

One Pot Synthesis 1,4 Dihydropyridines Catalyzed by Cu-doped ZnO Nanocatalyst

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Abstract

Cu-doped ZnO catalyst was used for convenient and efficient synthesis of 1, 4-dihydropyridine (DHP) derivatives under solvent free conditions. The main advantages of these protocol includes short reaction time, high yields, recyclable catalyst, selectivity towards 1,4-dihydropyridine derivatives, practical simplicity and work up free reaction conditions.

Keywords: Cu-doped ZnO, Nano catalyst, 1,4dihydropyridines, solvent free, nonconventional.

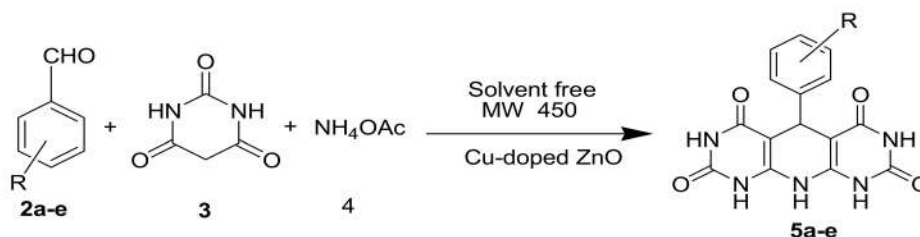
INTRODUCTION

Recently 1, 4-dihydropyridines prepared by direct condensation of aldehydes, malononitrile and barbituric acid in aqueous media has been reported under ultrasound irradiation,¹ or catalyzed by diammonium hydrogen phosphate.² 1, 4-dihydropyridines compounds are most important classes of drug molecules and were introduced for medical use in 1911.³ They have attracted much attention due to their antiviral,⁴ antibiotic,⁵ anti-inflammatory,⁶ and antitumor⁷⁻⁸ activities.

Heterogeneous catalysis for organic synthesis has gained popularity due to desirable separation of product and eco-friendly nature. Nanosized catalyst for organic synthesis is expected to bridge the gap between homogenous and heterogeneous catalysis.⁹ Heterogeneous nanocatalysis has advantages due to ecofriendly aspect, economical nature¹⁰, easy handling, greater selectivity and reusability of the catalyst¹¹. Furthermore, the nano-catalyzed reactions offer the benefits of high atomic efficiency, simplified isolation of product, easy recovery and recyclability of the catalysts. Synthesis of dihydropyrimidin-2(1H)-ones/thiones derivatives has been carried out using various nanostructure metal oxides such as TiO₂¹², Fe₂O₃¹³, ZrO₂-Al₂O₃-Fe₂O₃¹⁴ and ZnO¹⁵. However, all these synthesis require the solvents and support of homogenous organic acids.

Experimental:

Solvents, reagents and chemicals were purchased from Sd-fine Chemicals and Process Chemicals generally used without further purification. IR spectra were recorded on a Perkin FT-IR spectrometer. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400 and 100 MHz, for ¹H for ¹³C, respectively, in CDCl₃ solution with TMS as an internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents.



Scheme-: Synthesis of 1, 4-dihydropyridines

General procedure for the synthesis of Cu-doped ZnO NPs:

Nano powders of Cu-doped ZnO, have been synthesized via co precipitation method using zinc nitrate ($Zn(NO_3)_2 \cdot 6H_2O$), copper (II) nitrate trihydrate ($Cu(NO_3)_2 \cdot 3H_2O$) and sodium hydroxide (NaOH) as starting materials. For preparation of Cu-doped ZnO nanopowder, 0.5 M of zinc nitrate was dissolved in 100 ml deionized water and certain amount copper (II) nitrate trihydrate was added according to doping condition in solution. NaOH solution was slowly added into the precursor under vigorous stirring until pH of the solution reached to 14, leading to the precipitated product. After that, as-precipitated products were washed several times with deionized water and ethanol in the last step until they became neutral. Finally, the products were dried in oven at 85°C for 9 h.

General procedure for preparation 1, 4-dihydropyridines :(2a-e)

Mixture of aromatic aldehyde (5 mmol), barbituric acid (10 mmol) and ammonium acetate (8 mmol) 10 mmole Cu-doped ZnO nanocatalyst added was irradiated in microwave instrument (450 W) for a certain period of time without solvent. After completion of the reaction (monitored TLC), reaction mixture was diluted with ethyl acetate (20 mL), washed organic layer with saturated $NaHCO_3$ solution (3 x 15 mL) and then with brine solution. Dried organic layer over anhydrous Na_2SO_4 gave crude product, recrystallized from ethanol.

Results and discussion:

Present reaction is well known homogenous acid catalyzed reaction. It is also found that Lewis acids are superior over Brønsted acids due to better selectivity and higher yields having less reaction time require for completion. Various Lewis acids, $LiBr \cdot AlCl_3$, $InBr_3$, $BF_3 \cdot OEt_2$, $FeCl_3$ and $LaCl_3$ were reported for the synthesis of 1, 4 Dihydropyridines. In view of this, the synthesis of 1, 4 Dihydropyridines was carried out using nano sized Cu-doped ZnO catalyst. The synthesis of Cu-doped ZnO catalyst was carried out by solution based precipitation technique. Hence, the synthesis of proposed catalyst is carried out using precipitation technique as described in the experimental section.

Table 1. Synthesis 1, 4 Dihydropyridines Catalyzed by Cu-doped ZnO condition under microwave irradiation and conventional heating.

Sr. No.	Comp.(2a-2e)	Ar-CHO	Microwave Oven		Conventional Heating	
			Time (min.)	yield	Time (min.)	Yield
1.	2a	4- Cl- C_6H_5	20	88	90	72
2.	2b	C_6H_5	20	89	90	65
3.	2c	4- OCH_3 - C_6H_5	20	85	90	63
4.	2d	4- NO_2 - C_6H_5	20	77	90	61
5.	2e	4- F- C_6H_5	20	81	90	64

3.1. Spectral Data of as Synthesized Compounds

5a. mp: 300 °C, IR: 3661, 3175,1682, 1633, 1458, 776 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ 10.10 (s, 1H), 3.5 (s, 1H), 5.93 (s, 1H),7.18 (dd, J = 2.2 Hz, 2H), 7.04 (d, J = 7.8, 2H). ¹³C NMR (125 MHz, DMSO-d₆): δ 168.11, 152.12, 129.37, 127.77, 126.30, 40.49, 91.22. EI-MS (m/z): 418 (M+1).

5b. mp: 298-300 °C; IR: 3054, 1700, 1676, 1606, 1405, 1507 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ 10.01 (s, 1H), 3.6 (s, 1H), 7.09 (t, 1H), 7.18 (dd, J = 2.2 Hz, 2H), 7.05 (d, J = 7.8, 2H). ¹³C NMR (125 MHz, DMSO-d₆): δ 164.40, 150.10, 130.8, 128.12, 126.30, 38.20, and 79.10
EI-MS (m/z): 378 (M+1).

5c. mp: 285-286 °C; IR: 3056, 1676, 1606, 1405, 1507, 776 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ 10.01 (s, 1H), 6.75 (dd, J = 2.2 Hz, 2H), 7.01 (d, J = 7.8, 2H), 3.76 (s, 3H), 3.30 (s, 1H). ¹³C NMR (125 MHz, DMSO-d₆): δ 80.10, 152.40, 40.05, 152.10,165. 20, 135.30, 115.20, 132.10, 55.40. EI-MS (m/z): 406 (M+1)

5d. mp: 270-271 °C; IR: 3135, 1689, 1605, 1458, 1528, 776 cm⁻¹, ¹H NMR (400 MHz, DMSO-d₆): δ 10.01 (s, 1H), 6.01 (s, 1H), 8.05 (dd, J = 2.2 Hz, 2H), 7.38 (d, J = 7.8, 2H), 4.40 (s, 1H). ¹³C NMR (125 MHz, DMSO-d₆): δ 81.10, 150.40, 37.05, 150, 164.20, 150.30, 145.20, 120.10. EI-MS (m/z): 420 (M+1)

5e. mp: 255-256 °C; IR: 3661, 3175, 1682, 1633, 1458, 776 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ 10.01 (s, 1H), 6.01 (s, 1H), 6.82 (dd, J = 2.2 Hz, 2H), 7.08 (d, J = 7.8, 2H), 4.43 (s, 1H). ¹³C NMR (125 MHz, DMSO-d₆): δ 81.10, 150.40, 37.05, 150, 164.20, 150.30, 145.20, 120.10. EI-MS (m/z) : 391 (M+1).

Conclusion:

We have successfully accomplished green synthesis of dihydropyrimidone derivatives. Use of nanocatalyst Cu-dopes ZnO is found to be an efficient catalyst for heterogeneous 1, 4-dihydropyridines synthesis. Small amount of catalyst is sufficient to run the reaction. Solvent free reactions gave almost the same yield compared to the use of organic solvents. Proposed methodology used is easy to handle and scale up. The catalyst used is environmental friendly and can be recycled.

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