1H), 5.84 (d, J = 6.4 Hz, 1H), 6.22 (s, 1H, NH), 6.93 (bs, 1H, OH), 7.21 (d, J = 7.4 Hz, 2H), 7.29 (d, J = 7.4 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.65 (d, J = 7.8 Hz, 2H), ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 20.3, 33.8, 62.1, 104.5, 106.1, 124.7, 128.9, 130.6, 131.9, 132.7, 141.6, 141.9, 142.6, 147.4, 148.6, 168.3 ppm; Anal. Calcd. for $C_{21}H_{20}N_2O_5$ (%): C, 63.31; H, 5.30; N, 7.36. Found: C, 63.21; H, 5.28; N, 7.34.

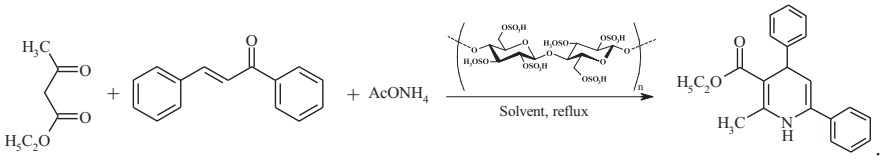
2.4.12. Ethyl 4-(4-hydroxyphenyl)-2-methyl-6-(4-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate
(4l)

IR (KBr): υ (cm^{-1}) 3336, 1670, 1731, 1339; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.22 (t, J = 6.6 Hz, 3H), 2.15 (s, 3H), 3.83 (q, J = 6.6 Hz, 2H), 5.64 (d, J = 6.3 Hz, 1H), 5.81 (d, J = 6.3 Hz, 1H), 6.20 (s, 1H, NH), 6.85 (bs, 1H, OH), 7.10 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 7.1 Hz, 2H), 7.68 (d, J = 7.1 Hz, 2H), ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.8, 21.4, 33.8, 63.5, 105.7, 106.8, 123.2, 126.9, 131.5, 131.8, 133.4, 141.5, 141.9, 143.8, 147.8, 148.7, 165.2 ppm; Anal. Calcd. for $C_{21}H_{20}N_2O_5$ (%): C, 63.31; H, 5.30; N, 7.36. Found: C, 63.21; H, 5.28; N, 7.34.

3. Results and discussion

We had the opportunity to further explore the catalytic activity of cellulose sulfuric acid in the synthesis of 1,4-dihydropyridines. Herein, we wish to report on a novel synthesis of 1,4-DHP promoted by a catalytic amount of cellulose sulfuric acid (CSA) in water under reflux conditions to excellent yields. In an initial endeavor, 1 mmol each of ethyl acetoacetate **1**, 1,3-diphenyl-2-propen-1-one **2a**, and ammonium acetate were stirred at 100 °C in water. After 6 h, only 35% of the expected product **4a** was obtained when after workup and recrystallization of the crude product from ethanol (Table 1, Entry 1). To improve the yield and optimize the reaction conditions, the same reaction was carried out in the presence of a catalytic amount of 0.02 g of CSA under similar conditions. Surprisingly, a significant improvement was observed and the yield of **4a** was dramatically increased to 90% after stirring; the mixture was stirred for only 3 h (Entry 2). With this optimistic result in hand, we further investigated the best

Table 2
Solvent screening for the reaction between ethyl acetoacetate **1**, chalcone **2a** and ammonium acetate.[a]



Entry	Solvent	Time (h)	Yield (%)[b]
1	EtOH	6.0	60
2	MeOH	6.0	50
3	Isopropanol	6.0	30
4	*t*-BuOH	24.0	25
5	THF	24.0	Trace
6	Acetonitrile	24.0	Trace
7	Water	6.0	80
8	Water	3.0	92
9	Water	1.5	98
10	None	3.0	85

[a] CSA (0.05 g), ethyl acetoacetate/1,3-diphenyl-2-propen-1-one/ammonium acetate = 1:1:1.
[b] Isolated yields.

reaction conditions using different amounts of CSA. An increase in the quantity of CSA from 0.02 g to 0.05 g not only decreased the reaction time from 3 h to 1.5 h, but also increased the product yield slightly from 90% to 98% (Entry 3). Although the use of 0.10 g of CSA permitted the reaction time to be decreased to 1 h, the yield unexpectedly decreased to 75% (Entry 4). A possible explanation for the low product yield is that the starting material or the product may have been destroyed during the reaction when an excess amount (0.10 g) of CSA was used in the exothermic reaction and that 0.05 g CSA was sufficient to catalyze the reaction effectively.

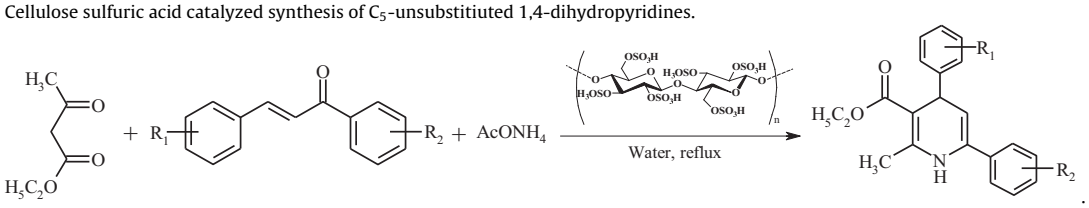
The efficiency of water as solvent compared to various organic solvents was also examined (Table 2). In this study, it was found that water is a more efficient and superior solvent (Entries 7–9) over other organic solvents (Entries 1–6) with respect to reaction time and yield of the desired dihydropyridine.

Based on above observations, we conducted the same reactions using ethyl acetoacetate **1**, variety of different substituted 1,3-diphenyl-2-propen-1-one **2a–j** and **3** in the presence of 0.05 g of CSA under similar conditions. As expected, satisfactory results were observed, and the results are summarized in Table 3.

It is shown that in general a wide range of chalcones could react with ethyl acetoacetate and ammonium acetate smoothly and give **4a–l** in good to excellent yields (Table 3, Entries 1–12). It is also notable that the electronic property of the aromatic ring of chalcones has some effects on the rate of the condensation process. Generally speaking, shorter reaction time was needed for the substrates bearing electron-withdrawing groups on the aromatic rings (Table 3, Entries 2, 3, 5, 6, 8, 9, 10 and 12). On the other hand, while substrates bearing electron-donating groups can afford the corresponding products with almost equally satisfactory yields. A little bit longer reaction period was necessary to complete the reaction (Table 3, Entries 1, 4, 7 and 11). A possible mechanism for the formation of title compounds **4a–l** is shown in Scheme 2.

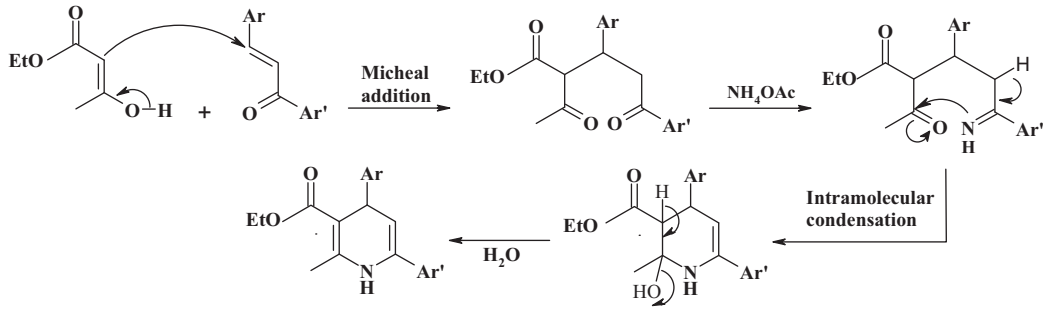
The reusability of the catalyst was checked by separating the cellulose sulfuric acid from the reaction mixture by simple filtration, washing with CH_2Cl_2, and drying in a vacuum oven at 60 °C for 5 h prior to reuse in subsequent reactions. The recovered catalyst can be reused at least three additional times in subsequent reactions without significant loss in product yield (Table 4).

Table 3
Cellulose sulfuric acid catalyzed synthesis of C_5-unsubstituted 1,4-dihydropyridines.



Entry	R_1	R_2	Product	Time (h)	Yield (%)[a]	Mp (°C)
1	H	H	**4a**	1.5	98	245–247
2	H	*p*-NO_2	**4b**	1.1	95	232–235
3	H	*p*-Br	**4c**	1.2	93	257–259
4	*p*-CH_3	H	**4d**	1.5	87	235–238
5	*p*-Cl	*p*-NO_2	**4e**	1.0	96	211–213
6	*m*-NO_2	*p*-Cl	**4f**	1.0	85	218–220
7	*p*-OCH_3	H	**4g**	1.5	85	223–225
8	*p*-Cl	H	**4h**	1.4	92	252–255
9	H	*p*-Cl	**4i**	1.3	90	264–266
10	*p*-NO_2	*m*-NO_2	**4j**	1.1	92	203–205
11	*p*-NO_2	*p*-OH	**4k**	1.5	93	271–274
12	*p*-OH	*p*-NO_2	**4l**	1.0	98	265–269

[a] Isolated yields.



Scheme 2. Plausible mechanism of C_5-unsubstitiuted 1,4-dihydropyridine derivatives.

Table 4
The effect of reusability of cellulose sulfuric acid catalyst on the product **4a** yield.[a]

Entry	Cycle	Yield (%)[b]
1	0	98
2	1	92
3	2	91
4	3	91

[a] *Reaction conditions*: ethyl acetoacetate (1 mmol), chalcone **2a** (1 mmol) and ammonium acetate (1 mmol), CSA (0.05 g), water (5 ml), 100 °C.
[b] Isolated yields.

4. Conclusion

Cellulose sulfuric acid, an efficient, non-toxic, reusable, and solid support biodegradable acid catalyst, has been prepared and utilized for the synthesis of C_5-unsubstitiuted 1,4-dihydropyridines via the three-component reaction of ethyl acetoacetate with a wide range of chalcone derivatives and ammonium acetate in aqueous media. Prominent of this modified methodology is superior to existing methodologies for the synthesis of 1,4-dihydropyridines.

Acknowledgment

We acknowleged the research council of University of Kashan.

References

[1] A. Domling, I. Ugi, Angew. Chem. Int. Ed. 39 (2000) 3168–3173.
[2] J. Zhu, H. Bienayme, Multi Component Reactions, Wiley-VCH, Weinheim, 2005.
[3] A. Domling, Chem. Rev. 106 (2006) 17–23.
[4] I. Ugi, Pure Appl. Chem. 73 (2001) 187–191.
[5] R.R. Nagawade, D.B. Shinde, Acta Chim. Slov. 54 (2007) 642–645.
[6] D.M. D'Souza, T.J. Mueller, Chem. Soc. Rev. 36 (2007) 3169–3173.
[7] C.C.A. Cariou, G.J. Clarkson, M. Shipman, J. Org. Chem. 73 (2008) 9762–9764.
[8] C. Kalinski, H. Lemoine, J. Schmidt, C. Burdack, J. Kolb, M. Umkehrer, G. Ross, Synlett (2008) 4007–4011.
[9] G.M. Reddy, M. Shiradkar, A.K. Chakravarthy, Curr. Org. Chem. 11 (2007) 484–487.
[10] R.A. Janis, D.A. Triggle, J. Med. Chem. 25 (1983) 775–779.
[11] R.H. Bocker, F.P. Guengerich, J. Med. Chem. 28 (1986) 1596–1601.
[12] A.C. Gaudio, A. Korolkovas, Y. Tkahata, J. Pharm. Sci. 83 (1994) 1110–1114.
[13] M.F. Gordeev, D.V. Patel, E.M. Gordon, J. Org. Chem. 61 (1996) 924–927.
[14] A. Dondoni, A. Massi, E. Minghini, V. Bertolasi, Tetrahedron 60 (2004) 2311–2314.
[15] A. Hantzsch, Ber. Dtsch. Chem. Ges. 14 (1881) 1637–1640.
[16] B. Love, K.M. Sander, J. Org. Chem. 30 (1965) 1914–1919.
[17] G.V.M. Sharma, K.L. Reddy, P.S. Lakshmi, P.R. Krishna, Synthesis (2006) 55–58.
[18] T. Itoh, K. Nagata, M. Miyazaki, H. Ishikawa, A. Kurihara, A. Ohsawa, Tetrahedron 60 (2004) 6649–6655.
[19] R. Ruppert, C. Jeandon, A. Sgambati, H. Callot, Chem. Commun. (1999) 2123–2124.
[20] S. Ko, C.F. Yao, Tetrahedron Lett. 62 (2006) 7293–7299.
[21] A. Kumar, R.A. Maurya, Synlett 6 (2008) 883–885.
[22] A. Debache, R. Boulcina, A. Belfaitah, S. Rhouati, B. Carboni, Synlett (2008) 509–512.
[23] A. Agarwal, P.M.S. Chauhan, Tetrahedron Lett. 46 (2005) 1345–1348.
[24] R. Sridhar, P.T. Perumal, Tetrahedron 61 (2005) 2465–2469.
[25] K. Shengkai, Y. Ching-Fa, Tetrahedron 62 (2006) 7293–7299.
[26] N. Tewari, N. Dwivedi, R.P. Tripathi, Tetrahedron Lett. 45 (2004) 9011–9014.
[27] S. Ko, M.N.V. Sastry, C. Lin, C.F. Yao, Tetrahedron Lett. 46 (2005) 5771–5774.
[28] L.M. Wang, J. Sheng, L. Zhang, J.W. Han, Z. Fan, H. Tian, C.T. Qian, Tetrahedron 61 (2005) 1539–1543.
[29] R. Breslow, Acc. Chem. Res. 13 (1980) 170–174.
[30] J.H. Clark, D.J. Macquarrie, Green Chemistry and Technology, Blackwell, Abingdon, 2002.
[31] S. Ahmad, M. Ali, Appl. Catal. A: Gen. 331 (2007) 149–153.
[32] S. Ahmad, M. Ali, R. Jafar, S. Ebrahim, Chem. Pharm. Bull. 55 (6) (2007) 957–961.
[33] J. Venu Madhav, Y. thirupathi Reddy, P. Narsimha Reddy, J. Mol. Catal. A: Chem. 304 (2009) 85–87.
[34] S. Ahmad, R. Abbas, B. Zahra, Catal. Commun. 9 (2009) 13–15.