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Original Research Article

HKUST-1 as an efficient and reusable heterogeneous catalyst for synthesis of 1,4-dihydropyridine at room temperature

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KEYWORDS

1,4-Dihydropyridines

Ethanol

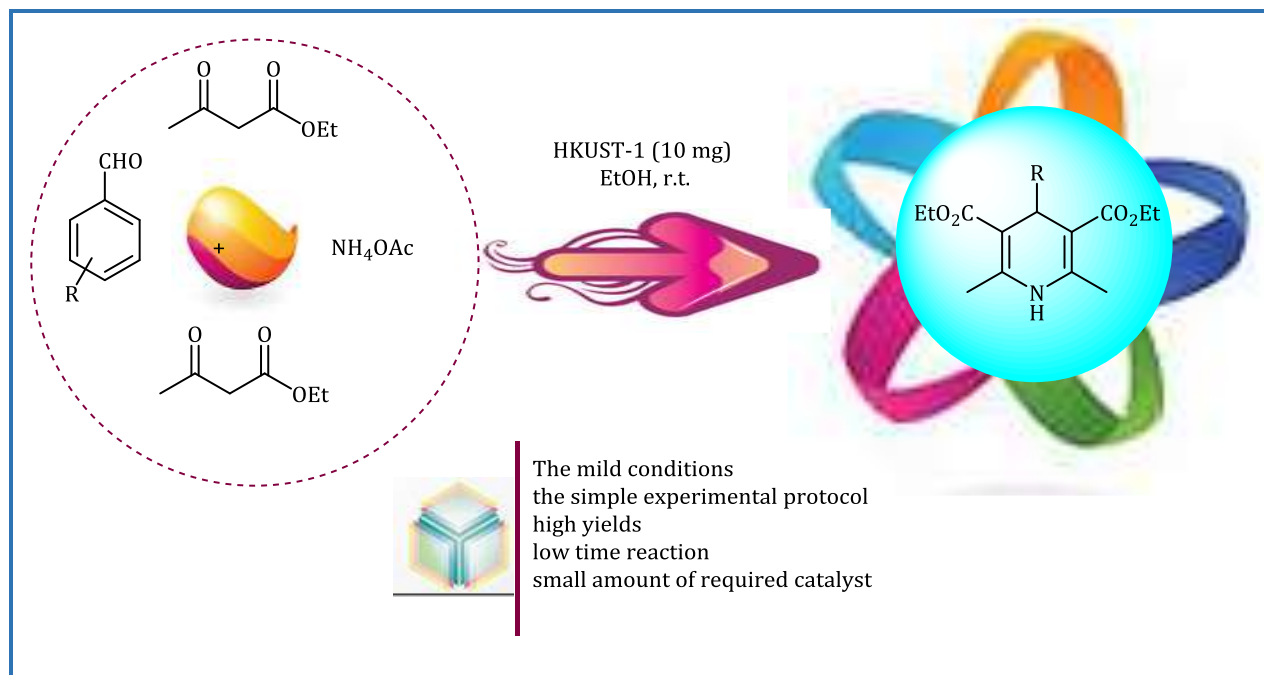
Aldehydes

HKUST-1

ABSTRACT

One-pot synthesis of Hantzsch 1,4-dihydropyridines (1,4-DHP) under solvent-free conditions catalyzed by HKUST-1 metal-organic frameworks is reported here. This method provides 1,4-dihydropyridines (1,4-DHP) in good to excellent yields with minimum amount of catalyst. The present methodology offers several advantages; including, ease of the preparation and handling of the catalyst, simple and easy work-up, short reaction time, high yields of the products and recyclability of the catalyst.

Graphical Abstract



Introduction

HKUST-1 metal organic frameworks are the important crystalline materials in the field of heterogeneous catalysts or catalyst supports for a variety of organic transformations [1, 2]. Metal organic frameworks (MOFs) open the possibility to design and synthesize variety of new porous materials. Some of the most significant features of MOFs include high internal surface area, microporosity, ease of the separation of the product, acid sites, base sites, stability, diffusion, and high metal content [3]. MOFs catalyze many reactions such as oxidation of organosulfide, cyclopropanation of alkene, *N*-methylation of aromatic primary amines, Sonogashira reaction, Suzuki cross-coupling, Friedel-Crafts alkylation and acylation, three-component coupling reaction of aldehyde, alkyne, and amine, the Biginelli reaction, Knoevenagel condensation, cycloaddition of CO₂ with epoxides, alkene epoxidation, oxidation of homocoupling of phenylboronic acid, trans esterification reaction, hydrolysis of ammonia borane, azaMichael condensation and 1,3-dipolar cycloaddition reactions [4–20].

1,4-Dihydropyridine (1,4-DHP) is one of the key scaffolds that has pharmaceutical, biological and drugs properties [21, 22]. 1,4-Dihydropyridines have been employed as synthetic intermediates for a wide variety of compounds such as activity as antioxidant, antidiabetic and antitumor agents, and NADH models [23–24]. Substituted dihydropyridine are usually prepared either by the cyclization reactions (Hantzsch ring closure) [25] or by reduction of pyridinium ions

[26]. In recent years, many catalysts have been reported for the synthesis of the 1,4-dihydropyridines such as barium nitrate [27], montmorillonite K10 clay [28], 12-tungstophosphoric acid (PW) supported on silica [29], triphenylphosphine [30], $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ [31], phenylboronic acid [32], molecular iodine [33], $\text{SiO}_2/\text{NaHSO}_4$ [34], $\{[\text{Cd}_3(\text{BDC})_3(\text{OPP})(\text{DMF})_2] \cdot 2\text{DMA}\}_n$ (TMU-33) [35], FeCl_3 [36], $\text{Bi}(\text{OTf})_2$ [37], and $\text{Cu}(\text{OTf})_2$ [38]. Meanwhile, many of these reactions suffer from several key limitations, such as low yield, long reaction time, using organic solvents, hard reaction conditions, and various by-products.

HKUST-1 was reported to be composed of 1,3,5 benzenetricarboxylate (BTC) ligands coordinating copper ions in a cubic lattice (Figure 1) [39]. To date, many studies have been conducted on evaluating the catalytic behavior of the HKUST-1 [40–43]. In this study, HKUST-1 is reported as an efficient heterogeneous copper-based catalyst without the assistance of any ligands for the synthesis of 1,4-dihydropyridines.

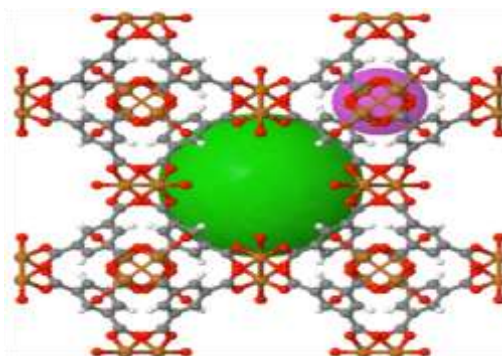
Experimental

Materials and methods

Synthesis of HKUST-1

The HKUST-1 was prepared according to the literature [44]. Benzenetricarboxylic acid (500 mg, 2.38 mmol) was mixed in 12 mL of a 1:1:1 mixture of DMF:EtOH:H₂O. $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (860 mg, 4.31 mmol) was mixed with 12 mL of the same solvent and, then, the mixtures were combined with stirring. Triethylamine (0.5 mL) was added to the reaction mixture, and stirred for 24 h. The product was collected by filtration, washed twice with DMF (25 mL), and then dried. The structures of the HKUST-1 were deduced from their FT-IR spectral data. The FT-IR spectra (Figure 2) displayed absorptions at about 3446 cm^{-1} for water molecule, 1625 and 1444 cm^{-1} for carbonyl group of benzenetricarboxylic acid and double bonds of benzene in the order of instrumentation.

Figure 1. Structure of HKUST-1



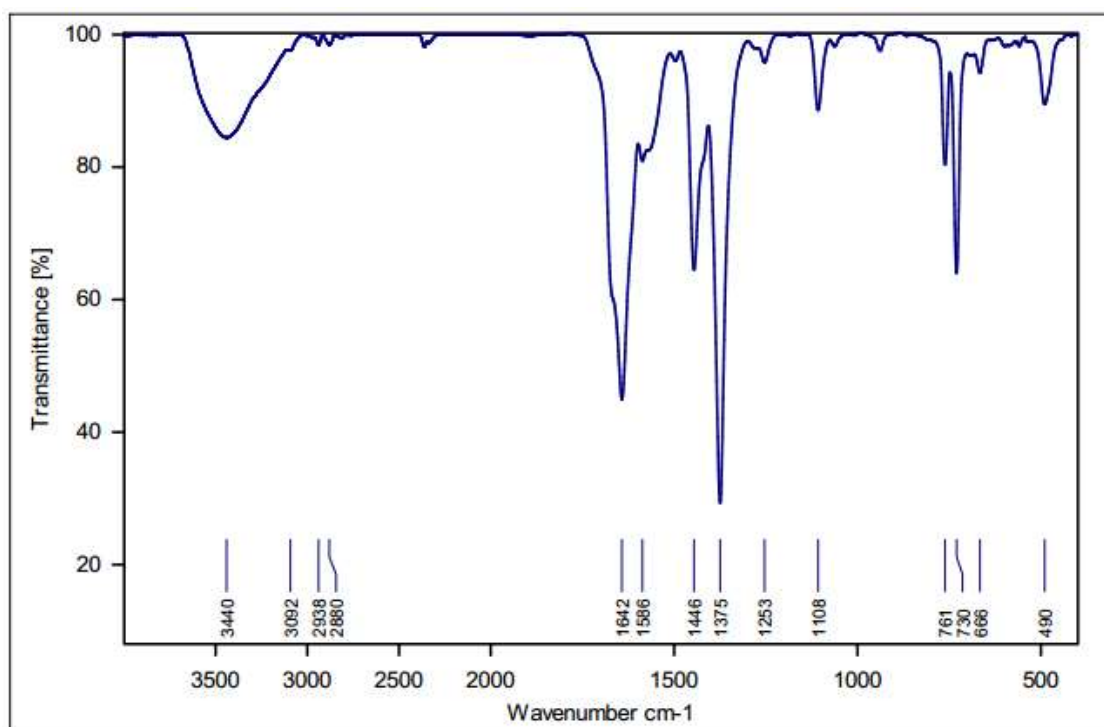


Figure 2. FT-IR spectral data for HKUST-1

General procedure for the synthesis of 1,4-dihydropyridine

A mixture of aldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1 mmol) and HKUST-1 (10 mg) was stirred in a flask containing 5 mL ethanol for the appropriate time. The progress of the reaction was followed by TLC. On completion of the reaction time, the catalyst was washed repeatedly with ethanol, dried at room temperature and, then, reused. The crude 1,4-dihydropyridine was purified by recrystallization. All the products are known compounds and are characterized by comparing the ^1H NMR and ^{13}C NMR spectroscopic data with that of their melting points in the literature values.

Results and discussion

In continuation of our studies toward the development of new and cleaner methods for organic transformations [45–48], we prepared HKUST-1 metal-organic frameworks for the one-pot synthesis of Hantzsch 1,4-dihydropyridines.

To explore this method, the reaction of benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol), and ammonium acetate (1 mmol) was chosen as the model. Initially, we tried the solvents such as H_2O , EtOH, MeOH, MeCN, CHCl_3 , and CH_2Cl_2 . EtOH was the most effective solvent for this reaction (Table 1, entry 2).

In the next step, the effect of the HKUST-1 amount was examined. The best result was obtained in the presence of 10 mg of HKUST-1 (Table 2, entry 4). In the absence of HKUST-1, the reaction rate was slow and even after the extended reaction time, the reaction yields were still low.

With optimal conditions, we report the synthesis of various 1,4-dihydropyridine using 10 mg of HKUST-1 in EtOH at room temperature with excellent yields. Results are summarized in Table 3. These reactions proceeded smoothly and no undesirable side reactions were observed. The results show the best yield in the presence of the electron-withdrawing groups on the aldehyde.

Table 1. Influence of different solvents on the synthesis of 1,4-dihydropyridine at room temperature

Entry	Solvent	Time (h)	Yield (%) ^a
1	H ₂ O	2	61
2	EtOH	2	95
3	MeOH	2	57
4	MeCN	2	42
5	CHCl ₃	2	31
6	CH ₂ Cl ₂	2	30
7	Solvent-free	2	45

^a reaction condition: aldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1 mmol) and HKUST-1 (10 mg), solvent (5 mL) and room temperature

^b Isolated yield

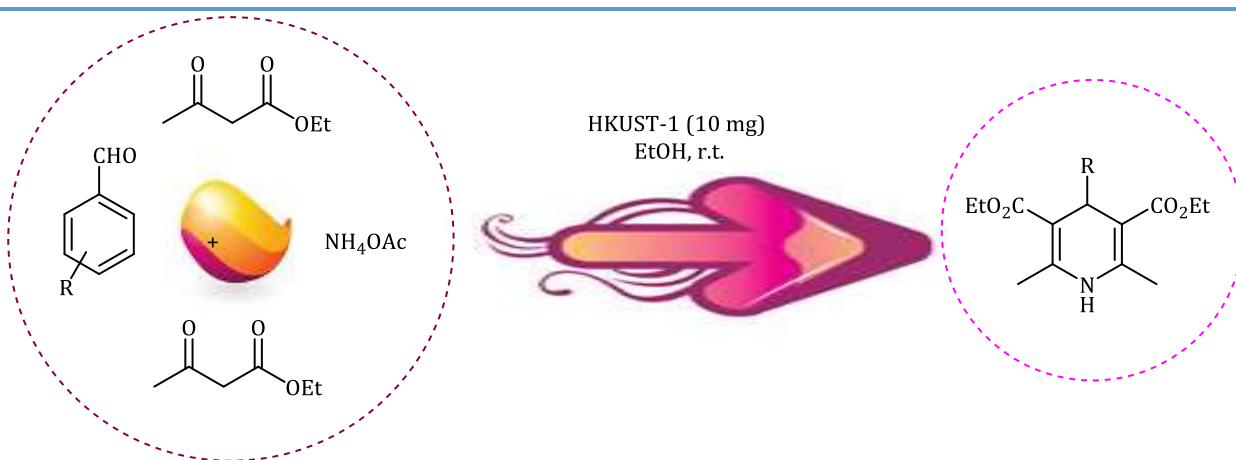
Table 2. Influence of the amount of HKUST-1 on the synthesis of 1,4-dihydropyridine

Entry	HKUST-1 (mg)	Time (min)	Yield (%) ^a
1	4	2	72
2	6	2	87
3	8	2	90
4	10	2	95
5	12	2	95
6	-	2	Trace

^a reaction condition: aldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1 mmol) and HKUST-1 (X mg), EtOH (5 mL) and room temperature

^b Isolated yield

Table 3. Synthesis of the 1,4-dihydropyridine



Entry	R	Yield (%) ^a	M.p. (°C) (Lit.)
1	C ₆ H ₅	95	200–203 200–202 [49]
2	4-Cl-C ₆ H ₄	95	210–213 209–211 [49]
3	4-Br-C ₆ H ₄	93	200–201 199–201 [49]
4	4-NO ₂ -C ₆ H ₄	94	208–211 207–210 [49]
5	4-Me-C ₆ H ₄	87	200–202 199–201 [49]
6	4-MeO-C ₆ H ₄	88	200–202 199–201 [49]
7	4-OH-C ₆ H ₄	83	220–223 225–226 [49]
8	3-Me-C ₆ H ₄	79	121–122 122–124 [32]
9	3-Cl-C ₆ H ₄	91	131–133 130–132 [32]
10	3-NO ₂ -C ₆ H ₄	92	165–167 164–166 [32]
11	3,5-Cl ₂ C ₆ H ₃	89	127–128 128–130 [32]

^a Isolated yield

The recycling of the catalyst was evaluated. To do so, the 1,4-dihydropyridine using 10 mg of HKUST-1 in EtOH at room temperature was investigated. As the reaction completed, the catalyst was removed (By filtration) from the mixture after 10 min of the reaction. The recovered catalyst was washed by acetone in order to remove the residual product, then it was dried in vacuum and recycled in further reactions. The results confirmed that almost no further conversion was observed for the synthesis of 1,4-dihydropyridine. The compounds can be synthesized in the presence of the HKUST-1 catalyst as the contribution of leached active Cu species soluble in the solution, if any, was insignificant (Figure 3 and 4).

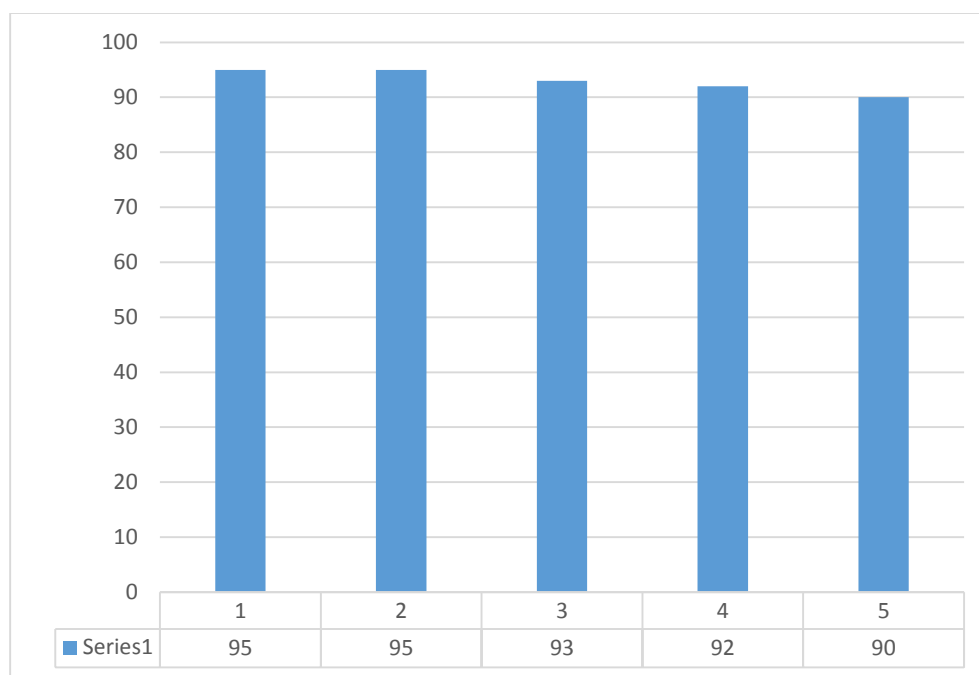


Figure 3. Catalyst recycling studies

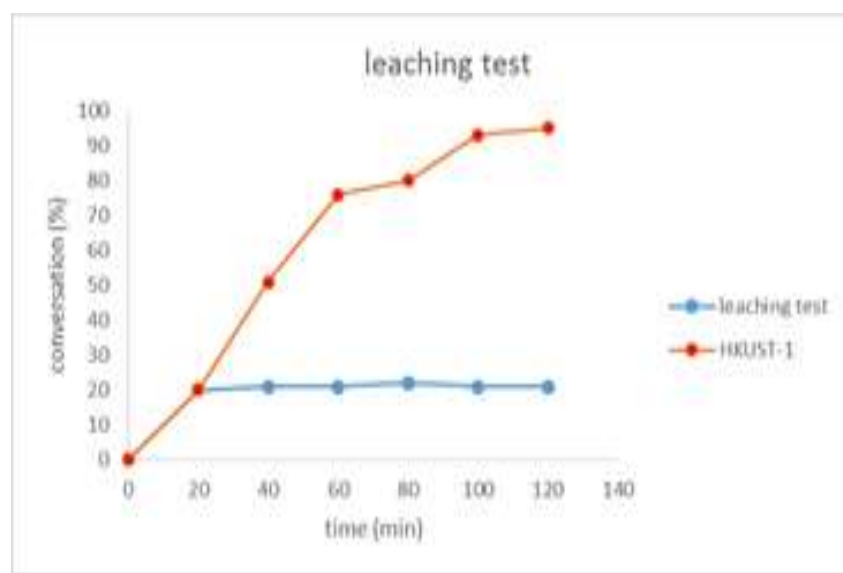


Figure 4. Leaching test

Conclusion

In this study, a simple and highly efficient method in the presence of HKUST-1 as a new, reusable, and solid catalyst for Hantzsch 1,4-dihydropyridines was studied. High efficiency, low time reaction, and small amount of the required catalyst are the most striking features of the

HKUST-1. The mild conditions, the simple experimental protocol, and high yields are the major advantages of this technique.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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