



SiO₂–CuCl₂: An efficient and recyclable heterogeneous catalyst for one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones



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ABSTRACT

Silica supported copper(II) chloride is prepared as a green heterogeneous catalyst for the synthesis of biologically and pharmaceutically important 3,4-dihydropyrimidin-2(1*H*)-ones under microwave and thermal conditions. The catalyst has been characterized by various instrumental techniques such as FTIR, SEM, TEM, TGA and AAS. In addition, products are characterized by ¹H NMR, IR, ¹³C NMR and mass spectral data. The reaction of *m*-nitrobenzaldehyde, ethylacetoacetate and urea produced 5-(ethoxycarbonyl)-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one and its structure has been determined using X-ray crystallography which also showed the inter-molecular H-bonding packing arrangement of molecules.

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1. Introduction

What makes researchers looking into the field of catalysis with continuous discovering every newer aspect of it is enfolded in its applicability in industry. Catalysis comprises a new way to meet the demands of energy and sustainability for the synthesis of organic compounds in the most economical way along with ecological concern [1,2]. Supporting transition metals onto the solid supports provide a large surface area for reactants to get adsorbed, come closer and get able to react faster followed by desorption of reactants leaving the catalyst to be regenerable. Among transition metals, copper as a choice to explore comes from its mild nature, easy availability and less toxic nature.

Synthesizing heterocyclic bioactive molecules by replacing the old classical methods with new eco-friendly techniques like as with heterogeneous catalysts represents one of the most vibrant research areas in organic chemistry. Dihydropyrimidinones (Bignelli compounds) and their derivatives belong to an important class of heterocyclic compounds that have attracted attention due to their interesting pharmacological and biological profiles [3]. Their applications in the field of drug research

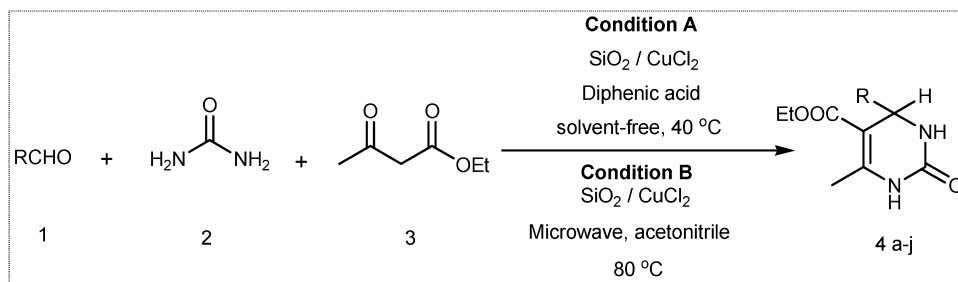
have stimulated the development of a wide range of synthetic methods for their preparation and chemical transformations. Aryl-substituted 3,4-dihydropyrimidin-2(1*H*)-one and their derivatives are an important class of substances in organic and medicinal chemistry. These derivatives have remarkable pharmacological properties such as calcium channel blockers, α -1a-antagonists, HIV inhibitors of gp-120-CD4, anti-hypertensive, anti-viral, anti-tumor, anti-bacterial, anti-fungal, anti-cancer, anti-inflammatory agents [4,5], melanin-concentrating hormone receptor antagonist [6] and neuropeptide Y (NPY) antagonist [7]. These can be used as therapeutics in cardiovascular diseases, angina pectoris, or benign prostatic hyperplasia [8]. Moreover, its derivatives are found in a large family of natural products with broad biological activities. Various marine alkaloids containing the dihydropyrimidinone moiety have interesting biological properties, such as batzelladine alkaloids that are potent HIV gp-120-CD4 inhibitors [9].

Many nucleosides that have 5-substituted pyrimidine moiety have been shown to inhibit the growth of murine mammary carcinoma virus. Pyrimidine cores with extended π -systems possess interesting fluorescent properties, and similar compounds are useful in the development of advanced electronic and photonic materials [10–12].

In history, the Bignelli reaction represents a classical approach for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones by the one-pot condensation of an aromatic aldehyde, β -ketoester and

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Scheme 1.

urea in the presence of a mineral acid catalyst and alcohol solvent. Various reagents have been used for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones such as chloroacetic acid [13], InBr_3 [14]; BF_3OEt_2 in combination with transition metal salts [15], amberlyst 15 [16], ZnCl_2 [17], $\text{SnCl}_2/\text{ChCl}$ [18], $\text{SiO}_2\text{-Cl}$ [19] and copper triflates [20]. But the reported reagents are associated with certain drawbacks such as larger reaction times, tedious work-up procedures and even handling of catalyst. In order to overcome these drawbacks, copper(II) chloride in combination with silica has been used as heterogeneous catalyst under thermal and microwave conditions for one-pot synthesis of Biginelli compounds as shown in Scheme 1.

2. Experimental

2.1. Preparation of catalyst- silica supported copper(II) chloride [$\text{SiO}_2\text{-CuCl}_2$]

In order to support copper(II) chloride onto silica, the silica gel (15 g, K 100) was activated by adding silica gel (15 g, K 100) to a solution of $\text{HCl}:\text{H}_2\text{O}$ (1:1, 300 mL) in a round-bottom flask (500 mL) and the reaction mixture was stirred at 120°C for 12 h. The activated silica was filtered at pump, washed with water till washings were neutral and dried in an oven at 110°C for 5 h. The yield obtained was 13.8 g. Then the activated silica (10 g, K 100) was stirred with anhydrous CuCl_2 (0.2 g) in dry ether (50 ml) at room temperature for 4 h. The catalyst was filtered, washed with water till washings were colorless and dried in an oven at $90\text{--}100^\circ\text{C}$ for 5 h. The yield obtained was 8.6 g (Scheme 2).

2.2. Characterization of catalyst

To conform the support of metal onto silica, the catalyst was thoroughly characterized by various instrumental techniques like FTIR, TGA, SEM, TEM and AAS and the results has been given as follows.

2.2.1. FTIR

The FTIR spectrum of catalyst showed strong absorption peaks at 473 cm^{-1} (Si–O–Si bending vibration), 805 cm^{-1} (symmetric stretching) and 1098 cm^{-1} (anti-symmetric stretching of Si–O), 1631 cm^{-1} (bending vibration of physically adsorbed water and 3433 cm^{-1} due to Si–OH stretching vibration). For $\text{SiO}_2\text{-CuCl}_2$, an additional peak was observed at 669 cm^{-1} which corresponds to Cu–Cl stretching vibrations (Fig. 1).

2.2.2. TGA

To check the thermal stability of the catalyst ($\text{SiO}_2\text{-CuCl}_2$), a thermo-gravimetric analysis (TGA) was done which showed a slight weight loss up to 225°C followed by continuous weight loss up to 718.3°C . The analysis indicated the stability of catalyst up to a range of $0\text{--}249.1^\circ\text{C}$ and hence is safe to be used in carrying out

the reaction under chosen conditions (room temperature, 40°C and 80°C) (Fig. 2).

2.2.3. Scanning electron microscope (SEM)

Further to study the microstructure and morphology of the catalyst ($\text{SiO}_2\text{-CuCl}_2$), a study of scanning electron microscope (SEM) has been performed. The SEM images of the catalyst showed that the surface of $\text{SiO}_2\text{-CuCl}_2$ was found to be a fine powder with porous structure and it was observed that copper chloride particles are adsorbed onto the surface of silica (Fig. 3).

2.2.4. Transmission electron microscope (TEM)

A TEM has also been performed to see the morphology of metal particles. The TEM micrographs indicated that Cu is uniformly distributed onto the surface of silica (Fig. 4). The mean diameter was found to be 2 nm which confirms the nano-size nature of the catalyst. It was found that no bulk aggregation of the metal occurred indicating that the Cu was finally dispersed onto the surface of silica. The TEM micrograph (a) infers formation of nano copper (average size 2 nm) and from (b) it is inferred that $\text{SiO}_2\text{-CuCl}_2$ shows the formation of molecular sieves which offers entrapment of metal particles inside these sieves of silica and thus displaying a host-guest relationship.

2.2.5. Atomic absorption spectrophotometric analysis (AAS)

The amount of copper loaded onto the surface of silica was determined by AAS analysis. The catalyst was stirred in dil. HNO_3 and then subjected to AAS analysis. $\text{SiO}_2\text{-CuCl}_2$ contained 0.015 g of Cu per gram of catalyst.

2.3. Instrumentation

All melting points were taken on Perfit melting point apparatus and are uncorrected. IR spectra were recorded using KBr disk on Perkin Elmer FTIR spectrophotometer. The mass spectra were recorded on Esquire 3000 Bruker Daltonics spectrometer (ESI). ^1H NMR spectra were recorded in $\text{DMSO-}d_6$ on Bruker Avance III (400 MHz) spectrometer using TMS as an internal standard. TGA was recorded on Linseis STA PT-1000 (Germany) Thermal Analyser with heating rate of $10^\circ\text{C}/\text{min}$. FTIR was recorded on Perkin Elmer-Spectrum RX-IFTIR spectrophotometer. X-ray diffractograms were recorded in 2θ range of $10\text{--}80^\circ\text{C}$ on a Panalytical's X'Pert Pro X-ray diffraction spectrometer using $\text{CuK}\alpha$ radiation. The atomic absorption spectrometric analysis (AAS) was done on Avanta-M atomic absorption spectrometric manufactured by GBC scientific agencies. SEM images were recorded on JEOL JSM-6400 Scanning Electron Microscope. TEM images were recorded on Technai G2 20 S Twin (FEI Netherland) Transmission Electron Microscope. Microwave reactions were carried out in microwave of CEM Discover of MaThews. NC made in USA with model: Discover System and model no.: 908010 having volts: 180/264 VAC, maximum current: 6.3 A, frequency: 50/60 Hz and maximum power: 700 w.

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