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Silica-Supported Cu–Zn Nanoparticles as a Heterogeneous Catalyst for Synthesis of B-Amino Esters Derivatives Via Sono Chemistry

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ABSTRACT
A novel and efficient Silica Supported Cu-Zn NPS as catalyzed one-pot reaction of aromatic amines, aromatic aldehyde or respective imine with malonic esters was described. This cascade reaction affords the corresponding β-amino esters in good to excellent yield at 50°C in the presence of ethanol as solvent via sono-chemistry. The present methodology includes an inexpensive catalyst, easy work-up, mild reaction conditions, no side reaction, and compatibility with the various substrates.
Keywords: *Green chemistry, sonochemistry, Nano catalyst, β amino esters derivatives*

1.INTRODUCTION

The mannich reactions are one of the classical carbon-carbon and carbon-nitrogen bond-forming reactions [1]. Due to this significant behavior of mannich reaction is important for the synthesis of *β*-amino carbonyl compounds [2]. *β*-Amino carbonyl compounds are endowed with a broad range of applications in pharmaceutical and biologically active compounds [1] such as dolastins, astins, onchidin, Jasplakindole, Mutuporin [3]. Besides, *β*-amino carbonyl compounds are practically utilized for the synthesis of peptides bonds, optically active amino acids, *β*-lactams, *β*-amino alcohols, bioactive molecules like Nikkomycins and Neopolyoxins antibiotics [4–8]. Due to numerous ap- plications of the mannich bases in the organic synthesis, much attention has been drowning on the efficient synthesis of *β*-amino carbonyl com- pounds to date [9]. Various methods have been reported includes silica/ sulphuric acid [10], Salen Zn complex [11], $ZrOCl_2$.$8H_2O$ [12], $CeCl_3$.$7H_2O$ [13], $Zn(OTf)_2$ [14], rare earth perfluorooctanoate [15],(bromodimethyl)sulfonium bromide [16], $BiCl_3$ [17], Cu-nanoparticles[18], Iodine [19], sulphamic acid [20], $NbCl_5$ [21], $HClO_4$-SiO_2 [22], Ionic liquid [23], $LiClO_4$ [24] etc. Although various methods reported to today suffers one or more problem such as use of expensive and toxic chemicals, no easy availability of reagent, additional time required for the preparation of catalyst, less shelf-life/stability of catalyst, diffi- culty in product separation, required column chromatographic separa- tion and/or purification, drastic reaction conditions result into other side reaction and decreases the expected product yield. Therefore, there is a wide scope for the introduction of new, efficient methods for the synthesis of *β*-amino carbonyl compound by using an inexpen- sive, readily available and nonpolluting reagent.

Ammonium chloride is inexpensive, non-toxic, readily available and most importantly easily removed from the reaction mixture makes re- action operationally simple. Due to this significant application in recent year, Silica supported Cu-Zn NPS has attracted much attention as catalyst in organic synthesis includes Ullmann coupling [25], thia-Michael addition [26], Claisen re- arrangement [27], synthesis of tetrahydrobenzo[*α*]xanthene-11-ones [28], Biginelli type synthesis of 3,4 dihydropyrimidin-2-(1*H*)ones [29], three component Groebke condensation reaction for the synthesis of imidazo[1,2-*α*]pyridines [30], three component synthesis of 5- iminooxazolines [31], synthesis of 4-imino-4*H*-3,1-benzoxazines [32], synthesis of imidazo[1,2-*α*]pyrimidines [33], synthesis of spirochromenes and spiroacridines [34], Ugi four component reaction [35], synthesis of dipeptides [36], synthesis of pyrrolo[3,4-*b*]pyridine- 5-ones [37], synthesis of quinoxalines [38], synthesis of arylbenzothiazoles and bisbenzothiazoles [39], crossed-aldol condensa- tion [40], condensation of carbonyl compounds and indoles [41], reduc- tion of aromatic nitro compounds to aromatic amine and reduction of azides to amines or amides, reductive cleavage of aza compounds to amines and in oxidation of alcohols.

MATERIALS AND METHODS:

Experimental section:

All essential raw materials were procured from the local chemical supplier, an analytical chemistry facility associated with the local testing laboratory for Mass spectra. Additionally, NMR were conducted by Sathi-BHU.

General procedure for the synthesis of Diethyl 2-(phenyl (phenyl amino) methyl) malonate (4a-4o) and Ethyl 2-{[(3-flourophenyl) amino] (phenyl) methyl} acetoacetate (a-b)

A mixture of benzaldehyde (1.5 mmol, 0.15 mL), anilines (2 mmol, 0.20 ml) and diethylmalonate (2.0 mmol, 0.30ml) by using Silica supported Cu-Zn Nps in a round bottom flask (RBF) was kept in sonication reactor for the time period from 10-15 min at 50 ^{0}C and the reaction were monitored by TLC (ethyl acetate/n-hexane, 8:2) (as showed in Table 1). After completion of the reaction, the reaction mixture was allowed to cool to room temperature, and the precipitates were filtered. The obtained crude products were purify by recrystallization with ethanol to give products high yield.

Diethyl [(2-chloroanilino)(2-chlorophenyl)methyl]propanedioate: White solid, ^{1}H NMR (400 MHz, CDCl3):δ 1.20-1.31 (6H), 4.16-4.31 (4H), 4.61 (1H), 5.26 (1H), 6.31 (1H), 6.95-7.16 (2H),7.25-7.58 (5H), ^{13}C NMR: δ 14.0-14.2 (2C),55.3(1C), 61.7-61.9 (2C),62.1 (1C), 120.0 (1C), 122.7 (1C), 125.2 (1C), 125.5 (1C), 128.5 (1C), 129.4-129.7 (2C), 129.4 (1C), 130.4(1C), 131.9 (1C), 133.5 (1C), 138.9 (1C), 168.0-168.1 (2C).Mass-Spectra(409.08):410.12

Diethyl [(3-chloroanilino)(phenyl)methyl]propanedioate: White solid, ^{1}H NMR (400 MHz, CDCl3): δ 1.20-1.26 (6H),4.13-4.19 (4H), 4.59 (1H), 5.38 (1H), 6.85 (2H), 7.15-7.36 (6H), 7.53 (1H), ^{13}C NMR: δ 14.2-14.4 (2C), 57.0 (1C), 61.6-61.9 (2C), 63.0 (1C), 119.2 (1C), 119.8 (1C), 123.9 (1C), 127.9 (2C), 128.1 (1C), 128.7 (2C), 130.2 (1C), 134.3 (1C), 138.1 (1C), 145.1 (1C), 168.0-168.1 (2C). Mass-Spectra (375.12):378.50

Diethyl [(4-chloroanilino)(phenyl)methyl]propanedioate: White solid, ^{1}H NMR (400 MHz, CDCl3): δ 1.16-1.40 (6H),4.13-4.19 (4H), 4.65 (1H), 5.52 (1H), 6.71 (2H), 6.85 (2H), 7.17-7.44 (5H), ^{13}C NMR: δ 14.2-14.5 (2C),55.7 (1C), 61.6-61.9 (2C), 62.4 (1C), 119.7 (2C), 127.3 (3C), 128.1 (1C), 128.9 (2C), 129.0 (2C), 139.1 (1C), 139.9 (1C),, 168.0 (2C). Mass-Spectra(375.12):376.50

Diethyl 2-(phenyl (phenylamino) methyl) malonate: White solid,. ^{1}H NMR (400 MHz, CDCl3): *δ* 7.38-7.36 (2H), 7.30 –7.22 (4H), 7.12-7.08 (2H), 6.69 (1H), 6.63 (2H),5.20 (1H), 4.17–4.28 (4H), 3.96 (1 H),1.16–1.12 (6H). ^{13}C NMR (100MHz, CDCl3) *δ*: 168.10, 146.65, 139. 73,129.12, 128.61, 127.60, 126.81, 117.84,113.77, 61.86, 58.24, 57.03, 13.97, Mass-Spectra (341.16):342.22

As a part of a continuing effort in our laboratory to study the Silica supported catalyzed organic reactions. We were interested in devel- oping a novel and efficient method to synthesized *β*-amino esters. Herein, we report a novel, rapid, and efficient, Silica supported Cu-Zn NPS promoted three- component mannich type reaction of amine, aldehyde and malonic esters for the synthesis of *β*-amino ester at room temperature.

The present method is cascade reaction for the synthesis of mannich bases by use of inexpensive, nontoxic and readily available chemicals and catalyst, shows good compatibility with various substrate, easy removal of catalyst, no side product, no further purification required.

Catalyst amount(w/w%)	Solvent	Temp/Time(Min)	Yield
5%	Ethanol	RT/30	78%
10%	Ethanol	50°C/15	95%
15%	Ethanol	50°C/15	90%
20%	Ethanol	50°C/15	87%
5%	ACN	RT/30	72%

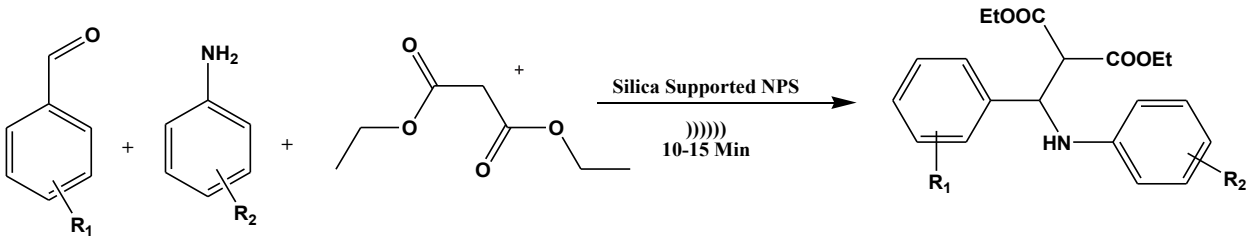
10%	ACN	50°C/15	75%
15%	ACN	50°C/15	79%
20%	ACN	50°C/15	81%
10%	Ethanol	50°C/15	95%

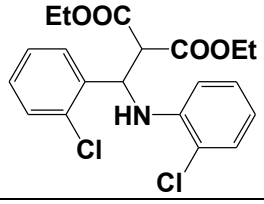
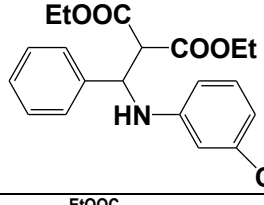
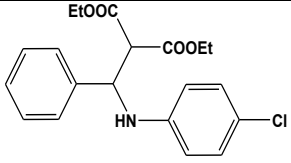
CONDITIONS OPTIMIZATION OF THE MANNICH REACTION UNDER DIFFERENT CONDITIONS.

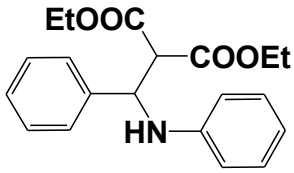
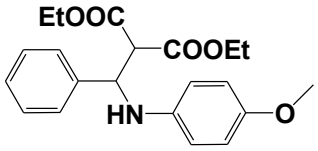
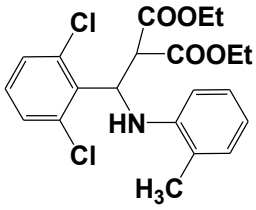
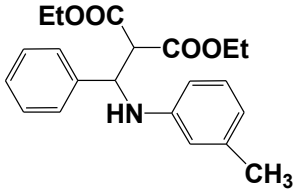
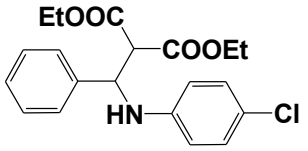
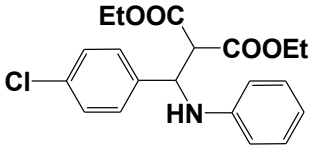
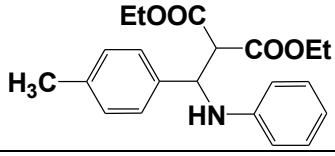
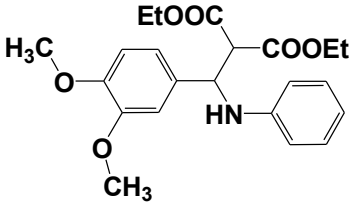
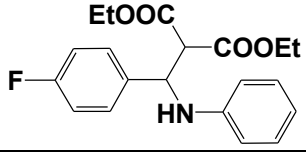
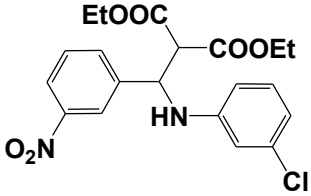
Table 1 presents the optimization data for a chemical reaction achieved by varying the catalyst loading, solvent, temperature, and reaction time to maximize the product yield. It offers a comparative analysis of ethanol and acetonitrile (ACN) as solvents under room temperature (RT) and 50 °C conditions under sonication. The yields reached a maximum of 95% in specific ethanol configurations under sonication at 50°C for 15 min. Ethanol consistently demonstrated superior performance compared to that of ACN. In contrast, ACN yields remained below 81%, indicating suboptimal compatibility. The optimal conditions were characterized by a moderate catalyst concentration (10–20%) in ethanol; excessive heat or catalyst loading marginally decreased the efficiency of productivity. This observation likely originates from a green chemistry optimization study, in which ethanol facilitates enhanced kinetics or solubility. For further studies, prioritizing a 10% catalyst in ethanol at 50°C under sonication is recommended to efficiently attain a 95% yield for various substituted aromatic aldehyde

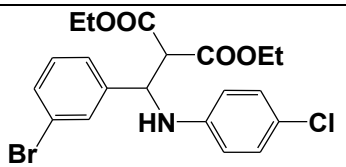
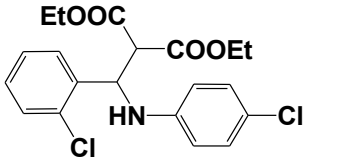
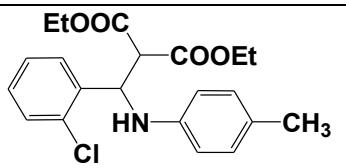
RESULT AND DISCUSSION

Table 2The Reaction of imines with malonic ester using Silica supported Cu-Zn NPS



Entry	R_1 (1)	R_2 (2)	Structure	Yield (%)
1.	2-Cl	2-Cl		60
2.	H	3-Cl		98
3.	H	4-Cl		97

4.	H	H		98
5.	H	4-OCH_3		91
6.	2,6 dichloro	2-CH_3		98
7.	H	3-CH_3		95
8.	H	4-Cl		85
9.	4-Cl	H		98
10.	4-CH3	H		90
11.	3,4-OCH3	H		78
12.	4-F	H		95
13.	3-NO2	3-Cl		98

14.	3-Br	4-Cl		89
15.	2-Cl	4-Cl		85
16.	2-Cl	4-CH_3		60

The initial experiment was conducted utilizing aniline diethyl malonate in ethanol with various aromatic aldehydes at ambient temperature (Scheme 1). Various amount of Silica supported Cu-Zn Nano particles evaluated as catalysts for the Mannich reaction. As illustrated in Table 1, the common catalyst at different concentrations did not yield the desired product (Table 1, entries 3–5); however, aniline derivatives produced the desired product with moderate yield (Table 1, entry 2). Notably, silica-supported Cu-Zn NPS efficiently catalyzed the Mannich reaction, resulting in high yields within a relatively short duration. Subsequently, the catalyst amount was assessed, revealing that 10 mol% of silica-supported Cu-Zn NPS was adequate to complete the reaction with a 95% yield. The study further explored the use of various aromatic aldehydes, aromatic amines, and malonic esters. The findings are summarized in Table 02. Generally, the three-component Mannich reaction proceeded smoothly, yielding the corresponding products in good to high yields. As depicted in Table 02, electron-deficient amines and aldehydes yielded the corresponding β-amino esters 4 in good to excellent yields (60–98%). Conversely, electron-rich amines and/or aldehydes resulted in poor yields (Table 02, entries 1–16) or no desired product (Table 02, entry 16). It was observed that ortho-substituted anilines produced low yields due to steric hindrance (Table 02, entries 1, 16). It is noteworthy that electron-donating groups such as –OCH_3 and –OH in benzaldehyde did not yield the expected Mannich bases. The bright yellow-colored shining crystals of derivatives distinctly differentiated them from Mannich bases. This table presents a substrate scope study for synthesizing a series of products via a multi-component reaction (MCR) with varying substituents R1 and R2 on the aryl rings and ester component. The yields ranged from 60% to 95%, indicating good tolerance for electron-withdrawing, donating, and sterically varied groups. This study builds on a previous optimization table, likely employing the optimal conditions (e.g., 10–20% catalyst in ethanol). The highest yields (95%) were observed with electron-rich/steric mixes, such as 2,4-dichloro/3-CH_3, and nitro/chloro associated with Lower yields (60%) due to symmetrical halogens or methoxy.

CONCLUSION

We have developed an innovative, straightforward, and efficient methodology for synthesizing β-amino esters. This process employs silica-supported Cu-Zn nanoparticles as catalysts in the Mannich-type reaction involving a malonic ester and an imine, which can be generated in situ from the corresponding aromatic amines and aromatic aldehydes under sonication conditions at 50°C, utilizing ethanol as an environmentally friendly solvent. The protocol is characterized by its operational simplicity, mild reaction conditions, cost-effectiveness, low catalyst loading, absence of side product formation, elimination of the need for column purification, and high product yields.

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