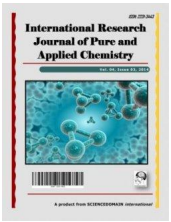

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Synthesis of Co^{2+}/Zn^{2+} Impregnated Bentonite-Chitosan Composite Hetero-catalyst and Application of Principal Component Analysis to Evaluate its Catalytic Activity for the Synthesis of Nitrogen Containing 5 and 6 Membered Heterocyclic Compounds

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Authors' contributions

This research work was carried out in collaboration between all authors. Author DA designed the study, performed the synthesis and wrote the first draft of the manuscript under the supervision of author VKK. Authors DA, AV and JD managed the spectral and statistical analyses of the study. Author AV managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

A hetero-catalyst, Co^{2+} and Zn^{2+} impregnated Bentonite-Chitosan composite (Co^{2+}-BCC and Zn^{2+}-BCC) has been developed separately and characterized using scanning electron microscope (SEM), for the synthesis of a different class of nitrogen containing 5 and 6 membered heterocyclic compounds. Co^{2+}-BCC showed high catalytic activity for octahydroquinazolinones and imidazoles;

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and Zn^{2+}-BCC for 1,4-dihydropyridines and benzimidazoles. Isoxazoles were synthesized in excellent yield by both Co^{2+}-BCC and Zn^{2+}-BCC. Different ratios of Co^{2+}/Zn^{2+}-BCC were analyzed to achieve high percentage yield of heterocyclic compounds. Principal component analysis was performed to further extract the systematic variation and evaluate the catalytic efficacy of Co^{2+}-BCC and Zn^{2+}-BCC for the different class of nitrogen-containing heterocyclic compounds.

Keywords: Co^{2+}-BCC; Zn^{2+}-BCC; heterocyclic compounds; octahydroquinazolinones; imidazoles; 1,4-dihydropyridines; benzimidazoles; isoxazoles; principal component analysis.

1. INTRODUCTION

Heterocyclic compounds are known for their applications in medicinal chemistry and due to its finite synthetic approach, it has created substantial interest in organic chemistry [1-2]. Heterocyclic chemistry deals with the most complicated streams of organic chemistry. Synthetic heterocyclic compounds are found to have a large impact on human life as it covers almost every field as agriculture, pharmaceuticals and industries. They have influenced biological processes as they act as herbicides, insecticides, fungicides, antiseptics, antiviral, anti-tumor, antibiotics etc [3-10]. Nitrogen-containing heterocyclic compounds such as octahydroquinazolinones, imidazoles, isoxazoles, 1,4-dihydropyridines and benzimidazoles have a broad spectrum of biological activity [11-23] and hence, their synthesis has always been an important concern to the chemist. Nowadays, a concept of multi-component reactions has been an emerging approach in modern synthetic organic chemistry, as a synthesis of complicated molecules can be carried out in an efficient and time-saving manner. As multi-component reactions require less effort and minimum energy to create several new bonds in one pot in a single step, so multi-component reactions are acceptable from a green chemistry point of view [24-26].

Clays are one of the common and easily available minerals on the earth's surface and have wide applications as absorbents and catalysts for the industrial field [27]. Clay supported catalysts with incorporated transition metal ions have been used for various organic reactions [28]. Bentonite is cationic clay and with some modifications or added chemicals, it has been used as a catalyst for synthesis of compounds [29]. Chitosan is a natural polysaccharide and has recently gained attention in the synthetic field as a green and mild solid catalyst [30-32]. Moreover, chitosan treated bentonite has been widely used in many ways [33].

In the present work, we report the synthesis of Co^{2+} and Zn^{2+} impregnated Bentonite-Chitosan composite (Co^{2+}-BCC and Zn^{2+}-BCC) separately, as a hetero-catalysts for the multicomponent reactions for nitrogen containing 5 and 6 membered heterocyclic compounds. In addition, catalytic activity of Co^{2+}- BCC and Zn^{2+}-BCC was evaluated using multivariate analysis, i.e. principal component analysis.

2. EXPERIMENTAL

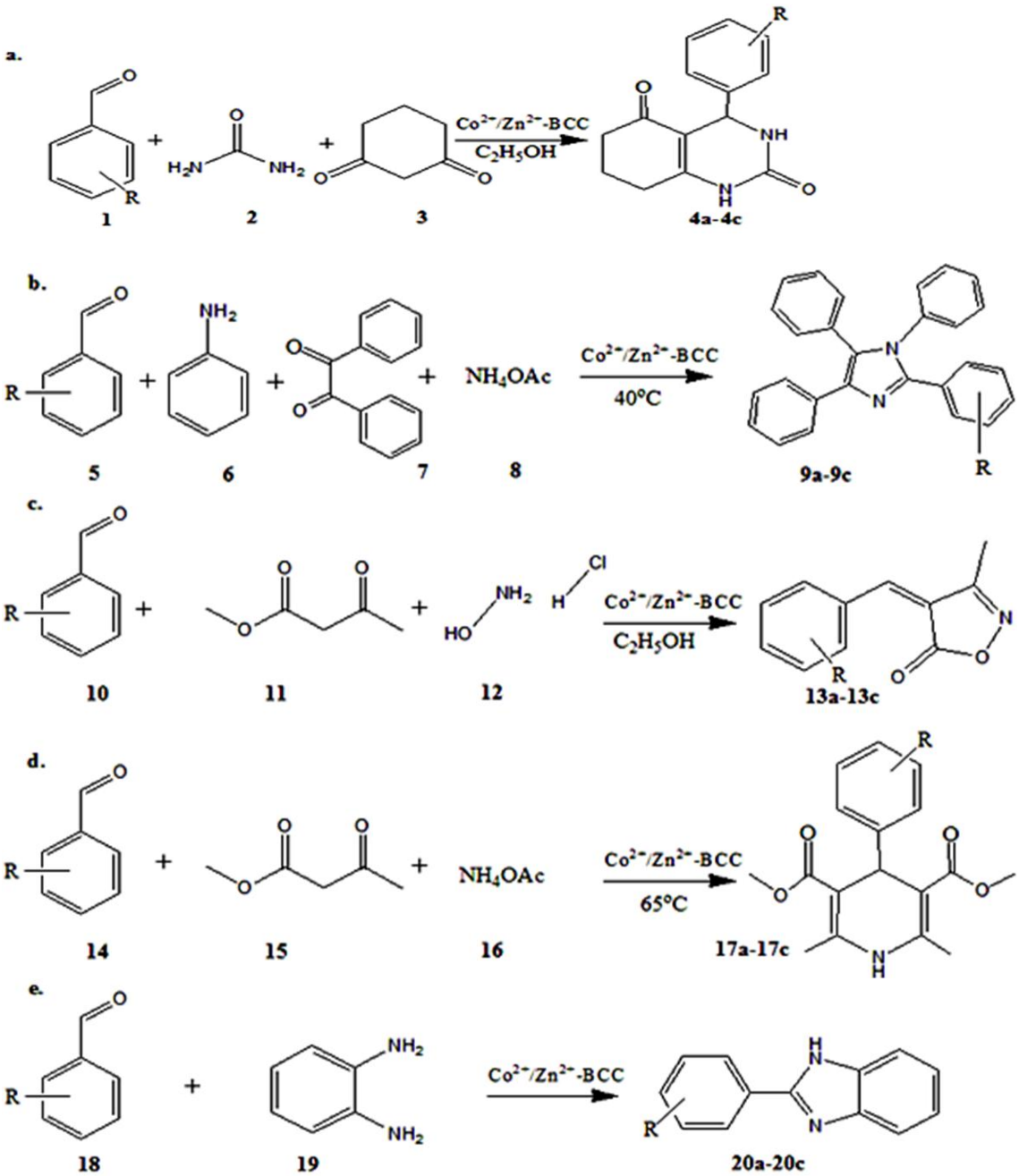
All the reagents and chemicals were obtained from Hi-media and used without further purification. ^{1}H NMR spectra were recorded at ambient temperature on a Bruker Avance II 400MHz NMR spectrophotometer using $CDCl_3$ or DMSO as a solvent and TMS as an internal standard.

The purity of new synthesized compounds and development of reactions was monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel G with respect to Rf values. Reactants and reaction mixture samples were spotted on TLC plates using capillary. Spots with different Rf values indicated reaction progress; the disappearance of spots representing reactants in the reaction mixture was indicative of the culmination of reaction. These spots were visualized by UV light.

2.1 General Procedure for the Synthesis of Co^{2+} and Zn^{2+} Impregnated Bentonite-Chitosan Composite (Co^{2+}-BCC and Zn^{2+}-BCC)

Co^{2+} and Zn^{2+} impregnated Bentonite-Chitosan composite was synthesized separately according to the procedure described by Futalan et al. [34] with slight modifications. To the 1000 mL measuring beaker, 10 g of chitosan was dissolved in 500 mL of 5% (v/v) hydrochloric acid by stirring the mixture on magnetic stirrer at 300 rpm for 1 hour. For Co^{2+} impregnated Bentonite-Chitosan composite, 2 g/ 5 mL aqueous solution of $CoSO_4.7H_2O$ and for Zn^{2+} impregnated

Bentonite-Chitosan composite, 2 g/ 5 mL aqueous solution of $ZnSO_4$ was added drop by drop to the above solution separately, followed by stirring for another 2 hr. To the same mixture, 150 g bentonite was added slowly and kept stirring for another 3 hr. The mixture was neutralized with 1N NaOH. The composite formed was then washed with deionized water, pulverized, sieved and oven dried at 55°C for 24 hr.



Scheme 1. Synthesis of a). octahydroquinazolinones, b). imidazoles, c). isoxazoles, d). 1,4-dihydropyridines, e). benzimidazoles using Co^{2+}/Zn^{2+} impregnated Bentonite-Chitosan composite (Co^{2+}/Zn^{2+}-BCC)

2.2 General Procedure for Synthesis of Octahydroquinazolinones

To the 100 mL round bottom flask, 1 mmol substituted benzaldehyde (1), 1 mmol urea (2), 1 mmol cyclohexane-1,3-dione (3) in 1 mL ethanol with 0.5 mmol Co^{2+}/Zn^{2+}-BCC as a heterogeneous catalyst were taken and stirred at room temperature (Scheme 1a). The reaction was monitored over silica gel TLC plates using hexane and ethyl acetate (80:20) solvent system. After completion of the reaction, ice cold water was added. The solid product obtained (4) was filtered and further washed with deionised cold water. The crude product obtained was oven dried and recrystallized using ethanol.

2.3 General Procedure for Synthesis of Imidazoles

2 mmol substituted benzaldehyde (5), 2 mmol aniline (6), 2 mmol benzil (7), 2 mmol ammonium acetate (8) and 0.5 mmol Co^{2+}/Zn^{2+}-BCC were taken in 100 mL round bottom flask and heated at 40ºC **(Scheme 1b)**. After completion of the reaction as monitored over silica gel TLC plates using hexane and ethyl acetate (80:20) solvent system, ice cold water was added to obtain solid crude product (9), which was further filtered and washed with cold water. The product was dried and recrystallized using ethyl acetate.

2.4 General Procedure for Synthesis of Isoxazoles

0.5 mmol Co^{2+}/Zn^{2+}-BCC, 2.5 mmol hydroxylamine hydrochloride (12) and 2 mL ethanol were taken in 100 mL round bottom flask. Then 2 mmol substituted benzalaldehyde (10) and 2 mmol methyl 3-oxobutanoate (11) were added to the reaction mixture and stirred at room temperature **(Scheme 1c)**. After completion of the reaction as indicated by TLC using hexane and ethyl acetate (70:30) solvent system, the reaction mixture was treated with ice chilled water. Further, recrystallization was done from acetone: hexane (1:1).

2.5 General Procedure for Synthesis of 1,4-dihydropyridines

To the 100 ml round bottom flask, 2 mmol substituted benzaldehyde (14), 4 mmol methyl 3-oxobutanoate (15), 2.5 mmol ammonium acetate (16) and 0.5 mmol Co^{2+}/Zn^{2+}-BCC were taken and heated at 65ºC **(Scheme 1d)**. Progress of the reaction was checked by silica gel TLC plate using hexane and ethyl acetate (80:20) solvent system. After completion of the reaction, reaction mixture was cooled on ice bath and then further washed with cold water. Recrystallization was done with ethanol to yield pure product (17).

2.6 General procedure for Synthesis of Benzimidazoles

2 mmol substituted benzaldehyde (18), 2 mmol benzene-1,2-diamine (19) and 0.5 mmol Co^{2+}/Zn^{2+}-BCC were mixed in 100 mL round bottom flask and stirred on magnetic stirrer at room temperature **(Scheme 1e)**. Reaction progress was monitored over silica gel TLC plates using hexane and ethyl acetate (80:20) solvent system. After completion of reaction, solid product was washed with water, dried and recrystallized with ethanol. If gummy product was obtained then it is first extracted with ethyl acetate and then organic phase was washed with water and dried over Na_2SO_4.

2.7 Statistical Analysis

All values represented in Table 1 are mean of three replicates (n=3). Principal component analysis was performed on the entire data using sofware The Unscrambler X 10.5 to evaluate the catalytic efficiency of Co^{2+} and Zn^{2+} impregnated Bentonite-Chitosan composite (Co^{2+}-BCC and Zn^{2+}-BCC) for the synthesis of nitrogen containing 5 and 6 membered heterocyclic compounds.

3. RESULTS AND DISCUSSION

3.1 $Co^{2+}$and Zn^{2+} Impregnated Bentonite-Chitosan Composite (Co^{2+}-BCC and Zn^{2+}-BCC) and Synthesis of Nitrogen Containing 5 and 6 Membered Heterocyclic Compounds

Percent (%) yield and reaction time for nitrogen containing 5 and 6 membered heterocyclic compounds (octahydroquinazolinones, imidazoles, isoxazoles, 1,4-dihydropyridines and benzimidazoles) obtained by multicomponent reactions using Co^{2+}/Zn^{2+} impregnated Bentonite-Chitosan composite (Co^{2+}/Zn^{2+}-BCC)

are presented in table 1. Perusal of table 1 reveals that Co^{2+}-BCC gave octahydroquinazolinones and imidazoles in good yield, whereas, Zn^{2+}-BCC gave 1,4-dihydropyridines and benzimidazoles in excellent yield. Moreover, isoxazoles were efficiently synthesized by both Co^{2+}-BCC and Zn^{2+}-BCC. Also, Co^{2+}-BCC: Zn^{2+}-BCC in ratio 1:2 showed high catalytic activity for all the above class of nitrogen containing heterocyclic compounds. The plausible mechanism for the formation of octahydroquinazolinones, imidazoles, isoxazoles, 1,4-dihydropyridines and benzimidazoles catalyzed by Co^{2+}-BCC or Zn^{2+}-BCC is suggested in scheme 2, scheme 3, scheme 4, scheme 5 and scheme 6 respectively.

3.2 Characterization of heterogeneous catalyst- $Co^{2+}$and Zn^{2+} impregnated Bentonite-Chitosan composite (Co^{2+}-BCC and Zn^{2+}-BCC)

3.2.1 SEM analysis

Development of Co^{2+} and Zn^{2+} impregnated Bentonite-Chitosan composite (Co^{2+}- BCC and Zn^{2+}-BCC) was confirmed by scanning electron microscope (SEM). Fig. 1 shows SEM micrograph of Bentonite-Chitosan composite which appeared to be rigid and compact surface, whereas, Figs. 2 and 3 demonstrated morphological changes on the surface of Co^{2+} and Zn^{2+} impregnated Bentonite-Chitosan composite respectively. Following changes were noticed on the surface of Co^{2+}-BCC and Zn^{2+}-BCC: small beads like appearance with irregular bumps.

3.3 Characterization of Synthesized Compounds

Compound 4a: 3,4,7,8-tetrahydro-4-(4-nitrophenyl)quinazoline-2,5(1*H*,6*H*)-dione

^{1}H NMR (DMSO, TMS, 400 MHz): δ (ppm) 1.9-2.4 (m, 6H), 5.8 (s, 1H), 7.1-7.4 (m, 4H), 7.8 (s, 1H), 8.05 (s, 1H).

Compound 4b: 4-(2-chlorophenyl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione

^{1}H NMR (DMSO, TMS, 400 MHz): δ (ppm) 2.1-2.45 (m, 6H), 5.55 (s, 1H), 7.05-7.35 (m, 4H), 8.0 (s, 1H), 8.15 (s, 1H).

Compound 4c: 4-(4-fluorophenyl)-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione

^{1}H NMR (DMSO, TMS, 400 MHz): δ (ppm) 1.8-2.25 (m, 6H), 5.7 (s, 1H), 7.15-7.4 (m, 4H), 7.95 (s, 1H), 8.0 (s, 1H).

Compound 9a: 2-(4-nitrophenyl)-1,4,5-triphenyl-1*H*-imidazole

^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ (ppm) 7.15-7.8 (m, 19H).

Compound 9b: 2-(2-chlorophenyl)-1,4,5-triphenyl-1*H*-imidazole

^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ (ppm) 6.95-8.0 (m, 19H).

Compound 9c: 2-(4-fluorophenyl)-1,4,5-triphenyl-1*H*-imidazole

^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ (ppm) 7.6-8.15 (m, 19H).

Compound 13a: 4-(4-nitrobenzylidene)-3-methylisoxazol-5(4*H*)-ones

^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ (ppm) 2.65 (s, 3H), 7.25 (d, 2H), 8.0 (s, 1H), 8.35 (d, 2H).

Compound 13b: 4-(2-chlorobenzylidene)-3-methylisoxazol-5(4*H*)-ones

^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ (ppm) 2.55 (s, 3H), 7.6 (d, 2H), 8.1 (s, 1H), 8.5 (d, 2H).

Compound 13c: 4-(4-flourobenzylidene)-3-methylisoxazol-5(4*H*)-ones

^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ (ppm) 2.85 (s, 3H), 7.55 (d, 2H), 8.25 (s, 1H), 8.45 (d, 2H).

Compound 17a: dimethyl 1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.25-7.85 (m, 4H), 2.25 (s, 6H), 3.65 (s, 6H), 3.9 (s, 1H).

Compound 17b: dimethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.4-8.25 (m, 4H), 2.4 (s, 6H), 3.4 (s, 6H), 4.1 (s, 1H).

Compound 17c: dimethyl 4-(2-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.3-7.8 (m, 4H), 2.35 (s, 6H), 3.45 (s, 6H), 3.75 (s, 1H).

Compound 20a: 2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole

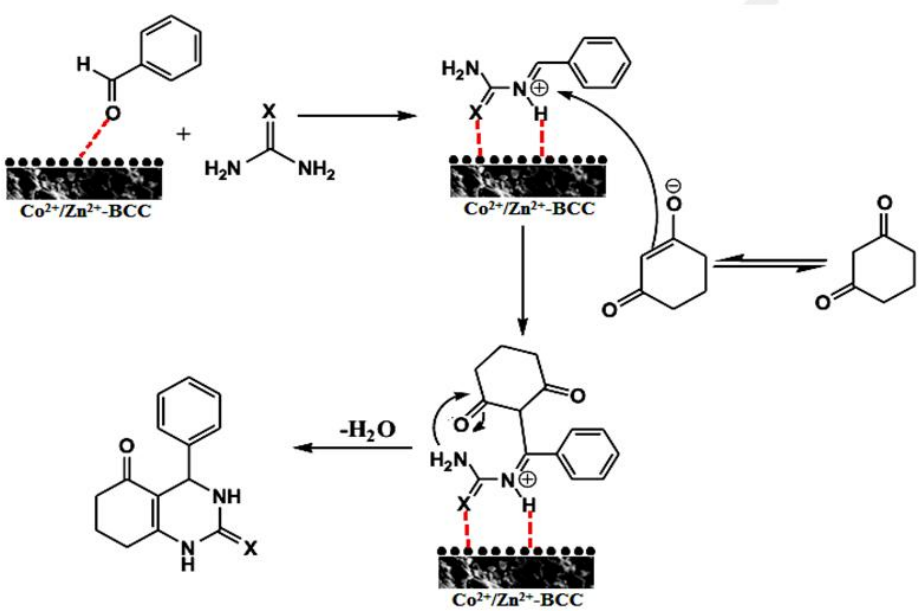
^{1}H NMR ($CDCl_3$, 400 MHz): δppm 7.1-7.8 (m, 4H), 8.1-8.3 (m, 4H), 8.45 (s, 1H).

Compound 20b: 2-(3-nitrophenyl)-1*H*-benzo[*d*]imidazole

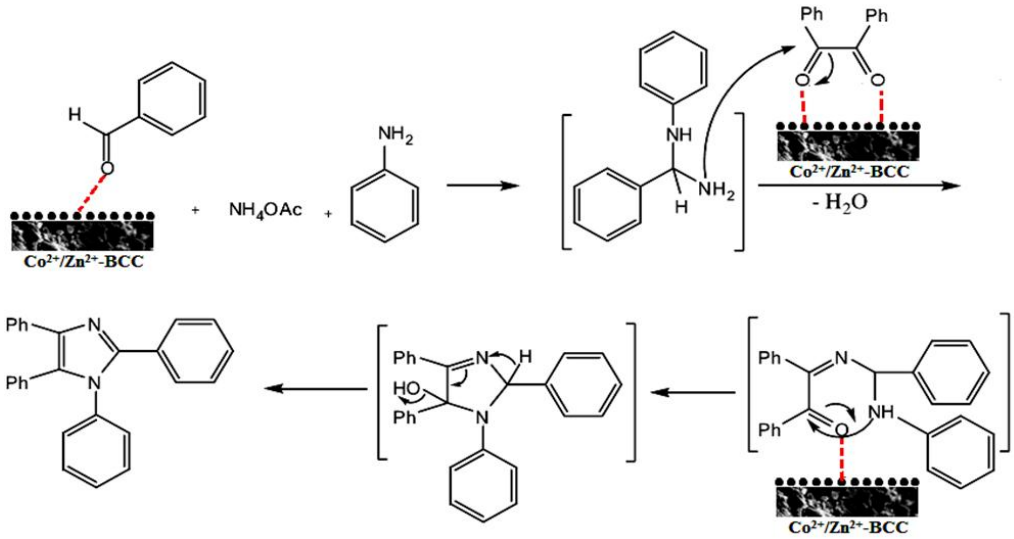
^{1}H NMR ($CDCl_3$, 400 MHz): δppm 7.2-7.66 (m, 4H), 7.9-8.1 (m, 4H), 8.35 (s, 1H).

Compound 20c: 2-(2-chlorophenyl)-1*H*-benzo[*d*]imidazole

^{1}H NMR ($CDCl_3$, 400 MHz): δppm 7.05-7.7 (m, 4H), 7.95-8.2 (m, 4H), 8.4 (s, 1H).



Scheme 2. Plausible mechanism for the formation of octahydroquinazolinone

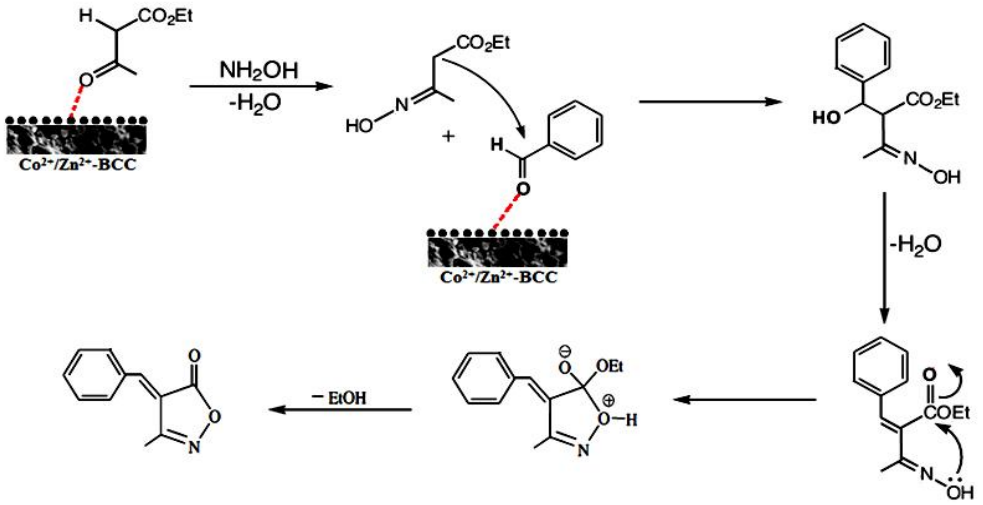


Scheme 3. Plausible mechanism for the formation of imidazoles

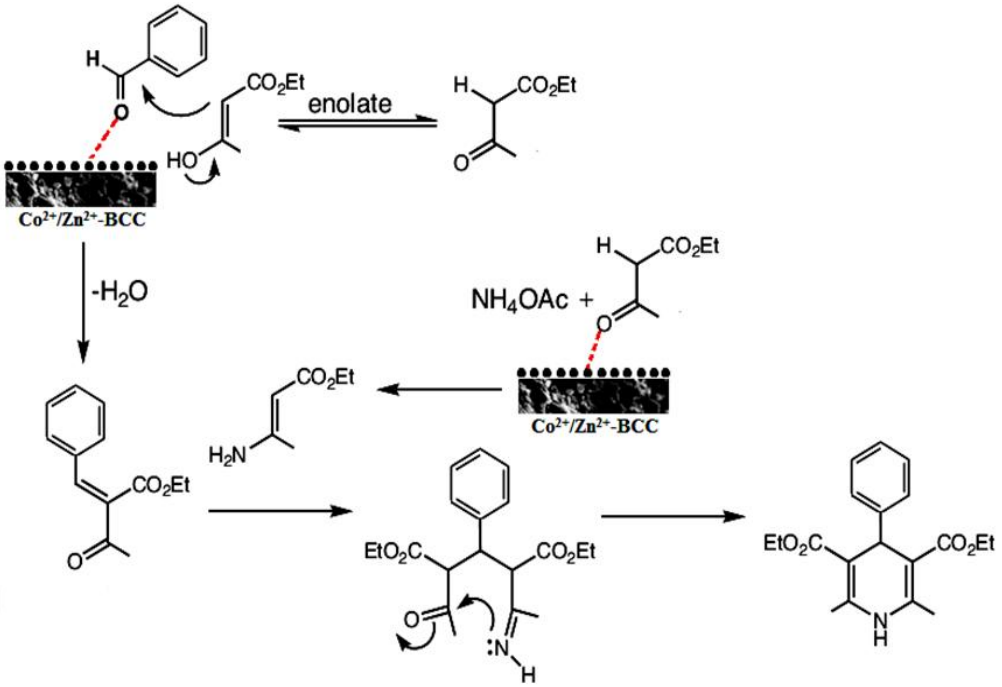
Table 1. % Yield of synthesized nitrogen containing 5 and 6 membered heterocyclic compounds using different ratios of Co^{2+} and Zn^{2+} impregnated bentonite-chitosan coxmposite (Co^{2+}-BCC and Zn^{2+}-BCC)

Compound	Co^{2+}/Zn^{2+} impregnated Bentonite-Chitosan composite (Co^{2+}/Zn^{2+}-BCC)									
	Co^{2+}-BCC :Zn^{2+}-BCC [1:0] (C1)		Co^{2+}-BCC :Zn^{2+}-BCC [0:1] (C2)		Co^{2+}-BCC :Zn^{2+}-BCC [1:2] (C3)		Co^{2+}-BCC :Zn^{2+}-BCC [1:1] (C4)		Co^{2+}-BCC :Zn^{2+}-BCC [2:1] (C5)	
	Synthesized nitrogen containing 5 and 6 membered heterocyclic compounds									
	% Yield	Time (min)	% Yield	Time (min)	% Yield	Time (min)	% Yield	Time (min)	% Yield	Time (min)
4a(S1)	85	15	65	20	83	10	71	20	83	25
4b (S2)	82	20	61	25	84	15	75	25	85	15
4c (S3)	79	25	55	20	86	15	79	15	81	20
9a (S4)	77	30	64	40	81	30	76	50	82	55
9b (S5)	81	35	63	30	79	40	77	45	80	45
9c (S6)	76	45	59	50	78	50	80	40	75	40
13a (S7)	87	20	84	30	85	25	84	35	88	35
13b (S8)	89	10	85	15	84	25	81	30	85	40
13c (S9)	82	15	84	20	80	25	82	25	81	35
17a (S10)	61	45	84	40	81	45	69	40	59	50
17b (S11)	68	50	86	50	84	45	85	40	65	40
17c (S12)	69	40	81	45	85	40	82	35	61	45
20a (S13)	54	20	82	25	81	20	79	25	55	20
20b (S14)	59	40	83	30	80	35	77	40	64	35
20c (S15)	61	35	86	25	87	30	81	50	63	40

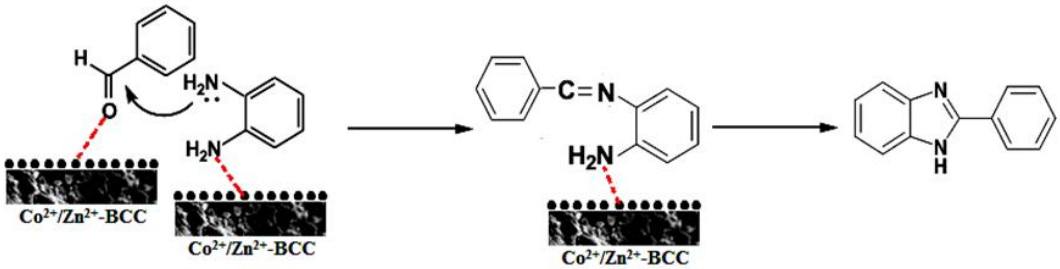
4a: 3,4,7,8-tetrahydro-4-(4-nitrophenyl)quinazoline-2,5(1H,6H)-dione
4b: 4-(2-chlorophenyl)-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione
4c: 4-(4-fluorophenyl)-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione
9a: 2-(4-nitrophenyl)-1,4,5-triphenyl-1H-imidazole
9b: 2-(2-chlorophenyl)-1,4,5-triphenyl-1H-imidazole
9c: 2-(4-fluorophenyl)-1,4,5-triphenyl-1H-idazole
13a: 4-(4-nitrobenzylidene)-3-methylisoxazol-5(4H)-ones
13b: 4-(2-chlorobenzylidene)-3-methylisoxazol-5(4H)-ones
13c: 4-(4-flourobenzylidene)-3-methylisoxazol-5(4H)-ones
17a: dimethyl 1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate
17b: dimethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate
17c: dimethyl 4-(2-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
20a: 2-(4-nitrophenyl)-1H-benzo[d]imidazole
20b: 2-(3-nitrophenyl)-1H-benzo[d]imidazole
20c: 2-(2-chlorophenyl)-1H-benzo[d]imidazole



Scheme 4. Plausible mechanism for the formation of isoxazoles



Scheme 5. Plausible mechanism for the formation of 1,4-dihydropyridines



Scheme 6. Plausible mechanism for the formation of benzimidazoles

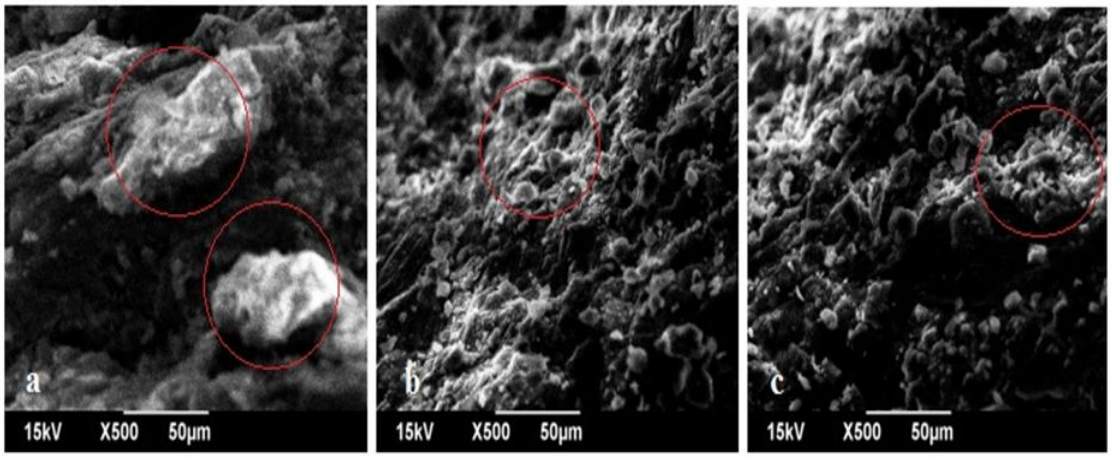


Fig. 1. a). SEM micrograph of Bentonite-Chitosan composite, b). SEM micrograph of Co^{2+} impregnated Bentonite-Chitosan composite (Co^{2+}-BCC), c). SEM micrograph of Zn^{2+} impregnated Bentonite-Chitosan composite (Zn^{2+}-BCC)

3.4 Principal Component Analysis

The principal component analysis was performed on the entire data to evaluate the efficacy of Co^{2+} and Zn^{2+} impregnated Bentonite-Chitosan composite (Co^{2+}-BCC and Zn^{2+}-BCC) and their different ratio combinations. The loadings and scores plots of three rotated principal components obtained by PCA show the distribution and grouping of different Co^{2+}/Zn^{2+}-BCC and synthesized samples respectively (Fig. 2). The study of loadings plot states that catalyst C1 (Co^{2+}-BCC) and C5 (Co^{2+}:Zn^{2+}-BCC [2:1]); C3 (Co^{2+}/Zn^{2+}-BCC [1:2]) and C4 (Co^{2+}/Zn^{2+}-BCC [1:1]) have almost similar catalytic effects (Fig. 2a). 2D Rotated scores plot (Fig. 2b) and 3D scores plot, PC-1-2-3 (Fig. 3) distributed samples into 3 clusters as:

Cluster I- S1, S2, S3, S4, S5, S6
Cluster II- S7, S8, S9
Cluster III- S10, S11, S12, S13, S14, S15

Cluster II with compounds S7, S8 and S9 (isoxazoles) were synthesized in excellent yield under each catalytic structure (C1, C2, C3, C4 or C5). Cluster I consists of octahydroquinazolinones and imidazoles and cluster II consists of 1,4-dihydropyridines and benzimidazoles.

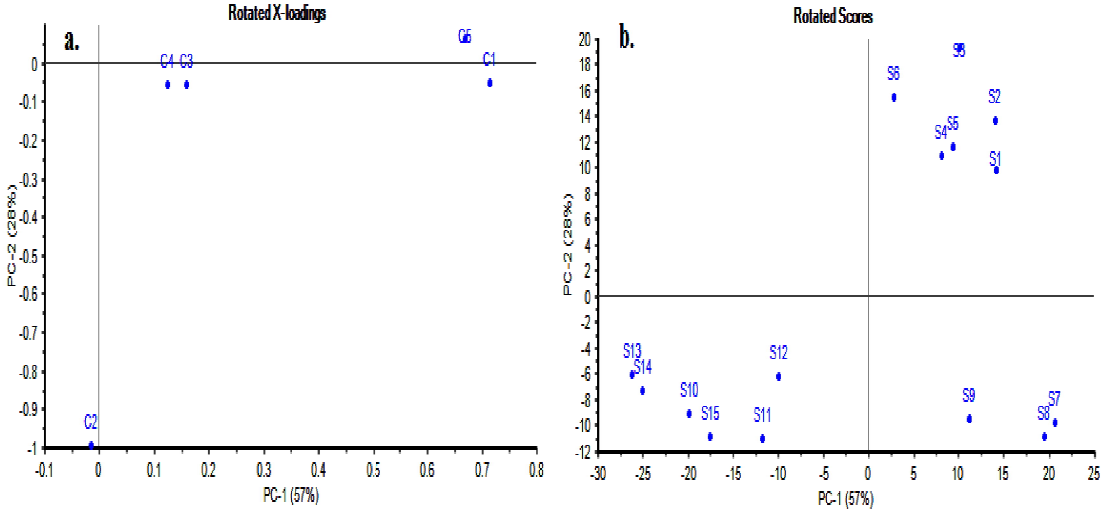


Fig. 2. The loadings plot (a) and scores plot (b)

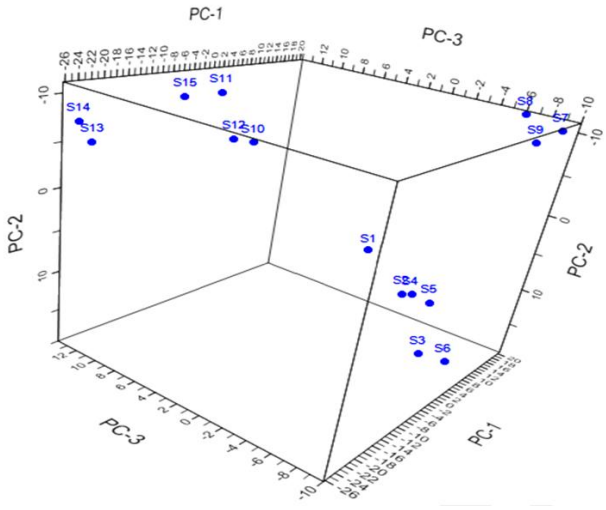


Fig. 3. 3D PCA scores plot (PC1-2-3)

4. CONCLUSIONS

Co^{2+} and Zn^{2+} impregnated Bentonite-Chitosan composite (Co^{2+}-BCC and Zn^{2+}-BCC) was found to be efficient, economical and environmentally benign hetero-catalyst for synthesizing a different class of nitrogen containing 5 and 6 membered heterocyclic compounds. Principal component analysis has proved to be an important study for analyzing the catalytic activity of different ratios of Co^{2+}-BCC and Zn^{2+}-BCC for the synthesis of octahydroquinazolinones, imidazoles, isoxazoles, 1,4-dihydropyridines and benzimidazoles. Co^{2+}-BCC: Zn^{2+}-BCC in ratio 1:2 gave high percentage yield of all the class of heterocyclic compounds and isoxazoles were synthesized in excellent yield by all set ratios of Co^{2+}/Zn^{2+}-BCC.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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