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Short Communication

Zn-VCO_3 hydrotalcite: A highly efficient and reusable heterogeneous catalyst for the Hantzsch dihydropyridine reaction

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ABSTRACT

The Zn-VCO_3 hydrotalcite was found to be an excellent solid catalyst for the one-pot synthesis of triphenylpyridine-3,5-dicarboxamide *via* Hantzsch reaction of acetoacetanilide, ammonium hydroxide and various aromatic aldehydes. The combinatorial syntheses were achieved for the first time using hydrotalcite as a heterogeneous catalyst. The catalyst was active for the Hantzsch reaction in water at 60 °C. The products were isolated in good yields (85–93%) with short reaction times (2–3 h). The resulting substituted dihydropyridines were characterized and confirmed by ^1H and ^{13}C NMR, FTIR, and HRMS spectral data and the solid catalyst was characterized by XRD, BET, SEM and TEM. The newly synthesized heterogeneous solid catalyst offers simple means for recovery and the isolated catalyst was reused for five rounds for the synthesis of compound **4a**, without significant loss of catalytic activity. For all the other reactions carried out with the recycled catalyst, results were similar to with the fresh catalyst.

1. Introduction

Hydrotalcites are layered with anionic species such as hydroxide and carbonate located in the interlayer, which have been reported to be used as ion exchangers [1], drug delivery agents [2] and catalysts or catalyst supports [3–7]. These materials have been developed and applied as a heterogeneous catalysts and metal support for highly efficient liquid-phase organic transformations including alkylations, isomerizations, condensations, and cycloadditions [8–16]. Their reactivity under relatively benign conditions is an incentive for the synthesis of fine chemicals, when ecofriendly and green chemistry is in great demand.

Dihydropyridines represent important and extensively studied compounds belonging to the class of calcium channel blockers [17–21]. The known Hantzsch reaction that was first reported it in 1882 [22], is the convenient way to prepare the 1,4-dihydropyridines which exhibit significant biological activities in the treatment of congestive heart failure and angina pectoris [23]. 4*H*-pyran is an isoelectronic displacement analog of dihydropyridines and this pharmacophore is a main structural motif present in several natural products [24] and several bio-active compounds [25,26]. More importantly, 4*H*-pyrans can be transformed into corresponding pyridines resulting in valuable dihydropyridine type calcium channel modulators [27,28].

Few reports are available for the synthesis of dihydropyridines [29–31] and modifications for Hantzsch reaction were reported, where β-diketones, malonic acid esters, β-keto acids, β-aminocrotononitrile, ethyl cyanoacetate, and cyanoacetamide were used instead of β-keto esters [32]. Most of the researchers have focused on the modification and optimization of the Hantzsch reaction to maximize reaction conversion, minimize reaction time and offer high yield of dihydropyridines. Many of these methods give unsatisfactory yields with other side products and use of large quantity of volatile organic solvents. Thus, the developments in this area require diversity in selected building blocks to generate the target libraries possessing different heterocyclic scaffolds. Hydrotalcites have received attention as heterogeneous catalysts, due to the stability and the scope for modification of their surface properties by incorporating various metal ions in its structure. Sahu et al. [33,34] investigated one-pot multi-component synthesis in the presence of hydrotalcite as the catalyst and achieved as an ecologically and economically good results. Ebitani et al. [35] reported that hydrotalcites provide a unique acid–base bi-functional surface capable of promoting the Knoevenagel and Michael reactions of nitriles with carbonyl compounds. In view of the advantages associated with the use of hydrotalcites in performing synthetic organic chemistry, we report a multicomponent and simple approach using hydrotalcite as a catalyst. The Hantzsch reaction towards the synthesis of target molecules with good yields in less reaction time with no need for solvents is described. This is the first report of a heterogeneous solid catalyst, Zn-VCO_3 hydrotalcite capable of catalyzing the reaction to produce dihydropyridines in the presence of water. Furthermore, this hydrotalcite catalyst system can promote the aqueous Hantzsch reaction using carbonyl compounds.

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2. Experimental

2.1. Preparation of hydrotalcite

The layered double hydroxide Zn-VCO_3 hydrotalcite with a molar ratio of 1:0.8:0.2 was prepared by co-precipitation method at constant pH. The mixed solution containing metal nitrates of Zn (Zinc nitrate) and V (ammonium metavanadate) with desired concentrations, 0.35 mol NaOH and 0.15 mol Na_2CO_3 were added simultaneously to a 1 L beaker at the rate of 50 mL/h under constant stirring condition at 35 °C at the pH of 10–11.5. The precipitate formed was aged for 18 h at 65 °C at the end of which the precipitate was separated by filter. This was followed by repeated washing with deionized water until free of NO_3^-. The wet solid was slowly dried at 80 °C for 12 h to obtain the hydrotalcite. The catalyst was calcined at 500 °C for 4 h.

2.1.1. Characterization of catalyst and textural properties

The Brunauer–Emmett–Teller (BET) surface area, total pore volume and average pore size were measured using a Micrometrics TriStar II surface area and porosity analyzer. Prior to the analysis, the powdered samples (~0.180 g) were degassed under N_2 for 12 h at 200 °C using a Micromeritics FlowPrep 060 instrument. Textural properties of catalyst sample were measured by N_2 adsorption–desorption isotherms obtained at −196 °C.

Metal oxide phases in the catalyst were observed using powder X-ray diffraction (XRD) performed on a Bruker D8 Advance instrument, equipped with an Anton Paar XRK 900 reaction chamber, a TCU 750 temperature control unit and a CuKα radiation source with a wavelength of 1.5406 nm at 40 kV and 40 mA. Diffractogram was recorded over the range 15–90 °C with a step size of 0.5 per second.

The Transmission Electron Microscopy (TEM) images were viewed on a Jeol JEM-1010 electron microscope. The images were captured and analyzed by using iTEM software. High resolution TEM images were recorded by using a Jeol JEM 2100 electron microscope. The Scanning Electron Microscopy (SEM) measurements were carried out using a JEOL JSM-6100 microscope equipped with an energy-dispersive X-ray analyzer (EDX). The images were taken with an emission current = 100 μA by a Tungsten (W) filament and an accelerator voltage = 12 kV. The catalysts were secured onto brass stubs with carbon conductive tape, sputter coated with gold and viewed in a JEOL JSM-6100 microscope. The pre-treatment of the samples consisted of coating with an evaporated Au film in a Polaron SC 500 Sputter Coater metallizator to increase the catalyst electric conductivity.

2.2. General experimental procedure for the synthesis of dihydropyridine derivatives

A mixture of freshly distilled benzaldehyde (1.0 mol) in water (2 mL) at room temperature, acetoacetanilide (2.0 mol), ammonium hydroxide (1.5 mol) and hydrotalcite (20.0 mg) were added to a round bottom flask equipped with a magnetic bar and condenser. Then, the reaction mixture was heated at 60 °C for appropriate time as shown in Table 3. The reaction progress was monitored by Thin Layer Chromatography (TLC) (EtOAc/hexane = 5:5). After completion of the reaction, the mixture was cooled to room temperature and extracted with ethyl acetate. After filtering the hydrotalcite solid, the solvent layer was washed with water, dried with anhydrous sodium sulfate and the solvent removed to obtain essentially pure product **4a** (93% yield) as off-white solid. The recovered hydrotalcite solid was washed with dichloromethane and evaporated solvent under reduced pressure and reused in the next cycles.

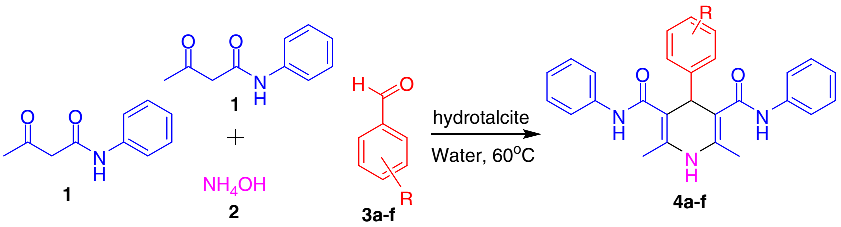
3. Results and discussion

A systematic study was carried out to optimize the reaction conditions, including the quantity of catalyst, reaction medium and nature of catalyst. For the Hantzsch reaction of acetoacetanilide **1**, with aromatic aldehydes, **2a**–**f** and ammonium hydroxide, **3** (molar ratio: 2:1:1.5) (Scheme 1), the results reflecting the impact of various parameters are summarized in Table 1. Using NaOH and $[Bmim]BF_4$ and ethanol, water or dichloromethane (DCM) as solvents, the reactions gave no expected products (Table 1, entries 3–5). In solvent-free conditions the desired product **4a** was obtained with 55% yield (Table 1, entry 8) under 60 °C using ionic liquid, $[Bmim]BF_4$ as a catalyst. Best yields were obtained using hydrotalcite as a heterogeneous catalyst in aqueous media at 60 °C (Table 1, entry 11).

To establish the optimal amount of catalyst, the title reaction was run with different initial amounts of the hydrotalcite (10, 20 and 30 mg) and the product yields were 60, 93 and 95% respectively (Table 1, entries 11–13). The results suggest that for chosen reaction conditions 20 mg of hydrotalcite catalyst was adequate to carry out the reaction efficiently.

We next investigated the scope of reuse the hydrotalcite catalyst. After completion of the reaction, task-specific hydrotalcite catalyst was recovered and subjected to another run, affording the product in 93% yield. This process was repeated four more times, affording the desired product in good yields, with undiminishing efficiency (Table 2). The simple experimental and product isolation procedures combined with the ease of recovery and reuse of the reaction medium are expected to contribute to the development of a green strategy for the Hantzsch reactions. Using five different substrates, the formation of dihydropyridine (4a–f) has occurred in good yields spontaneously and exclusively. Notably, even sterically hindered substrate also participated effectively to afford the dihydropyridine derivative (Table 3, entry 6).

Based on the results of this study, it's clear that the hydrotalcite as catalyst improves the yields of products significantly. The zinc and vanadium loading on hydrotalcite provided scope for altering the properties like acidity, pore size and surface area resulting in appropriate surface characteristics suited for its performance as good catalyst. The Hantzsch reaction mechanism may cautiously be visualized to occur *via* a tandem sequence of the reactions depicted in the reaction scheme in Mechanism 1. Possibly, the catalyzed reaction proceeds through a cyclic transition state in the interlamellar space of the catalyst, which is helped by its highly effective acid–base bi-functional surface character capable of mediating the Hantzsch reaction and Michael addition of carbonyl compounds. We propose, the surface Lewis base species abstracts active hydrogen of acetoacetanilide as a pronucleophile in the aqueous phase to generate a carbanion intermediate, which can be paired with the cationic surface



Scheme 1. Multicomponent reaction catalyzed by hydrotalcite.

Table 1
Optimization of reaction conditions of the Hantzsch synthesis.

Entry	Product no.	Catalyst	Amount	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	4a	–	–	EtOH	Room temp	12.0	[b]
2	4a	–	–	EtOH	80	12.0	25
3	4a	NaOH	1.0 (equiv.)	H_2O	Room temp	6.0	[c]
4	4a	$[Bmim]BF_4$	6 drops	EtOH	Room temp	10.0	b
5	4a	$[Bmim]BF_4$	6 drops	DCM	60	8.0	b
6	4a	$[Bmim]BF_4$	6 drops	H_2O	Room temp	10.0	b
7	4a	$[Bmim]BF_4$	6 drops	–	Room temp	5.0	b
8	4a	$[Bmim]BF_4$	6 drops	–	60	5.0	55
9	4a	$[Bmim]BF_4$	6 drops	H_2O	60	6.0	20
10	4a	HT	10.0 mg	H_2O	Room temp	5.0	b
11	4a	HT	10.0 mg	H_2O	60	3.0	60
12	4a	HT	20.0 mg	H_2O	60	2.0	93
13	4a	HT	30.0 mg	H_2O	60	2.0	95

[a] Isolated yields.
[b] Products were not found.
[c] Trace.

of the hydrotalcite (Pathway B). In Pathway A, protonated carbonyl is attacked by the amine from ammonium hydroxide to form the enamine. The reaction is typically run under Lewis acidic conditions, which can be paired with the metal cationic surface of the hydrotalcite. The resulting intermediates followed by Michael reaction. We sense that ammonia produced from ammonium hydroxide in water is well stabilized by hydrogen bond formation in 60 °C, which will be a rare phenomenon in the solvent media. The structures of all the dihydropyridine derivatives have been characterized and confirmed by ^{1}H NMR, ^{13}CNMR, FTIR and HRMS spectra (Supplementary data).

3.1. Characterization of hydrotalcite

3.1.1. SEM (Scanning Electron Microscopy), TEM (Transmission Electron Microscopy) and & ICP-OES

ICP-OES analysis showed that zinc to vanadium metal ratio is 1:3 which a stoichiometric metal ratio of the hydrotalcite. The SEM micrograph (Supplementary data Fig. 1) shows that agglomeration of the metal oxide particles which is caused by the calcination of the hydrotalcite precursor and these aggregates are in the size ranging from 0.86 μm to 1.73 μm. EDS analysis of this catalyst showed that Zn and V are homogenously distributed in the catalyst, and the metal ratio (Zn:V) is also in agreement with the ICP elemental analysis. The catalyst morphologies as indicated by the SEM image clearly point out the homogeneity in shapes for the sample and high crystallinity. TEM micrograph showed in (Supplementary data Fig. 2) that calcined catalyst has a square plated like structures, TEM micrographs showed the square plate like structure, which is one, the typical vanadate structures. These square planar structures are in the size of 25 ± 3 nm. The selected area diffractions showed that catalyst is in polycrystalline in nature which is further observed by the XRD-diffractogram.

3.1.2. BET (Brunauer–Emmett–Teller)

Fig. 1 shows the N_2 adsorption–desorption isotherms for the V-doped carbonate mesoporous catalyst loaded with Zn. The isotherms for the sample were of type-IV with a H_2 hysteresis loop [36]. This was symptomatic of their mesoporous structure. The pore size distribution for the V-doped carbonate mesoporous was quite narrow and mono modal. The adsorption–desorption curves showed hysteresis loops in the relative-pressure (P/P_0) range of 0.5–0.9, indicating good homogeneity and fairly small pore size [37]. This indicated that the average pore size increased with an increase in the amount of carbonate loaded. The specific surface area (13.4 m^2/g), pore size (0.044 cm^3/g) and total pore volume (131 A°). The sample had large surface areas and high pore volumes and the pore size distribution was very narrow.

Table 2
Recyclability of hydrotalcite catalyst tested for compound **4a**.

Entry	Catalyst	Time (h)	Yield[a] (%)
1	Fresh	2.0	93.0
2	2nd run	2.0	93.0
3	3rd run	2.0	91.0
4	4th run	2.0	91.0
5	5th run	2.0	90.0

[a] Isolated yields.

Table 3
Hydrotalcite (Zn-V/CO_3) catalyzed synthesis of the dihydropyridine (**4a**–**f**) derivatives.

Entry	Product no.	R_1	Time (h)	Yield[a] (%)
1	4a	H	2.0	93.0
2	4b	4-Br	2.0	90.0
3	4c	4-$N(CH_3)_2$	3.0	92.0
4	4d	4-OCH_3	2.5	90.0
5	4e	4-OH	3.0	89.0
6	4f	2-NO_2	3.0	85.0

[a] Isolated yields.

3.1.3. XRD (X-ray diffractogram)

Powder XRD of calcined catalyst (Supplementary data Fig. 3) is in agreement in the standard hydrotalcite peaks, which indexes are correlating with the reported hydrotalcites [38]. The value of the c-axis calculated corresponds to the three times the thickness of the 'sandwich' formed between the two consecutive brucite like structures and the interlayer where carbonate ions together with the water molecules exist. The thickness calculated from the position of the diffraction peak corresponding to the (0 0 3) plane, was recorded in the range of 7.3–7.6 A° for carbonate precursors. Other main peaks correspond to the plane (0 0 6), recorded in the range of 3.5–3.8 A° for carbonate precursors. These values coincide with those reported in the literature for carbonate hydrotalcite. After calcination due to the removal of water from the hydrotalcite structure, mixed metal oxides of hydrotalcite precursors are formed. Powder diffractograms and the *d*-spacing values of mixed metal oxide precursor for Zn-VCO_3 are in correlation with the ICDD file no. 34-378.

4. Conclusions

In summary, we have developed a highly efficient and green one-pot methodology for the synthesis of a wide range of dihydropyridine derivatives *via* Hantzsch reaction using hydrotalcite as a heterogeneous catalyst. Solvent-free conditions and non-toxic reusable heterogeneous catalyst make this method simple, convenient, cost-effective and

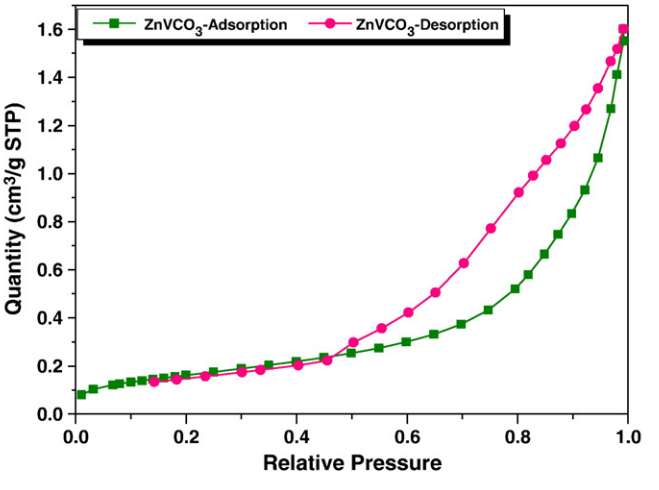
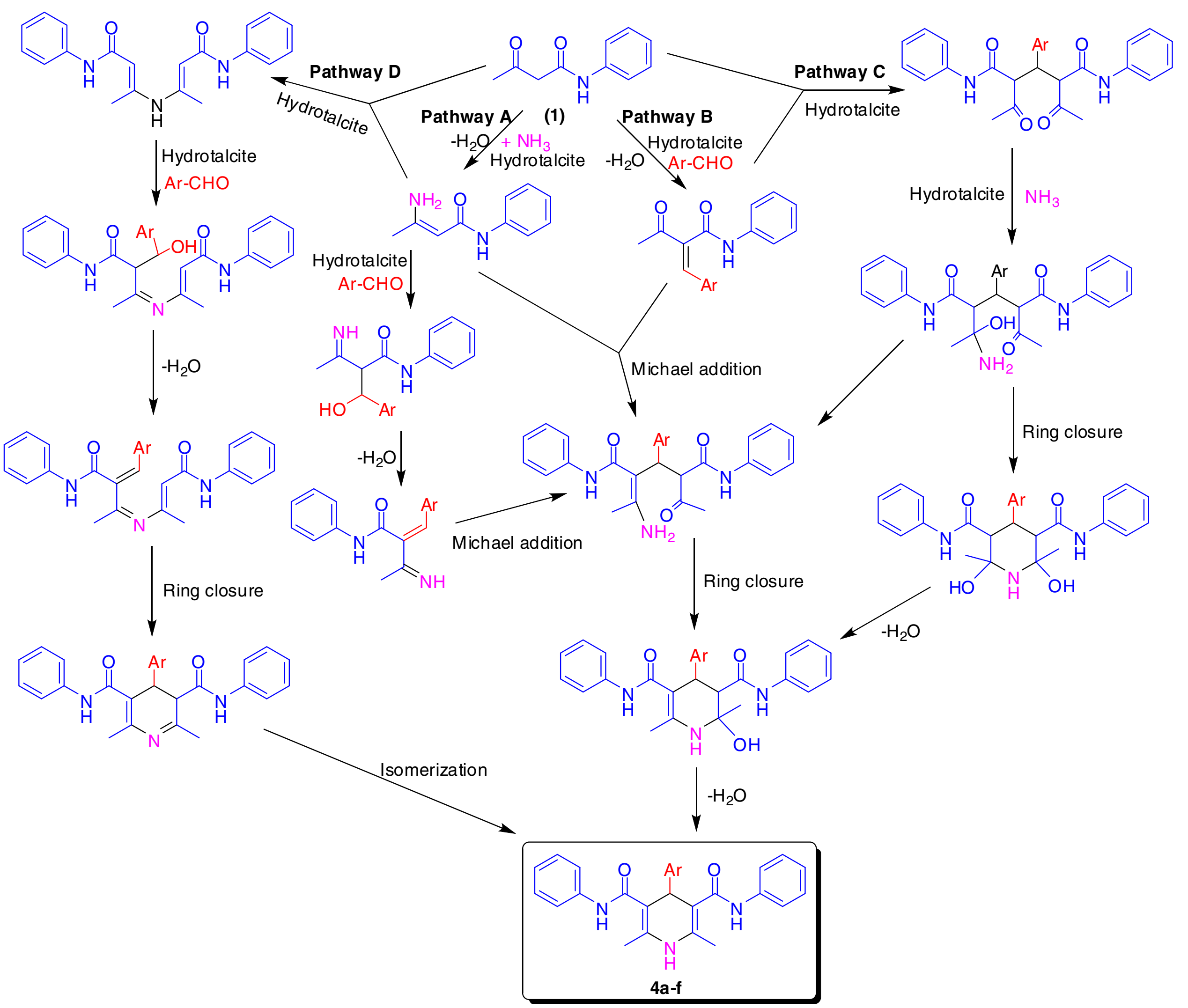


Fig. 1. N_2 adsorption–desorption isotherm of calcined Zn-VCO_3 hydrotalcite sample.



Mechanism 1. Reaction pathways for the Hantzsch synthesis.

environmentally friendly in character, which will have an advantage over other existing methodologies. The present method significantly expands the scope of the multicomponent reaction by studying the reactivity of substituted aromatic aldehydes.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2013.11.012.

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