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EFFICIENT AND RAPID HANTZSCH SYNTHESIS OF1,4-DIHYDROPYRIDINES USING A NANO ISOPOLYOXOMOLYBDATE AS A REUSABLE CATALYST UNDER SOLVENT-FREE CONDITION

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Abstract:Hantzsch synthesis of 1,4-dihydropyridines from commercially available aliphatic\aromatic aldehydes, ammonium acetate, and ethyl acetoacetate in the presence ofa Kepleratetypegiantnanoporousisopolyoxomolybdate, $(NH_4)_{42}[Mo^{VI}_{72}Mo^{V}_{60}O_{372}(CH_3COO)_{30}(H_2O)72]$, represented as $\{Mo_{132}\}$, as anefficientcatalystunder solvent free conditionisreported.The catalyst was prepared according to a previously published literature procedure using inexpensive and readily available starting materials. Furthermore, the catalyst could be recovered conveniently and reused efficiently such that a considerable catalytic activity still could be achieved after sixth run. Other beneficial features of this new synthetic approach include short reaction times, high yields, clean reaction profiles, and a simple work-up procedure.

Keywords: Giant nanoporousisopolyoxomolybdate,Keplerate, $\{Mo_{132}\}$, Hantzsch reaction, 1,4- dihydropyridines, Solvent-free.

1. INTRODUCTION

Polyoxometalates (POMs) are polyatomic ions, usually an anion, that consists of three or moretransition metal oxyanions linked together by shared oxygen atoms to form a large, closed 3-dimensional framework. The metal atoms are usually group 5 or group 6 transition metals in their high oxidationstates. In this state, their electron configuration is d^0 or d^1. For example, niobium(V),vanadium(V), tantalum(V), molybdenum(VI), and tungsten(VI) are most important transition metals in thesestructures[i,ii].POMs are familiar to have a variation of sizes and structures, and have been studied according to their electron absorbing and molecular properties such as highly versatile redox potentials, acidities, polarities, and solubilities which give appear to a different of applications in catalysis, biomedicine, magnetism, and nanomaterials science[iii,iv].

According to the excellent acidic properties of solid polyoxometalateacids, in the last three decades, many applications as the useful and versatile acid catalysts for some acid-catalyzed reactions have found inthesestructures[v]. Polyoxometalate acidsare generally solids that are unsolvable in non-polar solvents but extremely soluble in polar ones and they can be used in both homogeneous and heterogeneous systems. Furthermore, these structures have a number of utilities involving powerful flexibility in qualification of the acid potency, easy handling, environmental friendly, non-toxicity and facile synthesis[vi,vii].

Giant nanosized porous Keplerate-type POMs, reported for the first time by Müller and co-workers[viii]. The Keplerate and giant nanosized porous POMsshow unique features which can be considered as the basis of a new type of nanochemistry and nanomaterials science[ix,x]. They find a large variety of applications in principal and applied science, such as in modelling passive cation transport through membranes, encapsulation, nanoseparation chemistry, magnetic and optics properties[xi,xii].

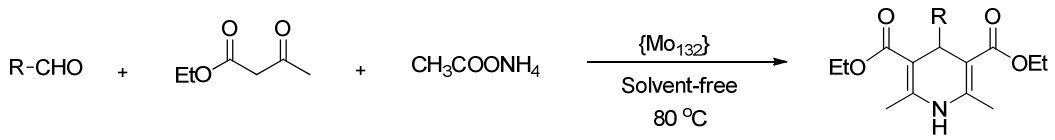
Multicomponent reactions (MCRs) are one-pot processes in which three or more available components react to form a new product that contains basically most or all atoms of the reactants used[xiii]. 1,4-Dihydropyridines (DHPs) are an important class of organic compounds with low molecular weight thatsynthesized *via*MCR.These structures attract tremendous concentration in medicinal chemistry research because of their large range of pharmacological effects and providing important ligands for biological receptors[xiv,xv]. 1,4-DHPs includes the condensation of aldehyde, ethyl acetoacetate, and ammonia as primary reagents[xvi]. These compounds specified for the first time by Arthur Hantzsch in 1882[xvii]. Hence, the reaction is referred to as the Hantzsch reaction.

Someliteratures demonstratedtherapeutic effects of 1,4-DHPs such as calcium channel antagonism[xviii],geroprotection[xix], and neuroprotection[xx]. 1,4-DHPs are excellent starting synthons for antidyslipidemic[xxi],antiarrhythmic[xxii],antitumor[xxiii], antibacterial andantitubercular[xxiv],antidiabetic[xxv], anti-HIV[xxvi],anticonvulsant[xxvii],andantithrombotic[xxviii] effects.

Many synthetic protocols were developed to accelerate the rate of1,4-DHPs reaction and to improve the yield.These compounds have been synthesized in the presence of various catalyst such asTMSCl-NaI[xxix],VB1[xxx],SiO_2-$NaHSO_4$[xxxi],PEG-400[xxxii],silica sulfuric acid[xxxiii],$CeCl_3$-$7H_2O$[xxxiv],salicylic acid[xxxv],iodine[xxxvi],triphenylphosphine[xxxvii],*t*-BuOK[xxxviii],cellulose sulfuric acid[xxxix],PDAG-Co[xl],silica gel/$NaHSO_4$[xli],TBAHS[xlii],[PS-IM$(CH_2)_4SO_3H$][HSO_4][xliv]have been utilized in the construction of the 1,4-DHP skeleton.Major drawbacks of these procedures include expensive reagents, use of large amounts of toxic organic solvents, prolonged heating and side reactions.

All of these disadvantages make further improvement of the synthesis of such molecules essential. Therefore, the development of a new greener and more convenient method using a new catalyst with high catalytic activity for the synthesis of 1,4-DHPsis highly desirable.

In continuation of our previous works on the application of $(NH_4)_{42}[Mo^{VI}_{72}Mo^{V}_{60}O_{372}(CH_3COO)_{30}(H_2O)_{72}]$, a Keplerate-typegiant-ball nanoporousisopolyoxomolybdate, represented as $\{Mo_{132}\}$,as a catalyst for a series of organic transformations[xliv,xlv], we report here the application of this materialas highly efficient and reusable novel catalyst to promote the synthesis of 1,4-DHPs from the reaction ofaliphatic\aromatic aldehydes with ammonium acetate, and ethyl acetoacetate under solvent-free condition. The diameter of this ball-shaped POM which calculated theoretically is 2.9 nm[viii,ix]. For the first time this molybdenum cluster has been characterized by the TEM image by Polarzetal[x]. The TEM picture clearly shows a periodic structure with an average size approximately 3 nm diameter. This experimentally obtained diameter fits nicely with the theoretical value for the inner diameter of the ball-shaped POM[viii,ix].



1a-1m **2** **3** **4a-4m**

a: R= Ph
b: R= 4-ClC_6H_4
c: R= 4-FC_6H_4
d: R= 4-BrC_6H_4
e: R= 3-BrC_6H_4
f: R= 4-MeC_6H_4
g: R= 4-$MeOC_6H_4$
h: R= 4-$O_2NC_6H_4$
i: R= 3-$O_2NC_6H_4$
j: R= 4-HOC_6H_4
k: R= 2-thienyl
l: R= Et
m: R= n-propyl

Scheme 1. $\{Mo_{132}\}$ catalyzed synthesis of 1,4-dihydropyridins.

2. RESULTS AND DISCUSSION

2.1. Characterization of the catalyst

The $\{Mo_{132}\}$catalyst was characterized by FT-IR and UV/Vis spectroscopy. The FT-IR spectrum of the catalyst shown in Fig. 2(1) exhibits the characteristic vibrational bonds of Mo=O at 969 and 936, the COO and NH_4^+ at1544 & 1407 as well as H_2O at 2500-3600 & 1618. The locations of these featured peaks for the prepared catalyst as well as other bonds at 854, 792, 724, 628, 568, 513 and 476 were in well agreement with those reported by Müller[viii] and Zhou[ix]. The UV/Vis spectrum also confirms the structure of the prepared catalyst indicating the characteristic absorption bonds at 213, 232, 265, and 447 nm which are in agreement with literature[viii].

2.2. Evaluation of catalytic activity of $\{Mo_{132}\}$in the synthesis of1,4-DHPs

The catalytic activity of $\{Mo_{132}\}$was evaluated in the synthesis of 1,4-DHPs. At first, the synthesis of compound**4b** was selected as a model reaction to determine suitable reaction conditions. The reaction was carried out by mixture of 4-chlorobenzaldehydes (1 mmol), ammonium acetate (1 mmol), and ethyl acetoacetate (2 mmol) in the presence of $\{Mo_{132}\}$in different solventssuch as H_2O, EtOH, MeOH, CH_2Cl_2, CH_3CN,and also solvent-free conditions at different temprature (Table 1). It was found that the yield of compound**4b**was strongly affected by the catalystamount and reaction temperature in solvent-free conditions.Low to moderate yields of the product was obtained in the absence of the catalyst at 80 °C (entry 1) or in the presence of the catalyst at room temperature (entry 2) indicating that the catalyst and temperature are necessary for the reaction. Increasing the amount of the catalyst and reaction temperatureup to 0.08 g and 80 °C, respectively, increased the yield of the product **4b**, whereas further increase in both catalystamount and temperature did not improve the product yield and reaction time (entry 15).

Table 1. Optimization of reaction conditions for synthesis of compound **4b** catalyzed by $\{Mo_{132}\}^*$.

Entry	Catalyst (g)	Solvent	T (°C)	Time (min)	Isolated yield (%)
1	-----	-----	80	60	-----
2	0.08	-----	r.t.	50	65
3	0.02	-----	60	38	56

4	0.02	-----	80	35	62
5	0.04	-----	60	33	67
6	0.04	-----	80	27	74
7	0.04	-----	100	30	73
8	0.06	-----	60	23	79
9	0.06	-----	80	19	82
10	0.06	-----	100	20	83
11	0.08	-----	60	18	86
12	0.08	-----	80	14	92
13	0.08	-----	100	14	91
14	0.10	-----	80	15	92
15	0.10	-----	100	20	90
16	0.08	CH_2Cl_2	Reflux	80	42
17	0.08	H_2O	Reflux	80	37
18	0.08	CH_3OH	Reflux	80	55
19	0.08	CH_3CH_2OH	Reflux	80	67
20	0.08	CH_3CN	Reflux	80	29

*Reaction conditions: 4-chlorobenzaldehydes (1 mmol), ammonium acetate (1 mmol), and ethyl acetoacetate (2 mmol).

Encouraged by this success, and in order to evaluate the generality of this model reaction, we extended the reaction of ammonium acetate and ethyl acetoacetate with a range of other aromatic/aliphatic aldehydes under the optimized reaction conditions.The $\{Mo_{132}\}$ efficiently catalyzed the reactions, giving the products **4a-4m** in high yields over relatively short reaction times.Easy separation of obtained products from the catalystmakes this method useful for the synthesis of 1,4-DHPs.Purity checks with melting points, TLC and the ^{1}H NMR spectroscopic data reveal that only one product is formed in all cases and no undesirable side-products are observed. The structures of all known products **4a-4m** were deduced from their ^{1}H NMR and FT-IR spectral data and a comparision of their melting points with those of authentic samples. For example, as shown in Fig. 1, the ^{1}H NMR spectrum of **4k** in $CDCl_3$ showed a triplet at δ 1.32 ppm and a sharp singlet δ 2.36 ppm related to four methyl groups, a multiplet at δ 4.17-4.27 ppm for diastereotopic protons in two methylene groups, two singlet signals at δ 5.37 ppm and δ 5.95 ppm for methine and NH groups respectively as well as the signals in the aromatic region due to 3 aromatic protons in thienylmoiety, indicating the formation of the compound **4k**.

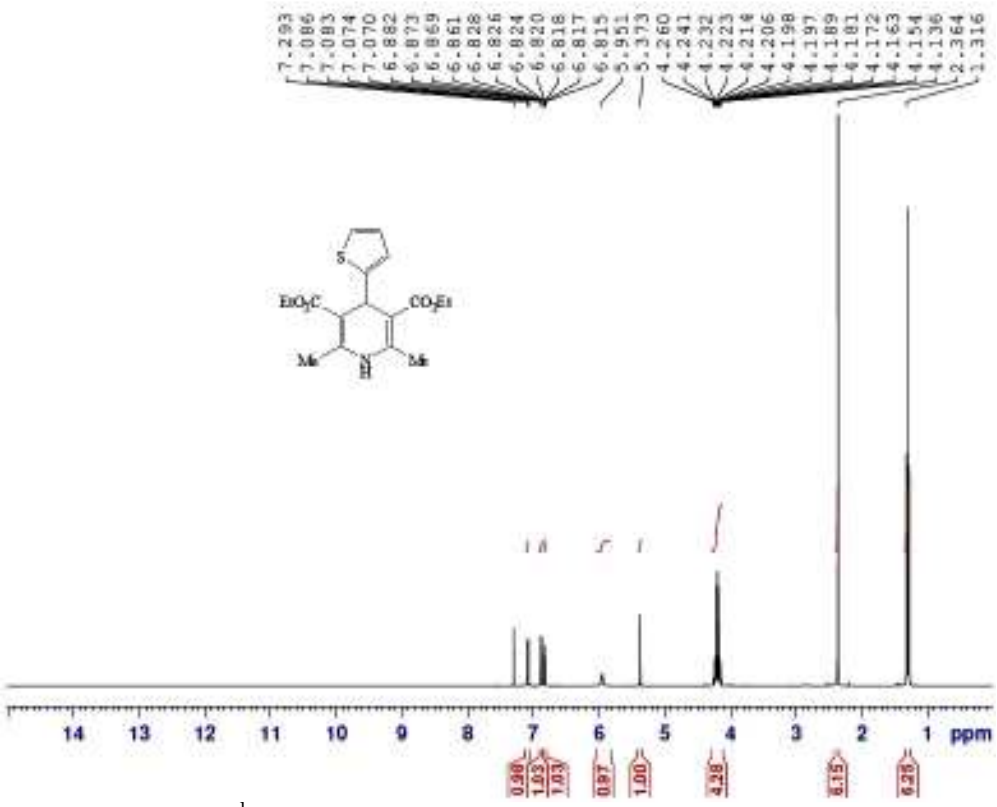


Fig. 1. The ^{1}H NMR spectrum of compound **4k** in $CDCl_3$ solvent.

We compared the results we obtained using {Mo_{132}}as catalyst with previously reported results for the synthesis of 1,4-DHPsin the presence of various catalysts (Table 2). Our reaction conditions showed shorter reaction times than all the other conditions and gave high yields of the desired products.

Table 2. Comparison of the efficiencies of different catalysts for the one-pot four-component synthesis of 1,4-DHPs.

Catalyst	Conditions			Time (min)	Yield (%)	Ref.
	Solvent	T/ºC	Other			
TMSCL-NaI	CH_3CN	r.t	-----	360-480	73-80	xxix
VB_1	-----	r.t	-----	40	80-94	xxx
SiO_2 -$NaHSO_4$	-----	r.t	-----	300-480	75-90	xxxi
PEG-400	-----	90	-----	240-420	75-95	xxxii
silica sulfuric acid	-----	r.t	-----	15-45	90-97	xxxiii
$CeCl_3$_7H2O	CH_3CN	r.t	-----	180-360	61-94	xxxiv
Salicylic Acid	-----	80	-----	120	64-89	xxxv
Iodine (I_2)	-----	40	-----	45-300	64-89	xxxvi
PPh_3	EtOH	reflux	-----	120-300	72-95	xxxvii
t-BuOK	-----	60	-----	120-600	23-84	xxxviii
Cellulose sulfuric acid	-----	100	-----	120-300	78-92	xxxix
PDAG-Co	-----	80	-----	360-480	75-99	xl
SiO2 -NaHSO4	-----	r.t	-----	300-480	75-90	xli
TBAHS	-----	80	-----	30-90	90-98	xlii
[PS-IM(CH2)4SO3H][HSO4]	EtOH	reflux	-----	120-210	80-95	xliii
{Mo_{132}}	-----	r.t	-----	9-21	88-97	This work

We also used the model reaction under optimized reaction conditions to evaluate the reusability of the catalyst {Mo_{132}}. After completion of the reaction, the catalyst was recovered as described in the experimental section. The separated catalyst was washed with hot ethanol and subsequently dried at 50 °C under vacuum for 1 h before being reused in a similar reaction. We found that the catalyst could be used at least six times with only a slight reduction in activity (Fig. 1). Furthermore, the FT-IR spectra of the recovered catalysts (Fig. 2(b)–(f)) were almost identical to the spectrum of the fresh catalyst (Fig. 2(a)), indicating that the structure of the catalyst was unchanged by the reaction.

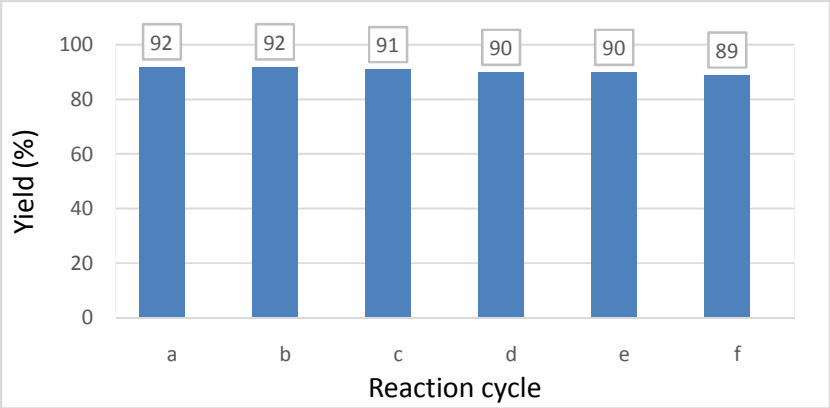


Fig. 1. Effect of recycling on catalytic performance of {Mo_{132}}in the synthesis of **4b** in model reaction.

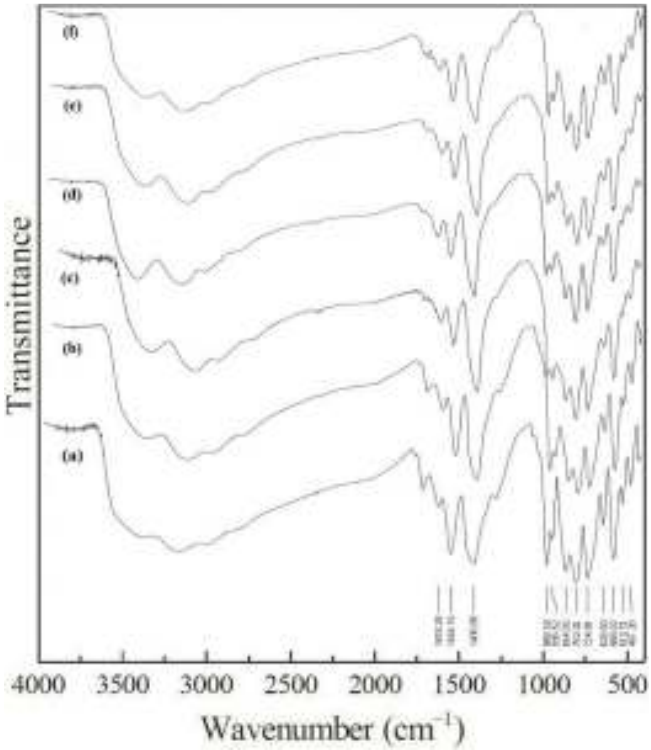
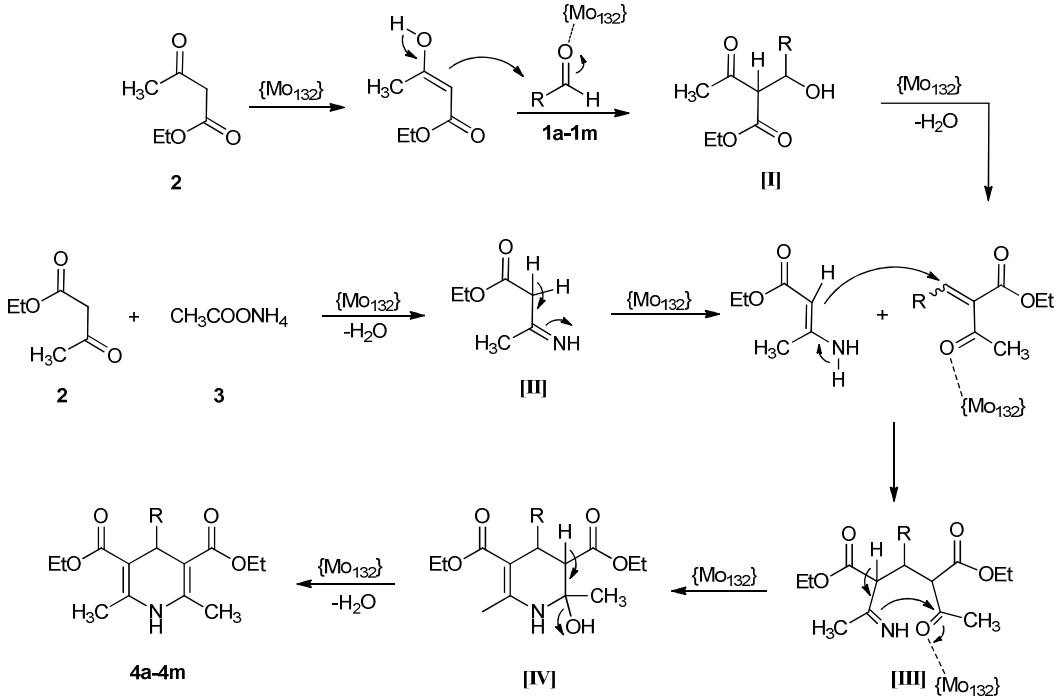


Fig. 2. FT-IR spectra of fresh catalyst {Mo_{132}}((a), first run), and recovered catalysts ((b-f), second to sixth runs, respectively) for synthesis of compound **4b**in model reaction.

Although we did not investigate the reaction mechanism, a plausible mechanism for this reaction may proceed as depicted in Scheme 2. On the basis of our previous reports[xliv,xlv]it isreasonable to assume that several accessible Mo sites and NH_4groups in $\{Mo_{132}\}$ could act as Lewis acid and Brönsted acid centers respectively, and therefore promote the necessary reactions.The catalystwould play a significant role in increasing the electrophiliccharacter of the electrophiles in the reaction.According to this mechanism, the $\{Mo_{132}\}$ catalystwould facilitate the formation of intermediates **I**, **II, III** and **IV**.Under theseconditions, however, attempts to isolate the proposed intermediatesfailed even after careful monitoring of the reactions.



Scheme 2. Plausible mechanism for the $\{Mo_{132}\}$-catalyzedformation of 1,4-DHPs.

3. EXPERIMENTAL

3.1. Chemicals and Apparatus

All chemicals were available commercially and used without additional purification. The catalyst was synthesized according to the literature[viii]. Melting points were recorded using a Stuart SMP3 melting point apparatus. The FT-IR spectra of the products were obtained with KBr disks, using a Tensor 27 Bruker spectrophotometer. The ^{1}H NMR spectra were recorded using Bruker 400 and 500 spectrometers.

3.2. General experimental procedure for the synthesis of 1,4-DHPs4a-4m catalyzed by $\{Mo_{132}\}$

A mixture of 4-chlorobenzaldehydes (0.14 g, 1 mmol), ammonium acetate (0.77 g, 1 mmol), and ethyl acetoacetate (0.26 g, 2 mmol),and $\{Mo_{132}\}$ (0.08 g) as catalyst was heated in the oil bath at 80 °C for 9-21 min. The reaction was monitored by TLC. Upon completion of the transformation, hot ethanol was added and the catalyst removed by filtration under hot conditions. The catalyst was washed with a small portion of hot ethanol. After cooling, the combined filtrate was allowed to stand at room temperature. The precipitated solid was

collected by filtration, and recrystallized from ethanol to give compounds **4a-4m** in high yields.

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4a)
Yield: 0.29 g, 91%; 17 min; M.p.: 155-157 °C (lit.[xxxii]156-158 °C); FT-IR (ν, cm^{-1}KBr disc):3342, 3061, 2982, 1688, 1651, 1489, 1372, 1211, 1167, 828;^{1}H NMR (500 MHz, $CDCl_3$):δ1.25 (t, *J* = 7.1 Hz, 6H,$2CH_3$), 2.37 (s, 6H, $2CH_3$), 4.05-4.18 (m, 4H, $2CH_2$, diastereotopic protons), 5.02 (s, 1H, CH), 5.58 (s br., 1H, NH), 7.10-7.35 (m, 5H, aromatic CH).

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4b)
Yield: 0.33 g, 92%; 14 min; M.p.: 147-149 °C (lit.[xxxii]148-150 °C); FT-IR (ν, cm^{-1}KBr disc): 3358, 3094, 2987, 1696, 1651, 1487, 1334, 1213, 1118, 1094, 843;^{1}H NMR (500 MHz, $CDCl_3$):δ1.25 (t, *J* = 7.1 Hz, 6H,$2CH_3$), 2.36 (s, 6H, $2CH_3$), 4.05-4.18 (m, 4H, $2CH_2$, diastereotopic protons), 4.99 (s, 1H, CH), 5.66 (s br., 1H, NH), 7.20 (d, *J* = 8.3 Hz, 2H, aromatic CH), 7.24 (d, *J* = 8.3 Hz, 2H, aromatic CH).

Diethyl 4-(4-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4c)
Yield: 0.34 g, 97%; 12 min; M.p.: 146-148 °C (lit.[xxxiv]147-149 °C); FT-IR (ν, cm^{-1}KBr disc):3343, 3067, 2985, 1687, 1652, 1489, 1334, 1211, 1123, 1091, 866;^{1}H NMR (400 MHz, $CDCl_3$):δ1.24 (t, *J* = 7.2 Hz, 6H,$2CH_3$), 2.36 (s, 6H, $2CH_3$), 4.05-4.20 (m, 4H, $2CH_2$, diastereotopic protons), 4.99 (s, 1H, CH), 5.68 (s br., 1H, NH), 6.91 (t, *J* = 8.4 Hz, 2H, aromatic CH), 7.26 (dd, *J*= 8.2, 6.0 Hz, 2H, aromatic CH).

Diethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4d)
Yield: 0.38 g, 93%; 13 min; M.p.: 161-163 °C (lit.[xxxvii]162-164 °C); FT-IR (ν, cm^{-1}KBr disc):3360, 3092, 2987, 1693, 1650, 1486, 1370, 1334, 1212, 1169, 1117, 1012, 843; ^{1}H NMR (500 MHz, $CDCl_3$):δ1.25 (t, *J* = 7.1 Hz, 6H, $2CH_3$), 2.36 (s, 6H, $2CH_3$), 4.05-4.18 (m, 4H, $2CH_2$, diastereotopic protons), 4.98 (s, 1H, CH), 5.61 (s br., 1H, NH), 7.19 (d, *J* = 8.4 Hz, 2H, aromatic CH), 7.35 (d, *J* = 8.4 Hz, 2H, aromatic CH).

Diethyl 4-(3-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4e)
Yield: 0.37 g, 90%; 15 min; M.p.: 160-162 °C (lit.[xlvi]162-164 °C); FT-IR (ν, cm^{-1}KBr disc):3324, 3083, 2980, 1702, 1650, 1487, 1370, 1334, 1215, 1098, 1054, 1023, 855;^{1}H NMR (400 MHz, $CDCl_3$):δ1.25 (t, *J* = 7.1 Hz, 6H, $2CH_3$), 2.36 (s, 6H, $2CH_3$), 4.04-4.20 (m, 4H, $2CH_2$, diastereotopic protons), 4.98 (s, 1H, CH), 5.71 (s br., 1H, NH), 7.10 (t, *J* = 7.8 Hz, 1H, aromatic CH), 7.22-7.28 (m, 2H, aromatic CH), 7.42 (t, *J* = 1.8 Hz, 1H, aromatic CH).

Diethyl 2,6-dimethyl-4-(4-methylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4f)
Yield: 0.31 g, 91%; 15 min; M.p.: 138-140 °C (lit.[xxxvii]136-138 °C); FT-IR (ν, cm^{-1}KBr disc):3336, 3069, 2959, 1651, 1606, 1492, 1398, 1366, 1222, 1146;^{1}H NMR (500 MHz, $CDCl_3$):δ1.26 (t, *J* = 7.1 Hz, 6H,$2CH_3$), 2.31 (s, 3H, CH_3), 2.36 (s, 6H, $2CH_3$), 4.05-4.18 (m, 4H, $2CH_2$, diastereotopic protons), 4.99 (s, 1H, CH), 5.60 (s br., 1H, NH), 7.04 (d, *J* = 7.8 Hz, 2H, aromaticCH), 7.20 (d, *J* = 7.8 Hz, 2H, aromatic CH).

Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4g)
Yield: 0.33 g, 92%; 13 min; M.p.: 160-162 °C (lit.[xxxii]159-160 °C); FT-IR (ν, cm^{-1}KBr disc):3342, 3089, 2984, 1689, 1650, 1509, 1490, 1372, 1338, 1210, 1140, 1031, 834;^{1}H NMR (500 MHz, $CDCl_3$):δ1.26 (t, *J* = 7.1 Hz, 6H,$2CH_3$), 2.36 (s, 6H, $2CH_3$), 3.79 (s, 3H, OCH_3), 4.05-4.20 (m, 4H, $2CH_2$, diastereotopic protons), 4.96 (s, 1H, CH), 5.58 (s br., 1H, NH), 6.78 (d, *J* = 8.6 Hz, 2H, aromatic CH), 7.23 (d, 2H, *J* = 8.6 Hz, aromatic CH).

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4h)
Yield: 0.33 g, 95%; 9 min; M.p.: 131-133 °C (lit.[xxxii]130-132 °C); FT-IR (ν, cm^{-1}KBr disc):3345, 3090, 2991, 1706, 1645, 1525, 1487, 1347, 1213, 1118, 1051, 879;^{1}H NMR (500

MHz, $CDCl_3$, ppm):δ1.25 (t, *J* = 7.1 Hz, 6H,$2CH_3$), 2.39 (s, 6H, $2CH_3$), 4.05-4.18 (m, 4H, $2CH_2$, diastereotopic protons), 5.13 (s, 1H, CH), 5.72 (s br., 1H, NH), 7.48 (d, *J* = 8.7 Hz, 2H, aromatic CH), 8.11 (d, *J* = 8.7 Hz, 2H, aromatic CH).

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

Yield: 0.32 g, 92%; 11 min; M.p.: 161-163 °C (lit.[xxxii]162-164 °C); FT-IR (ν, cm^{-1}KBr disc):3346, 3091, 2991, 1706, 1646, 1525, 1488, 1446, 1371, 1348, 1301, 1214, 1119, 1052, 879;^{1}H NMR (400 MHz, $CDCl_3$):δ1.25 (t, *J* = 7.1 Hz, 6H,$2CH_3$), 2.40 (s, 6H, $2CH_3$), 4.05-4.20 (m, 4H, $2CH_2$, diastereotopic protons), 5.13 (s, 1H, CH), 5.75 (s br., 1H, NH), 7.40 (t, *J* = 7.9 Hz, 1H, aromatic CH), 7.67 (dt, *J* = 7.7, 1.3 Hz, 1H, aromatic CH), 8.03 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H, aromatic CH), 8.16 (t, *J* = 1.9 Hz, 1H, aromatic CH).

Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4j)

Yield: 0.30 g, 88%; 20 min; M.p.: 229-231 °C (lit.[xxxii]228-231 °C); FT-IR (ν, cm^{-1}KBr disc):3417, 3343, 3067, 2985, 1687, 1651, 1489, 1454, 1372, 1245, 1211, 1143, 1091, 883;^{1}H NMR (400 MHz, $CDCl_3$):δ 1.14 (t, *J* = 7.1 Hz, 6H, $2CH_3$), 2.25 (s, 6H, $2CH_3$), 3.90-4.06 (m, 4H, $2CH_2$, diastereotopic protons), 4.75 (s, 1H, CH), 6.58 (d, J = 8.4 Hz, 2H, aromatic CH), 6.93 (d, *J*= 8.4 Hz, 2H, aromaticCH), 8.73 (s br., 1H, NH or OH), 9.10 (s br., 1H, NH or OH).

Diethyl 2,6-dimethyl-4-(thiophen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4k)

Yield: 0.31 g, 94%; 10 min; M.p.:170-172 °C (lit.[xxxvii]172-174 °C); FT-IR (ν, cm^{-1}KBr disc):3344, 3110, 2979, 1692, 1655, 1486, 1369, 1329, 1210, 1129, 1093, 853; ^{1}H NMR (400 MHz, $CDCl_3$):δ1.30 (t, *J* = 7.1 Hz, 6H, $2CH_3$), 2.36 (s, 6H, $2CH_3$), 4.17-4.27 (m, 4H, $2CH_2$, diastereotopic protons), 5.37 (s, 1H, CH), 5.95 (s br., 1H, NH), 6.82 (dt, *J*= 3.2, 0.8 Hz,1H,arom-H), 6.87 (dd, *J*= 5.2, 3.6 Hz,1H,arom-H), 7.08 (dd, *J*= 5.0, 1.2 Hz, 1H, arom-H).

Diethyl 4-ethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4l)

Yield: 0.25 g, 88%; 21 min; M.p.:111-113 °C (lit.[xlvii]110-112 °C); FT-IR (ν, cm^{-1}KBr disc):3316, 2968, 1699, 1652, 1499, 1369, 1303, 1134, 1073, 882; ^{1}H NMR (400 MHz, $CDCl_3$):δ0.78 (t, *J*= 7.4 Hz, 3H, CH_3), 1.32 (t, *J*= 7.0 Hz, 6H, $2CH_3$), 1.35-1.41 (m, 2H, CH_2), 2.32 (s, 6H, $2CH_3$), 3.94 (t, *J*= 5.2 Hz, 1H,CH), 4.12-4.29 (m, 4H, $2CH_2$, diastereotopic protons), 5.48 (s br., 1H, NH).

Diethyl 2,6-dimethyl-4-propyl-1,4-dihydropyridine-3,5-dicarboxylate (4m)

Yield: 0.26 g, 90%; 20 min; M.p.: 111-113 °C (lit.[xlvii]110-112 °C); FT-IR (ν, cm^{-1}KBr disc): 3351, 2956, 1699, 1645, 1491, 1300, 1211, 1160, 1082, 794; ^{1}H NMR (400 MHz, $CDCl_3$, δppm): 0.86 (t, 3H, *J*= 7.1 Hz, CH_3), 1.19-1.34 (m, 4H, $2CH_2$), 1.31 (t, 6H, *J*= 7.2 Hz, $2CH_3$), 2.30 (s, 6H, $2CH_3$), 3.94 (t, 1H,*J*= 5.2 HzCH), 4.12-4.29 (m, 4H, $2CH_2$, diastereotopic protons), 5.65 (s br., 1H, NH).

CONCLUSION

In summary, we showed that $\{Mo_{132}\}$, a Keplerate typegiant nanoporousisopolyoxomolybdate, efficiently catalyzed the synthesis of 1,4-DHPsby one-pot, three-component reaction of aliphatic\aromatic aldehydes, ammonium acetate, and ethyl acetoacetateat 80 ^oC under solvent-free conditions. The method was relatively fast and high yielding, and the work-up was easy. The catalyst can be recycled after simple handling, and used at least six times without any substantial reduction in its catalytic activity. The procedure is also advantageous in the sense that it is a fastreactionunder solvent-free conditions and therefore operates under environmentally friendly conditions.

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