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Cu(OH)_x-clay catalyst promoted synthesis of 4,5-dihydro-1,2,4-oxadiazole at room temperature

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Abstract: An easy and efficient scheme is described and designed for the preparation of 4,5-dihydro-1,2,4-oxadiazole using recyclable Cu(OH)_x-clay heterogeneous catalyst at room temperature. The cycloaddition reaction is carried out between imine and oxime using an easy protocol where nitrile oxides are produced *in situ* from aldoximes and reacted with imines to form 1,2,4-oxadiazolines in good yield and tremendous purity. Cu(OH)_x-clay catalyst shows excellent catalytic activity for the formation of 1,2,4-oxadiazole. This technique is practically uncomplicated, inexpensive, and excellent with a wide range of functional group tolerance to generate structurally different 1,2,4-oxadiazoles. The prepared catalyst was investigated by X-ray diffraction and scanning electron microscopy techniques. The final products of the synthesized compound were characterized by Fourier transform infrared, mass, and nuclear magnetic resonance spectroscopies.

Keywords: cycloaddition; green chemistry; heterogeneous catalyst; imines; oxadiazoles.

1 Introduction

As an essential category of compounds [1] 1,2,4-oxadiazoles have attracted significant attention as many of them were found to possess biological activity. 1,2,4-Oxadiazoles are

used as anti-inflammatory agents [2], pesticides and insecticides [3], benzodiazepine receptor agonists [4], histamine H-3 receptor antagonists [5], antiviral compounds [6], aldose reductase inhibitors [7] and also are employed as a bioisostere of urea in β 3 adrenergic receptor agonists [8].

Numerous schemes are described for the preparation of 1,2,4-oxadiazoles [9]. 1,3-Dipolar cycloaddition reactions were mostly reported for the preparation of diverse group of isoxazolines and 2-isoxazolidines [10]. In the same way, synthesis of 4,5-dihydro-1,2,4-oxadiazoles through 1,3-dipolar cycloaddition of imines and nitrile oxides is also well recognized [11]. In relay of our ongoing research to produce competent heterogeneous-catalyzed methodologies to form a variety of organic compounds from easily accessible starting materials [12–21], we herein report the Cu(OH)_x-clay catalyzed approach for the synthesis of 4,5-dihydro-1,2,4-oxadiazoles via the cycloaddition reaction of N-hydroxybenzimidoyl chloride and imine at room temperature.

Using heterogeneous catalysts for organic chemical transformations is a hot topic of research nowadays and has emerged as a knowledgeable approach to deal with the challenges of green synthesis. Cu(OH)_x-Clay has developed as a novel heterogeneous catalyst in our group owing to its distinguished features such as high selectivity, better reactivity, and simple work-up procedure [19, 20].

2 Materials and methods

2.1 Preparation of clay-encapsulated Cu(OH)_x catalyst

To a volume of 200 ml of distilled water, 2.012 g of CuCl₂·2H₂O was added and dissolved, followed by dropwise addition of 0.2 M aqueous NaOH with vigorous stirring till pH of the mixture reaches 6.0–6.5. The resulting oligomer was kept stirring for 8 h. On the other side 5 g montmorillonite-KSF was added to 200 ml distilled water and stirred vigorously at 80°C for 2 h. Copper oligomer Cu(OH)_x (prepared by base hydrolysis of cupric chloride keeping OH/Cu molar ratio equal to 2.0) was added dropwise to this suspension to get encapsulated Cu(OH)_x with 15 wt% of copper loading. The suspension thus formed was stirred at 90°C for 8 h. Heating causes expansion of clay interlayer and makes the intercalation of Cu-oligomer easy. The suspension was filtered and washed with distilled water a number of times. The solid residue was dried at room temperature and then at 110°C for 12 h. The catalyst was calcined at different temperatures

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ranging from 200°C to 425°C and the effect of calcination on the rate of reaction was studied.

2.2 Synthesis of 4,5-dihydro-1,2,4-oxadiazoles (general procedure)

In a 100 ml volume round-bottom flask, a mixture of benzohydroxymoyl chloride (1 mmol) and dichloromethane (DCM) (3 ml) was taken. To this, Cu(OH)_x-clay (10 mg) was added with vigorous stirring. Some 1 mmol imine (prepared *in situ*) was added to the reaction mixture and stirring was continued for 5–6 h. On attaining finishing point of the reaction, as monitored by thin layer chromatography, the mixture was centrifuged to remove the catalyst. After concentrating the filtrate under high vacuum, the reaction mixture was extracted with DCM. Washing the organic layer with water and drying over sodium sulfate, the crude mixture formed was purified by column chromatography on silica gel, where hexane-ethyl acetate (8.5:1.5) was used as an eluent. The purified products are characterized by nuclear magnetic resonance spectroscopy, high resolution mass spectrometry, and infrared spectroscopy. The spectral data were found to be reliable with authentic samples.

2.3 Spectral analysis of some representative compounds

2.3.1 Compound b: ¹H NMR (400 MHz, CDCl₃): δ 3.68 (s, 3H), 3.79 (s, 3H), 6.79 (s, 1H), 6.49–6.79 (m, 3H), 6.99–7.11 (m, 5H), 7.69–7.79 (m, 2H), 8.19–8.26 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 54.96, 55.89, 98.58, 109.68, 110.69, 115.97, 120.79, 122.96, 123.82, 125.58, 126.77, 126.94, 128.56, 140.67, 144.89, 147.92, 150.98, 154.87; *m/z*: 405 (M⁺); IR(KBr): ν 1619, 1547, 1245, 1354 cm⁻¹.

2.3.2 Compound c: ¹H NMR (400 MHz, CDCl₃): δ 6.47 (s, 1H), 6.99 (d, 2H), 7.09–7.18 (m, 5H), 7.49 (d, 2H), 7.73 (d, 2H), 8.18 (d, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 99.01, 122.99, 123.99, 125.00, 127.00, 127.96, 129.01, 129.57, 130.38, 136.84, 140.55, 145.29, 148.62, 154.44; *m/z*: 379 (M⁺), 381 (M + 2) in 3:1 ratio; IR(KBr): ν 1630, 1570, 1350 cm⁻¹.

2.3.3 Compound e: ¹H NMR (400 MHz, CDCl₃): δ 3.80 (s, 3H), 6.57 (s, 1H), 6.84 (m, 3H), 7.14–7.25 (m, 4H), 7.54 (d, 2H), 7.79 (d, 2H), 8.30 (d, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 54.87, 97.87, 113.87, 115.99, 123.29, 123.43, 124.67, 125.89, 127.96, 128.37, 129.44, 129.61, 141.18, 145.84, 148.62, 155.01, 161.51; *m/z*: 375 (M⁺); IR(KBr): ν 1613, 1512, 1214, 1335 cm⁻¹.

2.3.4 Compound o: ¹H NMR (400 MHz, CDCl₃): δ 3.78 (s, 3H), 3.58 (s, 3H), 6.61 (s, 1H), 6.81 (m, 4H), 7.24 (d, 2H), 7.08–7.19 (m, 3H), 7.51 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 55.29, 98.87, 113.98, 114.11, 117.67, 124.05, 125.33, 128.54, 129.11, 129.67, 131.09, 140.97, 149.85, 154.80, 160.63, 161.19; *m/z*: 360 (M⁺); IR(KBr): ν 1611, 1245 cm⁻¹.

2.4 Catalyst characterization

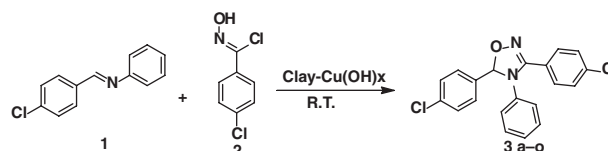
All reagents were purchased from Sigma-Aldrich (India). The catalyst was characterized by powder X-ray diffraction (XRD) using a D-8 ADVANCE (Bruker AXS, Germany). X-ray diffractometer with Ni filter and Gobel Mirror parallel beam geometry (CuKα: λ = 1.5418 Å) in the

2θ range of 5–70° in step scan mode (step size: 0.02°, scan speed: 2 s/step). The phases were identified by search match procedure with the help of DIFFRACPLUS software using JCPDS databank. To study the morphology, scanning electron microscopy (SEM) of the catalyst was carried out using JEOL JEM100CXII Electron Microscope with ASID accelerating voltage 40.0 KV.

3 Results and discussion

In our initial studies, preparation of 4,5-dihydro-1,2,4-oxadiazoles through the cycloaddition of (*E*)-N-(4-chlorobenzylidene)aniline with (*Z*)-4-chloro-N-hydroxybenzimidoyl chloride was selected as the model reaction for optimization of reaction settings (Scheme 1).

Cu(OH)_x-clay (preparation given in experimental section) demonstrates excellent catalytic activity without formation of any side product. With this catalyst, the model reaction provided 92% of the preferred product



Scheme 1: Synthesis of 4,5-dihydro-1,2,4-oxadiazoles at room temperature.

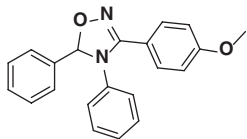
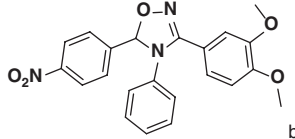
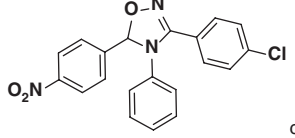
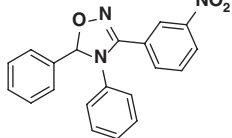
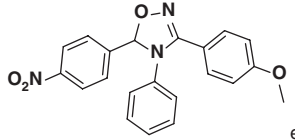
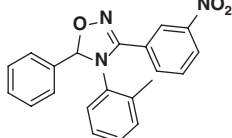
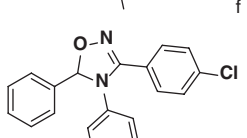
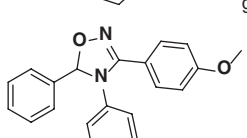
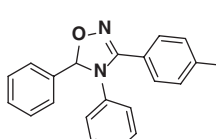
Table 1: Optimization of reaction conditions for the synthesis of 4,5-dihydro-1,2,4-oxadiazole.^a

Entry	Stirring condition (°C)	Solvent	Time (h)	Catalyst (mg)	Yield (%) ^b
1	25	Toluene	2	15	Traces
2	120	Toluene	2	15	Traces
3	25	Toluene	6	15	12
4	25	Acetonitrile	6	15	34
5	25	Methanol	6	15	21
6	25	Ethanol	6	15	26
7	25	DMF	6	15	52
8	25	DMSO	6	15	56
9	25	THF	6	15	19
10	25	Solvent free	6	15	07
11	25	DCM	6	15	92
12	25	DCM	5	15	92
13	25	DCM	10	15	92
14	25	DCM	5	10	92
15	25	DCM	5	5	78
16	25	DCM	5	3	65

^aReaction condition: benzohydroxymoyl chloride (1 mmol), imine (1 mmol), solvent (3 ml), Cu(OH)_x-clay (10 mg) at 25°C.

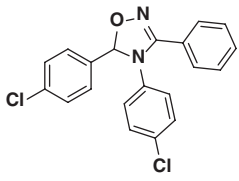
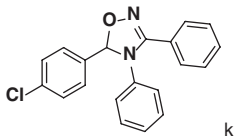
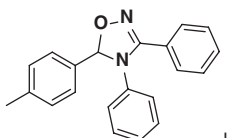
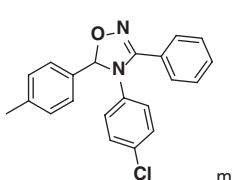
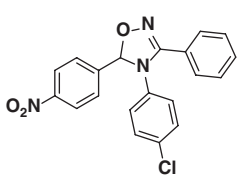
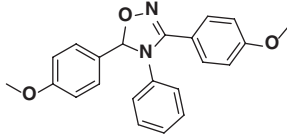
^bIsolated yield.

Table 2: Cu(OH)_x-clay catalyzed synthesis of 4,5-dihydro-1,2,4-oxadiazoles.^a

Entry	R	R'	R''	Product	Yield (%)
1	H	H	4-OMe		87
2	4-NO ₂	H	2, 4-OMe (2,3-dimethoxy)		63
3	4-NO ₂	H	4-Cl		68
4	H	H	3-NO ₂		66
5	4-NO ₂	H	4-OMe		71
6	H	2,3-Me (2,3-Dimethyl)	3-NO ₂		63
7	H	H	4Cl		92
8	H	H	4-OMe		90
9	H	H	4-Me		92

(continued)

Table 2 (continued)

Entry	R	R'	R''	Product	Yield (%)
10	4-Cl	H	H		96
11	4-Cl	H	H		91
12	4-CH ₃	H	H		87
13	4-CH ₃	4-Cl	H		94
14	4-NO ₂	4-Cl	H		77
15	4-OMe	H	4-OMe		85

^aReaction condition: benzohydroximoyl chloride (1 mmol), imine (1 mmol), solvent (3 ml), Cu(OH)_x-clay (10 mg) at 25°C.

within 5 h in DCM as solvent at the expense of the catalytic amount of Cu(OH)_x-clay.

The optimum amount of the catalyst in this one-pot, three-component reaction was found to be 10 mg (Table 1, entry 14). By reducing the catalyst amount to 3 mg, the preferred product was produced in lower yield (Table 1, entry 16), while as increased catalyst amount has no obvious conclusion on reaction kinetics as well as yield of the product (Table 1, entries 1–12).

With these optimized reaction conditions in hand, we proceeded to study the scope of this method, particularly in the construction of compound library. Different 4,5-dihydro-1,2,4-oxadiazoles were synthesized from various starting materials to evaluate this methodology. Cu(OH)_x-Clay proved as an excellent catalyst for one-pot synthesis of 4,5-dihydro-1,2,4-oxadiazoles and the preferred products

were obtained in good yields (Table 2). The methodology was investigated for several substituted benzaldehydes (of imines) under optimized conditions. To our delight, an excellent functional group tolerance reaction was found with a variety of functional groups like F, Cl, Br, Me, OMe (electron donating groups), and NO₂ (an electron withdrawing group). The reactions progressed smoothly, to produce the desired 4,5-dihydro-1,2,4-oxadiazoles with no significant variation in yields. In the substrates possessing an aryl-OMe group, methyl ether groups were found to tolerate the nucleophilic cleavage.

The X-ray diffractogram of Cu(OH)_x-clay is given in Figure 1. Peaks at $2\theta = 20.9^\circ$, 26.8° , 50.3° and 61° are attributed to the presence of silica [SiO₂] and at 12.4° , 19.8° and 27.8° owing to palygorskite. Montmorillonite shows diffraction peak at $2\theta = 8.9^\circ$ (d 001 reflection), 19.7° , 32.1° and

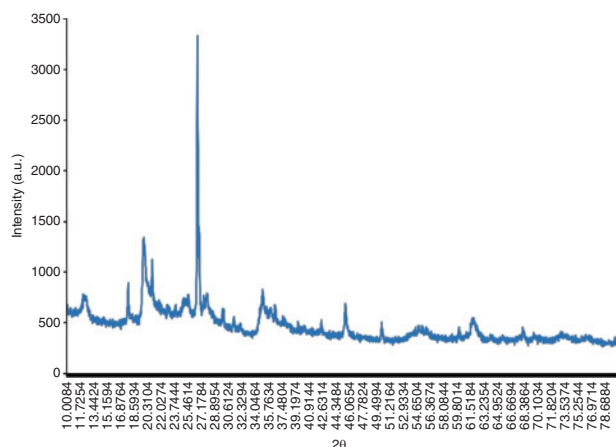


Figure 1: XRD spectra of Cu(OH)_x-clay catalyst.

62°. Presence of small peaks at 38.8° and 42.5° is implied to kaolinite. No characteristic peaks of CuO, Cu₂O and metallic Cu loaded on montmorillonite-KSF are present but peaks matching to Cu(OH)₂ and (Cu₂Cl(OH)₃) with very low intensity are observed at $2\theta = 16.1^\circ$, 18° , 25.1° , 32.3° and 50.3° . From XRD analysis it is obvious that copper hydroxide species are deposited with very low crystalline character. The SEM image of the Cu(OH)_x-clay catalyst shown in Figure 2 exhibits that surface of the catalyst is not smooth but very rough, so has increased surface area. The increased surface area of Cu(OH)_x-clay catalyst elevates its capability to adsorb the reactant to a large extent.

3.1 Recyclability of the catalyst

For the investigation on recyclability of Cu(OH)_x-clay on the test reaction, separation of the catalyst was done through centrifugation of the reaction mixture diluted

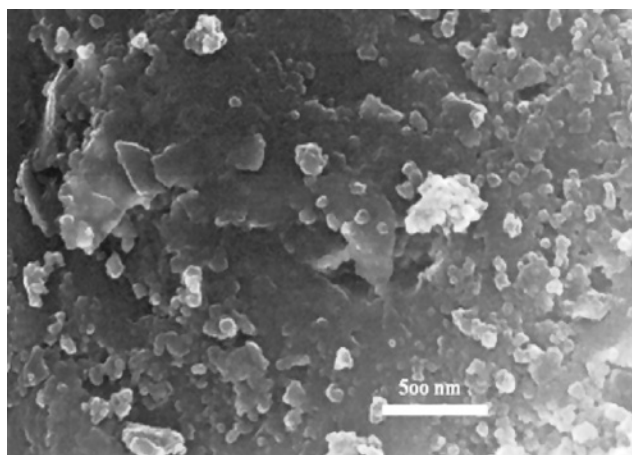


Figure 2: SEM images of Cu(OH)_x-clay.

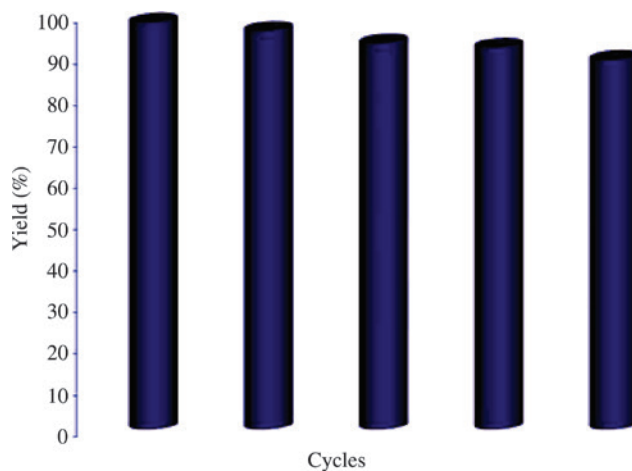


Figure 3: Recyclability of Cu(OH)_x-clay catalyst.

with DCM. The catalyst exhibits recyclability and reusability for a number of times without any significant loss in catalytic activity. In each cycle the products were generated with excellent purity. The catalyst reusability for five cycles is shown in Figure 3.

4 Conclusion

An efficient, chemo-selective, and simple protocol for the one-pot synthesis of 4,5-dihydro-1,2,4-oxadiazoles is presented. Catalytic amount of Cu(OH)_x clay, simple experimental procedures and absence of competitive side reactions add to the important features of this technique. The catalyst is competent, economical, shelf stable, heterogeneous and can be recovered from the reaction mixture by simply centrifugation and reused several times. The method is rapid and the desired products are produced in excellent yield with easy separation and purification. This simple procedure allows a synthesis of a series of 4,5-dihydro-1,2,4-oxadiazoles from low-cost and easily available starting materials.

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