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Another application of $(NH_4)_{42}[Mo^{VI}_{72}Mo^{V}_{60}O_{372}(CH_3COO)_{30}(H_2O)_{72}]$ as a highly efficient recyclable catalyst for the synthesis of dihydropyrano[3,2-*c*]chromenes

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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-type giant-ball nanoporous isopolyoxomolybdate, as a catalyst for the synthesis of heterocyclic compounds, in this paper, we report another application of this attractive catalyst in the synthesis of 2-amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitriles via a one-pot three-component reaction of 4-hydroxycoumarin, aldehydes and malononitrile. The reactions occur in ethanol–water as solvent at room temperature and the process is operative with various aldehydes, giving the corresponding products in high yields. Other beneficial features of this protocol include short reaction times, simple work-up and the recyclability and reusability of the catalyst for up to five consecutive runs. Copyright © 2016 John Wiley & Sons, Ltd.

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Keywords: dihydropyrano[3,2-*c*]chromenes; giant nanoporous isopolyoxomolybdate; Keplerate; $\{Mo_{132}\}$

Introduction

The synthesis of dihydropyrano[3,2-*c*]chromenes with biological and pharmacological properties such as spasmolytic, diuretic, anticoagulant, anticancer and antianaphylactic activities[1,2] is currently of great interest. The reported protocol for the synthesis of dihydropyrano[3,2-*c*]chromenes involves the one-pot three-component reaction of 4-hydroxycoumarin, aldehydes and malononitrile in the presence of a catalyst such as polymer-supported sulfanilic acid,[3] saccharose,[4] $H_6P_2W_{18}O_{62}\cdot 18H_2O$,[5] poly(ethylene glycol)-grafted *N*,*N*-dimethylaminopyridine-functionalized dicationic ionic liquid $[DMAP\text{-}PEG_{1000}\text{-}DIL][BF_4]$,[6] magnetic nanocatalyst $\gamma\text{-}Fe_2O_3@HAp\text{-}Si\text{-}(CH_2)_3\text{-}AMP$,[7] $Fe_3O_4@SiO_2\text{-imid-PMA}^n$ nanoparticles,[8] $RuBr_2(PPh_3)_4$,[9] NaCl,[10] crown ether complex cation ionic liquid,[11] tetrabutylammonium bromide[12] and $(NH_4)_2HPO_4$ or *S*-proline.[13] While each of these methods has its own advantages, many suffer from limitations such as prolonged reaction times, the use of relatively expensive catalysts and unsatisfactory yields. Thus the discovery of a new and efficient catalyst with high catalytic activity, short reaction times, recyclability and simple reaction work-up for the preparation of dihydropyrano[3,2-*c*]chromenes is of great interest.

Heterogeneous catalysis has been known for many years and has become strategically vital for efficient and ecofriendly organic transformations over the past few decades.[14–17] These catalysts have many advantages over homogeneous catalysts involving simple work-up, ease of handling, recoverability and reusability.[18,19] Catalysts of this type have the potential to make the processes in which they are applied cleaner, safer, higher-yielding and relatively inexpensive.[20–23]

Polyoxometalates (POMs) are a large class of metal oxide clusters of early transition metals, typically W(VI), V(V), Mo(VI), Nb(V) and Ta (V), bridged by oxygen atoms. They are of proven value in catalysis, magnetism, materials science and biomedicine,[24–28] because they are diverse and highly modifiable in size, shape, charge density, acidity and reversible redox potential. A number of very large POM anions have been synthesized and structurally characterized. Beginning with the big-wheel Mo_{154} anion,[29] Müller's group have reported several giant mixed-valence POMs with cyclic (Mo_{176}),[30] capped cyclic (Mo_{248})[31] and basket (Mo_{116})[32] architectures. Giant nanosized porous Keplerate-type POMs show a large variety of applications in fundamental and applied science, such as in modelling passive cation transport through membranes, encapsulation, nanoseparation chemistry and magnetic and optics applications.[33,34] In spite of these valuable properties, to the authors' knowledge, application of giant nanosized porous POMs as catalysts in organic transformations has been largely overlooked.[35] Müller and co-workers, for the first time, reported the synthesis of a Keplerate-type giant-ball nanoporous isopolyoxomolybdate which was formulated as $(NH_4)_{42}[Mo^{VI}_{72}Mo^{V}_{60}O_{372}(CH_3COO)_{30}(H_2O)_{72}]$ and denoted as $\{Mo_{132}\}$.[36] Recently, the application of $\{Mo_{132}\}$ as a catalyst for a series of organic transformations has been reported by our group. This new reusable catalyst performed well and showed a high level of catalytic activity in the synthesis of 1,2,4,5-tetrasubstituted imidazoles, 1,8-dioxooctahydroxanthenes, 1,8-dioxodecahydroacridines and polyhydroquinolines.[37–39]

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Prompted by these facts and as part of our research on the development of environmentally friendly methods for the synthesis of organic compounds using reusable catalysts,[40–51] we report here another application of {Mo_{132}} as a catalyst in the synthesis of 2-amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitriles (**4a–n**) via a one-pot three-component reaction of 4-hydroxycoumarin, aldehydes and malononitrile (Scheme 1).

Experimental

Chemicals and apparatus

All chemicals were available commercially and used without additional purification. The catalyst was synthesized according to the literature.[36] Melting points were recorded with a Stuart SMP3 melting point apparatus. Fourier transform infrared (FT-IR) spectra were obtained using a Bruker Tensor 27 spectrophotometer as KBr discs. ^{1}H NMR (300 and 400 MHz) spectra were recorded with Bruker 300 and 400 spectrometers.

General procedure for synthesis of dihydropyrano[3,2-*c*]chromenes 4a–n catalysed by {Mo_{132}}

A mixture of 4-hydroxycoumarin (**1**; 1.0 mmol), an aldehyde (**2a–n**; 1.0 mmol), malononitrile (**3**; 1.0 mmol) and {Mo_{132}} (0.07 g) in a mixture of EtOH–H_2O (1:1, 2 ml) as solvent was stirred at room temperature for the appropriate time. During the procedure, the reaction was monitored using TLC (*n*-hexane–ethyl acetate, 3:1). Upon completion of the transformation, the solvent was evaporated *in vacuo*, and hot ethanol (2 ml) was added to the residue. The catalyst was removed by filtration of the hot suspension and washed with a small portion of hot ethanol (2 × 2 ml). After cooling, the combined filtrate was concentrated by half and allowed to stand at room temperature. The precipitated solid was collected by filtration, and recrystallized from ethanol to afford compounds **4a–n** in high yields.

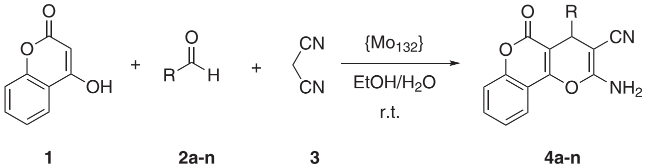
Table 1. Optimization of reaction conditions for synthesis of compound **4c** catalysed by {Mo_{132}}[a]

Entry	Catalyst (g)	Solvent	Temp. (°C)	Time (min)	Isolated yield (%)
1	—	EtOH	Reflux	80	Trace
2	—	H_2O	Reflux	90	Trace
3	—	EtOH–H_2O	r.t.	70	11
4	—	EtOH–H_2O	Reflux	65	12
5	0.07	—	110	30	38
6	0.07	—	130	23	52
7	0.03	EtOH–H_2O	r.t.	30	45
8	0.03	EtOH–H_2O	Reflux	30	39
9	0.04	EtOH–H_2O	r.t.	20	53
10	0.04	EtOH–H_2O	Reflux	23	51
11	0.05	EtOH–H_2O	r.t.	15	67
12	0.05	EtOH–H_2O	Reflux	15	68
13	0.06	EtOH–H_2O	r.t.	11	81
14	0.06	EtOH–H_2O	50	11	80
15	0.06	EtOH–H_2O	Reflux	10	79
16	0.07	EtOH–H_2O	r.t.	10	94
17	0.07	EtOH–H_2O	50	11	93
18	0.07	EtOH–H_2O	Reflux	12	91
19	0.08	EtOH–H_2O	r.t.	10	92
20	0.08	EtOH–H_2O	Reflux	10	93
21	0.07	EtOH	r.t.	20	85
22	0.07	EtOH	Reflux	25	86
23	0.07	CH_3OH	r.t.	45	54
24	0.07	CH_3OH	Reflux	40	59
25	0.07	CH_3OH–H_2O	r.t.	30	58
26	0.07	CH_3OH–H_2O	Reflux	30	61
27	0.07	CH_2Cl_2	r.t.	70	41
28	0.07	CH_2Cl_2	Reflux	60	49
29	0.07	$CHCl_3$	r.t.	60	37
30	0.07	$CHCl_3$	Reflux	60	51

[a] Reaction conditions: 4-hydroxycoumarin (**1**; 1 mmol), 4-chlorobenzaldehyde (**2c**; 1 mmol) and malononitrile (**3**; 1 mmol).

Results and discussion

The {Mo_{132}} catalyst was characterized using FT-IR and UV–visible spectroscopies as reported in our previous work.[37] To begin our study, the reaction of **1** (1.0 mmol), 4-chlorobenzaldehyde (**2c**; 1.0 mmol) and **3** (1.0 mmol) was selected as the test reaction and various reaction parameters were studied for the formation of corresponding dihydropyrano[3,2-*c*]chromene **4c**. Trace amounts or low yields of the product **4c** are obtained in the absence of the catalyst in refluxing EtOH or H_2O or in mixture of them at room temperature or reflux conditions (Table 1, entries 1–4). Also, in the presence of the catalyst under solvent-free conditions at high temperatures only moderate yields of the product **4c** are obtained (entries 5 and 6). These results indicate that the catalyst and solvent are necessary for the reaction. Table 1 indicates that under solvent-free conditions and from among the solvents tested such as EtOH, H_2O, MeOH, CH_2Cl_2 and $CHCl_3$ and using varying amounts of the catalyst, the reaction proceeds more easily and affords the highest yield when using 0.07 g of {Mo_{132}} in a mixture of EtOH and H_2O at room temperature (entry 16). No improvement in yields or reaction times is observed when using higher temperatures or higher amount of the catalyst.



Scheme 1. Synthesis of dihydropyrano[3,2-*c*]chromenes catalysed by {Mo_{132}}.

Under the optimized reaction conditions (0.07 g of {Mo_{132}} in EtOH–H_2O at room temperature), we investigated the scope and the limitations of the reaction employing a variety of aldehydes. The results are summarized in Table 2. Obviously, the reaction is practicable for various aromatic, heteroaromatic and aliphatic aldehydes. As evident, all reactions proceed very cleanly to give the corresponding dihydropyrano[3,2-*c*]chromenes **4a–n** in high yields over short reaction times. Melting points, TLC and ^{1}H NMR spectroscopic data were used to establish that only one product is formed in all cases with no undesirable side-products being present after purification.

The ability to recycle and re-use {Mo_{132}} was also studied. For this purpose, after separation of the catalyst according to the procedure outlined in the experimental section, the recovered catalyst was washed with hot ethanol and subsequently dried at 60°C under

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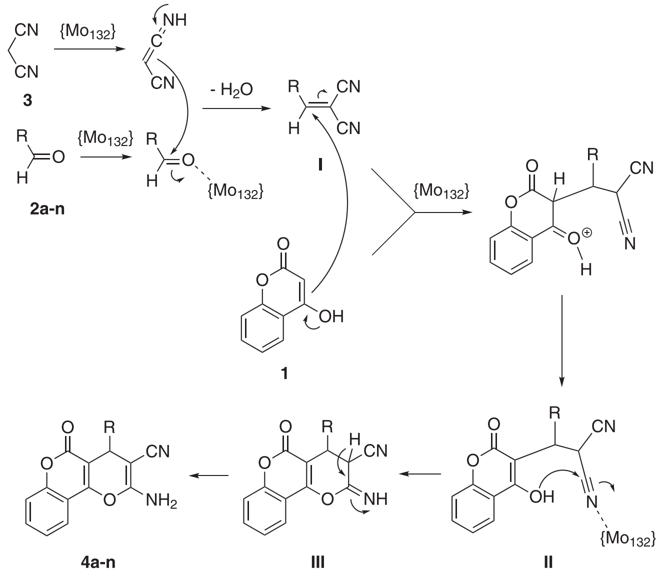
Table 2. $\{Mo_{132}\}$-catalysed synthesis of dihydropyrano[3,2-*c*]chromenes **4a–n**[a]

Entry	R	Products	Time (min)	Isolated yield (%)	M.p. (°C)	
					Found	Reported
1	C_6H_5	**4a**	12	92	259–261	255–256[4]
2	$2\text{-}ClC_6H_4$	**4b**	20	92	266–268	267–269[8]
3	$4\text{-}ClC_6H_4$	**4c**	10	94	265–266	263–264[6]
4	$4\text{-}FC_6H_4$	**4d**	20	90	260–261	262–263[6]
5	$3\text{-}O_2NC_6H_4$	**4e**	13	94	266–268	266–267[8]
6	$4\text{-}O_2NC_6H_4$	**4f**	10	95	253–255	252–254[8]
7	$4\text{-}HOC_6H_4$	**4 g**	20	90	261–262	261–263[8]
8	$4\text{-}MeOC_6H_4$	**4 h**	10	95	243–245	244–246[8]
9	2-Thienyl	**4i**	12	93	255–257	256–258[7]
10	3-Pyridyl	**4j**	15	91	254–256	257–259[11]
11	Me	**4 k**	19	92	227–228	227–229[7]
12	Et	**4 l**	25	90	238–240	239–241[7]
13	*n*-Pr	**4 m**	23	93	241–243	240–242[8]
14	*i*-Pr	**4n**	25	92	251–253	251–253[8]

[a] Reaction conditions: 4-hydroxycoumarin (**1**; 1 mmol), an aldehyde (**2a–n**; 1 mmol), malononitrile (**3**; 1 mmol), $\{Mo_{132}\}$ (0.07 g), EtOH–H_2O (1:1, 2 ml), room temperature.



Scheme 2. Plausible mechanism for the formation of dihydropyrano[3,2-*c*]chromenes in the presence of $\{Mo_{132}\}$ as catalyst.

vacuum for 1 h before being reused in a similar reaction. The catalyst could be used at least five times without significant reduction in its activity (94, 93, 93, 92 and 91% yields for first to fifth use, respectively) which clearly demonstrates the practical reusability of this catalyst. This reusability demonstrates the high stability and turnover of $\{Mo_{132}\}$ under the employed conditions.

Although we did not investigate the reaction mechanism, a plausible mechanism for this reaction may proceed as depicted in Scheme 2. As shown, the dicyano olefin **I** is readily formed *in situ* by Knoevenagel condensation of aldehydes **2a–n** and **3**. Compound **1** easily reacts with olefin **I** followed by cyclization to produce intermediates **II** and **III**, respectively. Finally, the products **4a–n** are obtained from the latter intermediate after tautomerization. On the basis of our previous reports,[37,38] it is reasonable to assume that several accessible Mo sites and NH_4 groups in $\{Mo_{132}\}$ could act as Lewis acid and Brønsted acid centres, respectively, and therefore promote the necessary reactions. The catalyst would play a significant role in increasing the electrophilic character of the electrophiles in the reaction.

Conclusions

We have found that $\{Mo_{132}\}$ can be used as a new, reusable and efficient catalyst for the preparation of a variety of dihydropyrano[3,2-*c*]chromenes by one-pot three-component reaction of 4-hydroxycoumarin, aldehydes and malononitrile. The reaction occurs in ethanol–water at room temperature and furnishes the expected products in high yields over short reaction times. This property combined with ease of recovery and catalyst reusability makes this method an economic, benign and waste-free chemical process for the synthesis of dihydropyrano[3,2-*c*]chromenes.

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