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Catalytic synthesis of 1,4-dihydropyridine derivatives using hexagonal mesoporous silicate (HMS)

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A simple and efficient one-pot synthesis of 1,4-dihydropyridine derivatives was achieved *via* condensation of ethyl acetoacetate with various aryl aldehydes and ammonium acetate in the presence of hexagonal mesoporous silicate (HMS) as a heterogeneous catalyst and EtOH as a solvent under reflux conditions with good to excellent yields.
Keywords: 1,4-Dihydropyridine, EtOH, Hantzsch Condensation, HMS, One-pot, Reflux conditions.

INTRODUCTION

Six-membered heterocyclic compounds are important materials in organic chemistry. These compounds exhibit diverse biological and medical activities, and may be used as constituents of synthetic compounds of medicinal interest [1,2]. Among them, 1,4-dihydropyridine (1,4-DHP) cores are important classes of drugs because 1,4-DHPs are analogues of NADH coenzymes that are an important class of drugs [3]. These heterocyclic compounds are some of the most important classes of drugs to inhibit the HIV virus [4]. They display neuroprotectant [5] and platelet anti-aggregatory activity [6]. They act as cerebral anti-ischemic agents in the treatment of Alzheimer's disease [7]. 1,4-DHPs have potential as chemo sensitizers in tumor therapy [8]. Some of their derivatives are well known as Ca^{2+} channel blockers [9,10].

The classical method for the synthesis of these compounds is the Hantzsch and Liebigs reaction involving multicomponent condensation of an aldehyde with a 1,3-dicarbonyl compound and NH_3 [11]. In the past, many methods for synthesis of 1,4-DHPs and their derivatives have been reported [12-15].

The synthesis of mesoporous molecular sieves using the templating effect of lyotropic liquid crystal mesophases was first proposed in 1992 [16,17]. Mesoporous structures with high surface area have attracted great interest in chemistry. These compounds have been used as nano-filters, photonic devices, and low-k dielectrics, support materials for catalysts, encapsulation, sensors, etc. [18-22]. So far, various strategies have been proposed to tailor a new class of mesoporous structures, to develop a more convenient route to syntheses and to understand their formation mechanisms [23-29].

Therefore, the use of a HMS compound as an efficient catalyst for the one-pot synthesis of some 1,4-dihydropyridines (1,4-DHPs) under thermal conditions was investigated.

The comparison of these data with those of other mesoporous compounds shows that using HMS is a simple and mild method which has advantages such as excellent yields, short reaction time and low cost. The synthesis of HMS is easy [30,31], and this catalyst is very stable in the atmosphere.

RESULTS AND DISCUSSION

Characterization of the catalyst

XRD analysis

The typical XRD pattern for the HMS material shows that it contains an intense diffraction peak at $2\theta = 2.3°$ corresponding to the diffraction of (100) plane, indicating that this sample has a typical characteristic peak of a mesoporous molecular sieve in agreement with the literature [32].

Surface and porosity

The physicochemical properties of HMS are presented in Table 1. The high surface area, the appropriate pore volume and average pore diameter confirm the formation of HMS material, in accordance with the XRD results.

Table 1. Physicochemical characteristics of the mesoporous support

Sample	Surface area ($m^2\ g^{-1}$)	pore volume ($cm^3\ g^{-1}$)	APD (Å)[a]
HMS	987	1.0	33.0

[a:] Average pore diameter

Initially, we studied the Hantzsch-type reaction of benzaldehyde (1a), ethyl acetoacetate, ammonium acetate and HMS as a Lewis acid in different solvents under various conditions (Scheme 1 and Table 2).

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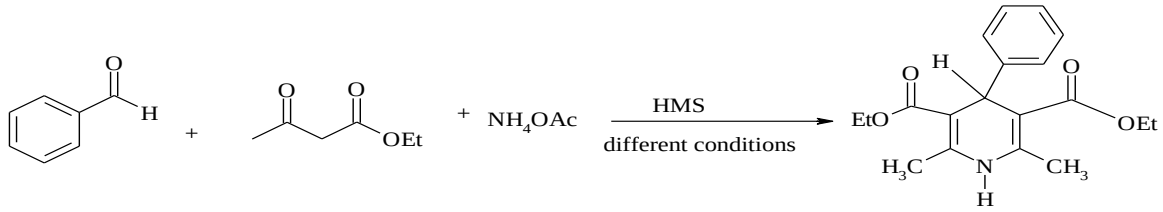


Scheme 1

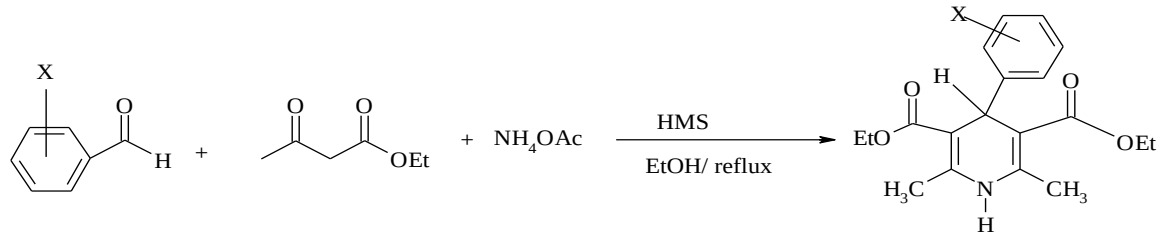
Table 2. Optimization of reaction conditions

Entry	HMS (g)	Solvent	T (°C)	Time (h) [a]	Yield% [b]
1	0.2	EtOH	90	3	30
2	0.5	EtOH	90	3	30
3	0.8	EtOH	90	3	45
4	0.9	EtOH	90	3	95
5	1.0	EtOH	90	3	60
6	1.1	EtOH	90	3	80
7	0.9	EtOH	70	3	80
9	0.9	EtOH	80	3	85
10	0.9	EtOH	90	3	95
11	0.9	EtOH	100	3	95
12	0.9	EtOH	90	3	95
13	0.9	CH_3CN	90	3	<10
14	0.9	H_2O	90	3	75
15	0.9	Solvent free	90	3.5	<10
16	0.9	EtOH	r.t	3	<10

[a] Required time for maximum progress of the reaction. [b]isolated yield.

We have developed a simple methodology for the one-pot synthesis of 1,4-dihydropyridines by HMS as a heterogeneous catalyst to give excellent yields.

Synthesis of 4-phenyl substituted-1,4-dihydropyridine (2a) as a model product was carried out in different solvents (Scheme 1 and Table 2). According to the data presented in Table 2, the use of 0.9 g of HMS at 90◦C gave the best result (Table 2, entry 10). Applying of heat was necessary for the reaction due to failure of reaction when carried out at room temperature. Also, various ethyl 4-substituted-1,4-dihydropyridine 3,5-dicarboxylates (2a-J) were obtained by the reaction of ethyl acetoacetate, different aldehydes and ammonium acetate under the same conditions (Scheme 2 and Table 3).



1a-j **2a-j**

Scheme 2

Table 3. HMS catalyzed synthesis of substituted 1,4-dihydropyridines in ethanol under reflux conditions

Comp.	R	Time (h)[a]	Yield (%)[b]	m.p. measured	m.p. reported
2a	C_6H_5-	3	95	160-161	158-160[33]
2b	4-CH_3-C_6H_4-	3	80	124-125	122-124[34]
2c	3-CH_3-C_6H_4-	3	80	124-125	122-124[34]
2d	4-MeO- C_6H_4-	3.5	80	160-161	158-160[33]
2e	4-Cl- C_6H_4-	3.5	80	149-150	147-148[33]
2f	2-Cl- C_6H_4-	3.5	85	122-124	122-126[35]
2g	4-Br- C_6H_4-	3.5	85	163-164	162-164[33]
2h	3-Br- C_6H_4-	3.5	80	116-118	115-117[35]
2i	4-NO_2- C_6H_4-	2.5	80	130-131	129-131[33]
2j	3-NO_2- C_6H_4-	2	85	163-164	162-164[33]

[a] Required time for maximum progress of the reaction. [b]isolated yield

Table 4. Reuse of HMS in the Hantzsch synthesis of 1,4-DHP (benzaldehyde : ethyl acetoacetate: NH_4 OAc, (1:2 :1.5) in EtOH as solvent at 90°C and 0.9 g HMS)

Run	1	2	3
Isolated yield (%)	95	60	40

Analysis of the data reported in Table 4 shows that the conversion is lower with a reused catalyst. These data suggested that the reaction occurs mainly within the pores of the catalyst.

CONCLUSIONS

We have successfully developed a simple and efficient method for the preparation of a variety of 4-substituted-1,4-dihydropyridines by one-pot three-component reactions of different aromatic aldehydes, β-ketoester and ammonium acetate in the presence of a catalytic amount of HMS catalyst and ethanol under reflux conditions. The main advantages of this methodology are: (a) operational simplicity, (b) short reaction time, (c) high yields of products, and (d) use of relatively non-toxic solvents.

We suggest that the reactivity of this catalyst is related to the number of pores in the HMS catalyst.

EXPERIMENTAL

Melting points were determined in an oil bath and were uncorrected. IR spectra were recorded for solid samples using KBr discs on a Shimadzu FT-IR apparatus Prestige 21. The ^{1}H NMR spectra ($CDCl_3$, standard TMS) were recorded with a Bruker 300 MHz instrument. They are reported as follows: chemical shifts, (multiplicity, number of protons, and assignment).

After maximum conversion of the reaction as indicated by TLC, the resultant solid product was washed with EtOH (30 mL). The pure product was obtained by further recrystallization from ethanol, and then washed with n-hexane. The spectral and analytical data for the selected compounds are presented below.

Preparation and characterization of the catalyst

The HMS catalyst was synthesized by a sol–gel method similar to the procedure reported by Tanev and co-worker [32]. The specific surface area, pore volume and average pore diameter of HMS were measured in an ASAP-2010 Micromeritics (USA) apparatus using low temperature N_2 physisorption isotherms. Before analysis, the sample was evacuated at 350 ºC under vacuum conditions.

General procedure for the preparation of 1,4-dihydropyridines (2a-j)

The mixture of ethyl acetoacetate (10 mmol), aromatic aldehydes (5.1 mmol), ammonium acetate (7.5 mmol) and HMS (1 g) in EtOH (6 mL) was refluxed for 3 h. The progress of the reaction was monitored by TLC. A yellow precipitate was obtained and was recrystallized from EtOH. The products were characterized by FT-IR, ^{1}H and ^{13}C NMR spectra.

The catalyst was washed with hot EtOH and dried at 530◦C for 5 h. It was available for reuse in further reactions. (Table 4)

*Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydro-pyridin-3,5-dicarboxylate (**2a**)*

M.p.: 160-161 ºC (lit. [33] m.p. 158-160 ºC). FT-IR (KBr): ν 3339.15 (N-H), 2880.44 (C-H), 1694.07-1727.51 (C=O), 1489.15 (C=C), 1274.83 (C-O) cm^{-1}. 1H NMR (CDCl3): δ = 1.51 (t, J= 7.1 Hz, 6 H), 2.22 (s, 6 H), 4.0 (q, J= 7.01 Hz, 4 H), 4.93 (s, 1 H), 9.2 (brd s, 1 H), 7.04-7.22 (m, 5 H) ppm. 13C NMR (CDCl3): δ = 14.26, 19.40, 39.63, 59.74, 103.93, 126.1, 127.84, 127.98, 144.23, 147.85, 167.81 ppm.

Diethyl 2,6-dimethyl-4-(3-methylphenyl)-1,4-dihydropyridin-3,5-dicarboxylate (2c)

M.p.: 124-125 ºC (lit. [34] M.p. 122-124 ºC). FT-IR (KBr): ν 3356.86 (N-H), 2986.39 (C-H), 1650.65-1696.65 (C=O), 1412.39 (C=C), 1273.05 (C-O) cm^{-1}.

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridin-3,5-dicarboxylate (2e)

M.p.: 149-150 ºC (lit. [33] m.p. 147-148 ºC). FT-IR (KBr): ν 3356.89 (N-H), 2986.39 (C-H), 1696.48-1650.65 (C=O), 1487.16 (C=C), 1293.15 (C-O) cm^{-1}. 1H NMR (CDCl3): δ = 1.15 (t, J= 7.1 Hz, 6 H), 2.10 (s, 6 H), 3.98 (q, J= 7.0 Hz , 4 H), 4.89 (s, 1 H) , 6.2 (brd s, 1 H), 7.03-7.16 (m, 4 H) ppm. 13C NMR (CDCl3): δ = 21.14 , 19.47 , 39.68 , 59.68 , 103.50 , 126.24 , 126.30 , 128.23 , 129.06 , 133.56 , 144.45, 149.81, 167.49 ppm.

Diethyl 4-(2-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridin-3,5-dicarboxylate (2f)

M.p.: 122-124 ºC (lit. [35] m.p. 122-126 ºC). FT-IR (KBr): ν 3351.94 (N-H), 2985.99 (C-H), 1647.58-1695.84 (C=O), 1481.68 (C=C), 1297.71 (C-O) cm^{-1}. 1H NMR (CDCl3): δ= 1.13 (t, J=6.9 Hz , 6 H) , 2.19 (s, 6 H) , 4.01 (q, J=7.0 Hz, 4 H), 4.89 (s, 1 H) , 6.30 (brd s, 1 H), 7.06-7.15 (m, 4 H) ppm. 13C NMR (CDCl3): δ : 14.27 , 19.31 , 39.24 , 59.85 , 103.50 , 127.92 , 129.36 , 131.66 , 144.45 , 145.45 , 167.68 ppm.

Diethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridin-3,5-dicarboxylate (2g)

M.p.: 163-164 ºC (lit.[33] m.p. 162-164 ºC). FT-IR (KBr): ν 3483.32 (N-H), 2933.21 (C-H), 1615.62-1707 (C=O), 3353.24 (C=C), 1202.30 (C-O) cm^{-1}.

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridin-3,5-dicarboxylate (2i)

M.p.: 130-131 ºC (lit. [33] m.p. 129-131 ºC). FT-IR (KBr): ν 3336.19 (N-H), 2995.05 (C-H), 1691.89-1727.86 (C=O), 1480.60 (C=C), 1290.19 (C-O) cm^{-1}.

Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridin-3,5-dicarboxylate (2j)

M.p.: 163-164 ºC (lit. [33] m.p. 162-164 ºC). FT-IR (KBr): ν 3360.62 (N-H), 2988.18 (C-H), 1645.61-1691.89 (C=O), 1480.6 (C=C), 1212.72 (C-O) cm^{-1}.

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КАТАЛИТИЧНА СИНТЕЗА НА 1,4-ДИХИДРОПИРИДИНОВИ ПРОИЗВОДНИ, ИЗПОЛЗВАЙКИ ХЕКСАГОНАЛЕН МЕЗОПОРЕСТ СИЛИКАТ (HMS)

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(Резюме)

Постигната е проста едно-стадийна синтеза на производни на 1,4-дихидропиридина чрез кондензация на етил-ацетоацетат с различни арилови алдехиди и амониев ацетат в присъствие на хексагонален мезопорест силикат (HMS) като катализатор. Използван е етанол като разтворител. Постигнати са отлични добиви.