

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 designed for the preparation of 4,5-dihydro-1,2,4-oxadiazole using recyclable Cu(OH)_x-Clay heterogeneous catalyst at room temperature. The cyclo-addition 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 construct 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. The technique is practically uncomplicated, inexpensive, and excellent with wide range of functional group tolerance to generate structurally different 1,2,4-oxadiazoles. The prepared catalyst was investigated by XRD and SEM techniques. The final products of synthesized compound were characterized by FTIR, NMR spectroscopy and mass spectrometry.

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

1. INTRODUCTION

As an essential category of compounds [1] 1,2,4-oxadiazoles have acknowledged significant attentiveness as numerous of them have been found to possess biological activity. 1,2,4-Oxadiazoles have been used as anti-inflammatory agent [2], pesticides and insecticides [3], benzodiazepine receptor agonist [4], histamine H-3 receptor antagonists [5] as antiviral compounds [6], aldose reductase inhibitors [7] and have been employed as a bioisostere of urea in β 3 adrenergic receptor agonists [8].

Numerous schemes have been described for the preparation of 1,2,4-oxadiazoles [9]. 1,3-Dipolar cycloaddition reactions have been 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 are also well recognized [11]. In the relay our ongoing research to produce competent heterogeneous catalyzed methodologies to produce variety of organic compounds from easily accessible starting materials

[12-21], we herein report Cu(OH)_x-Clay catalyzed approach for the synthesis of 4,5-dihydro-1,2,4-oxadiazoles via cycloaddition reaction of *N*-hydroxybenzimidoyl chloride and imine at room temperature.

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

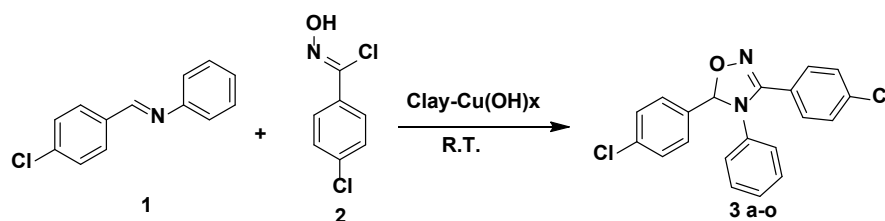
[Supplemental data \(full experimental detail, IR, ¹H-NMR, ¹³C-NMR and mass spectra\) can be accessed on the publisher's website.](#)

2. RESULTS AND DISCUSSION

In our initial studies preparation of 4, 5-dihydro-1,2,4-oxadiazoles through the cycloaddition

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of (E)-N-(4-chlorobenzylidene)aniline with (Z)-4-chloro-N-hydroxybenzimidoyl chloride was selected as model reaction for optimization of reaction settings (Scheme 1).



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.^b

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

^a isolated yield; ^bReaction condition: benzohydroximoyl chloride (1mmol), imine (1mmol), solvent (3 mL), Cu(OH)_x-Clay (10 mg) at 25 °C.

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 within 5 h in DCM as solvent at the expense of 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 lowering the catalyst amount to 3 mg, the preferred product was produced in lower yield (Table 1, entry 16), while increasing catalyst amount has no obvious conclusion on reaction kinetics as well as yield of the product (Table 1, entries 1-12).

With the 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 excellent catalyst for one pot synthesis of 4, 5-dihydro-1,2,4-oxadiazoles and the preferred products were obtained in good yields (Table 1 – See Supplementary Material). The methodology was investigated for several substituted benzaldehydes (of imines) under the 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 Fig. 1. Peaks at 2θ = 20.9°, 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 62° . Presence of small peaks at 38.8° , and 42.5° is implied to kaolinite. No characteristic peak 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 $2\theta = 16.1, 18^\circ, 25.1^\circ, 32.3^\circ$ and 50.3° . From XRD analysis it is obvious that copper hydroxide species are deposited with very low crystalline character. The Scanning Electron Microscope (SEM) image of the Cu(OH)_x-Clay catalyst shown in Fig. 2 which 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.

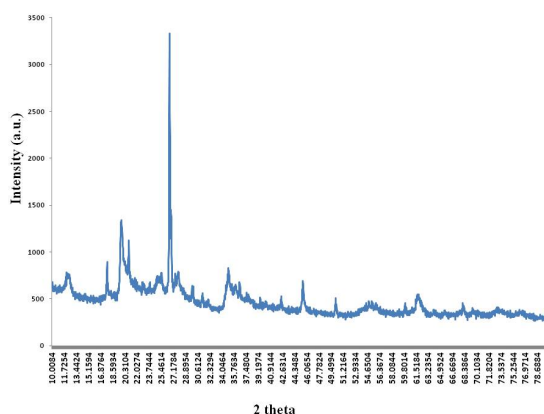


Figure 1. XRD spectra of Cu(OH)_x-Clay Catalyst

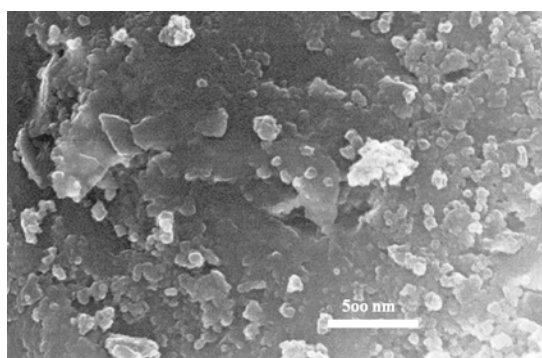


Figure 2. SEM images of Cu(OH)_x-Clay

Recyclability of the catalyst

For the investigation of recyclability of Cu(OH)_x-Clay on the test reaction, separation of the catalyst was done through centrifugation of the reaction mixture diluted with DCM. The catalyst exhibits recyclability and reusability a number of

times exclusive of any significant loss in catalytic activity. In each cycle the products were generated with excellent purities. The catalyst reusability for 5 cycles is shown in Figure 3.

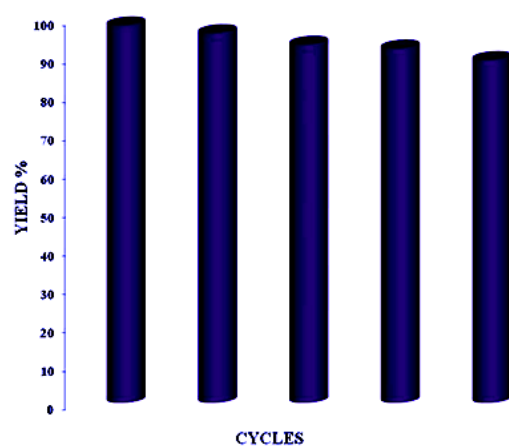


Figure 3. Recyclability of Cu(OH)_x clay catalyst

In 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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