

HNO₃ immobilized on nano SiO₂: A novel efficient heterogeneous catalytic system for the synthesis of 2-substituted oxazolines, imidazolines, thiazolines, and 2-aryl-1*H*-benzimidazoles under solvent-free conditions

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HNO₃ immobilized on nano SiO₂ (HNO₃@nano SiO₂) was examined for the synthesis of 2-substituted oxazolines, imidazolines, thiazolines and 2-aryl-1*H*-benzimidazole derivatives under solvent-free conditions. The results confirmed its excellent efficiency in the preparation of the mentioned heterocycles. The method proved to be simple, green, and convenient; the synthesized nanocatalyst was efficient in a vast domain of substrate transformations to the corresponding products in good yields. The recovery and reusability of the synthesized nanocatalyst was investigated in 4 runs without registering activity loss. The mechanism of the transformations is proposed.

Keywords: Benzimidazole; Imidazoline; Oxazoline; Thiazoline; Nanocatalyst; Reusable catalyst; Green chemistry

INTRODUCTION

In recent years developing new and efficient methods for the synthesis of heterocyclic biologically active natural compounds has received considerable attention in organic chemistry. This importance is due to their wide application in medicine. Oxazolines, imidazolines and thiazolines are important substructures in a large number of biologically active natural products [1,2]. Many derivatives of these heterocycles have shown anti-hypertensive [3], anti-depressive [4], anti-hypercholesterolemic [5], anti-diabetic [6], anti-tumor [7], and anti-inflammatory [8] properties. In addition to these important features, they are also known as valuable intermediates in organic transformations [9]. Several publications have been described for the synthesis of 2-substituted oxazolines, imidazolines and thiazolines from different precursors such as carboxylic acids [10], esters [11], nitriles [12, 13], amides [14], aziridines [15], and aldehydes [16].

Benzimidazole motif plays very important roles in numerous pharmaceutical molecules possessing anti-HIV [17], anti-fungal [18], anti-cancer [19], antihelminthic [20], anticoagulant [21], and proton pump inhibitor properties [22]. Benzimidazoles are a component of vitamin B12 and are related to the DNA base purine and the stimulant caffeine [23]. Methods for synthesis of benzimidazoles include the condensation reaction of *o*-phenylenediamines with aldehyde [24], carboxylic acids [25], and orthoester derivatives [26]. Various reaction conditions and a variety of homogeneous and heterogeneous catalysts such as S/Co(NO₃)₂ [27], sulfuric acid {[3-(3-

silicapropyl)sulfanyl]propyl}ester (SASPSPE) [28], zeolite [29], Fe(HSO₄)₃ [30], silica supported tungstosilicic acid [31], trichloroisocyanuric acid (TCCA) [32], and tribromomelamine [33] have also been applied for the preparation of these *N*-containing heterocycles.

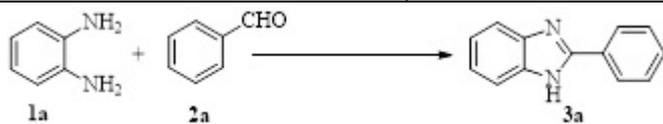
A variety of oxidants and catalysts have been used for the synthesis of imidazoline, thiazoline, oxazoline and benzimidazole derivatives. Although these methods worked nicely in many cases, however, some of them suffer from one or more limitations such as low yields, use of volatile or toxic organic solvents, requirement of excess amounts of catalysts or reagents, special apparatus and harsh reaction conditions. Consequently, development of a convenient, high yield environmentally benign procedure for synthesis of imidazoline, thiazoline, oxazolines, and benzimidazoles is still a challenging research.

In continuation of our research interest in nanochemistry [34-38] in this article we proposed a new protocol for the synthesis of oxazolines, imidazolines and thiazolines *via* the reaction of nitriles with 2-aminoethanol, ethylenediamine, and 2-aminoethanethiol in the presence of catalytic amount of HNO₃@nano SiO₂ under solvent-free conditions. In addition, the preparation of benzimidazoles under solvent-free conditions by the reaction of *o*-phenylenediamines with aldehydes or carboxylic acids in the presence of HNO₃@nano SiO₂ was reported.

RESULTS AND DISCUSSION

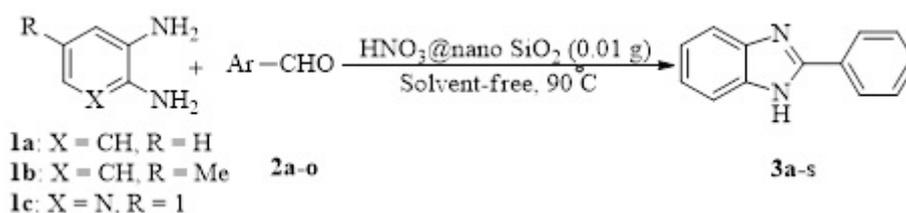
The nanocatalyst was synthesized *via* a simple procedure reported by our group [36] and was characterized by FI-IR and SEM techniques. The H⁺

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Table 1. Optimization the reaction conditions for the synthesis of **3a**.


Entry	Conditions ^a	Yield (%)	Time (h)
1	HNO ₃ @nano SiO ₂ (0.01 g)/ solvent-free/ r.t.	20	12
2	HNO ₃ @nano SiO ₂ (0.01 g)/ solvent-free/ 60 °C	45	7.30'
3	HNO ₃ @nano SiO ₂ (0.01 g)/ solvent-free/ 80 °C	60	5
4	HNO ₃ @nano SiO ₂ (0.01 g)/ solvent-free/ 90 °C	85	2.30'
5	HNO ₃ @nano SiO ₂ (0.01 g)/ solvent-free/ 100 °C	85	2.30'
6	HNO ₃ @nano SiO ₂ (0.01 g)/ H ₂ O/ reflux	20	12
7	HNO ₃ @nano SiO ₂ (0.01 g)/ CH ₃ CN/ reflux	— ^b	12
8	HNO ₃ @nano SiO ₂ (0.01 g)/ EtOH/ reflux	— ^b	12
9	HNO ₃ @nano SiO ₂ (0.01 g)/ CH ₂ Cl ₂ / reflux	— ^b	12
10	HNO ₃ @nano SiO ₂ (0.01 g)/ EtOH:H ₂ O (1:1)/ reflux	— ^b	12
11	HNO ₃ @nano SiO ₂ (0.01 g)/ CHCl ₃ / reflux	— ^b	12
12	HNO ₃ @nano SiO ₂ (0.01 g)/ CH ₃ OH/ reflux	— ^b	12
13	HNO ₃ @nano SiO ₂ (0.008 g)/ solvent-free/ 90 °C	75	3.30'
14	HNO ₃ @nano SiO ₂ (0.012 g)/ solvent-free/ 90 °C	85	2.30'
15	Catalyst-free/ solvent-free/ r.t.	10	24
16	Catalyst-free/ solvent-free/ 90 °C	15	24

^a The molar ratio of **1a**/ **2a** was 1/1; 5 mL of each solvent was used; ^b The substrates remained intact.

**Scheme 1.** Synthesis of 2-aryl-1H-benzimidazoles by HNO₃@nano SiO₂.

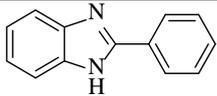
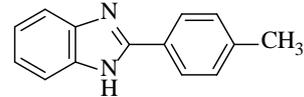
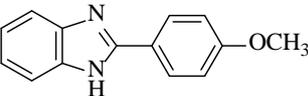
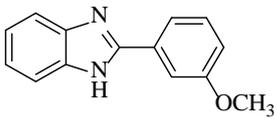
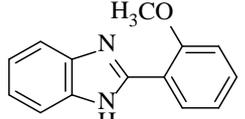
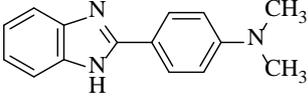
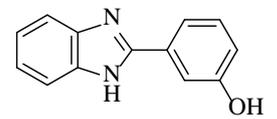
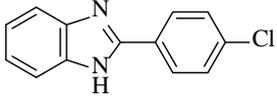
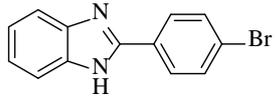
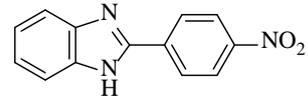
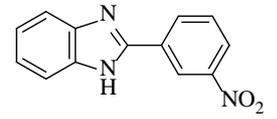
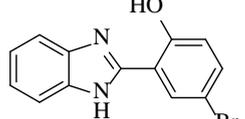
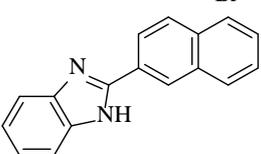
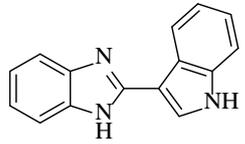
concentration on the surface of the catalyst, which was determined by titration of 0.1 g of the solid with NaOH (0.1 N), was equal to 4.3 meq/g.

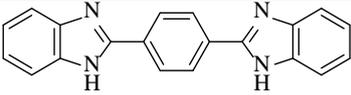
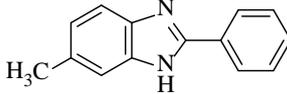
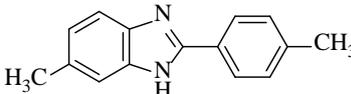
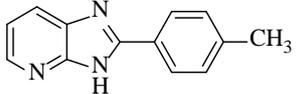
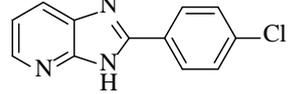
To evaluate the catalytic activity of HNO₃@nano SiO₂, the condensation of *o*-phenylenediamine and benzaldehyde to prepare 2-phenyl-1H-benzimidazole was chosen as model reaction (Table 1). Screening the temperature effect in the presence of 0.01 g of the nanocatalyst exhibited that the best results were obtained at 90 °C (entries 1-5). Performing the model reaction in different solvents did not lead to satisfactory results (entries 6-12). Investigating the nanocatalyst amount demonstrated that the best yield was obtained with 0.01 g of the catalyst (entries 4 and 13). Increasing the catalyst amount up to 0.012 g didn't affect the reaction progress (entry 14). In order to confirm the catalyst efficacy in preparation of **3a**, the model reaction was also examined in the absence of nanocatalyst at room temperature and 90 °C with low yields (entries 15,16).

In the next step the reaction of different aldehydes with 1,2-phenylenediamines was performed under the optimal conditions (Scheme 1). The results are summarized in Table 2.

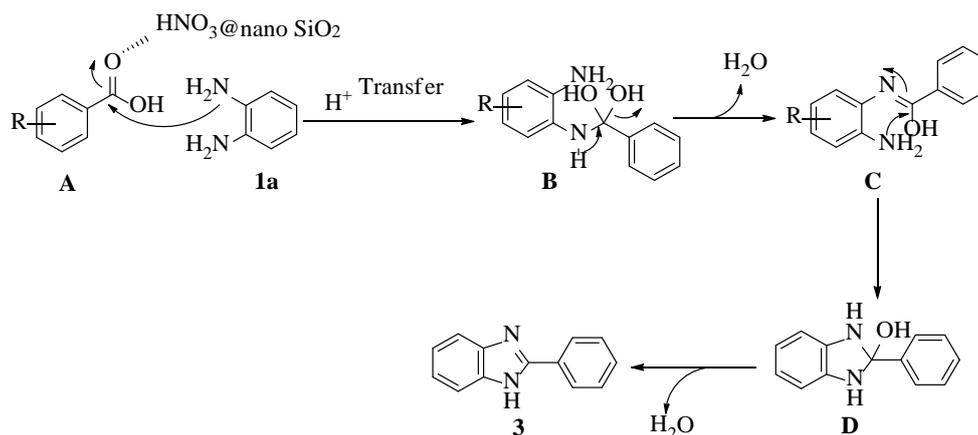
As can be seen in Table 2, the reaction of *o*-phenylenediamine (**1a**) with benzaldehyde and its various electron-donating and electron-withdrawing substituents was performed successfully (entries 1-12). The condensation of **1a** with 2-naphthaldehyde, with a sterically-hindered construction, eventuated to the corresponding benzimidazole **3a** in 71% yield (entry 13). The heteroaromatic massive indole-3-carbaldehyde (**2n**) gave its **3n** analogue in moderate yield (entry 14). Terephthalaldehyde, as a bifunctional aldehyde system, reacted with 2 mmol of **1a** in the presence of 0.02 g of HNO₃@nano SiO₂ to prepare 2-(4-(1H-benzimidazol-2-yl)phenyl)-1H-benzimidazole. This observation confirmed the selective operation of the nanocatalyst, that no mono-adduct was obtained as by-product. The prosperous condensation of 4-methyl-*o*-phenylenediamine (**2a**) with benzaldehyde and 4-methylbenzaldehyde affirmed the efficacy of the nanocatalyst (entries 16,17). 2,3-Diaminopyridine (**1c**) also generated the corresponding benzimidazoles in the reaction with **2b** and **2h**, respectively (entries 18,19)

Table 2. Synthesis of 2-aryl-1H-benzimidazoles using HNO_3 @nano SiO_2 (0.01 g) at 90 °C under solvent-free conditions.

Entry	Diamine	Ar	Product	Time (h)	Yield (%)	M.p., Ref. (°C) ^a
1	1a	C_6H_5	2a 	3a 2.50'	85	285-289, 286-288 [29]
2	1a	4- $\text{CH}_3\text{C}_6\text{H}_4$	2b 	3b 2.30'	86	268-272, 269-273 [39]
3	1a	4- $\text{OCH}_3\text{C}_6\text{H}_4$	2c 	3c 5.10'	75	223-225, 224-225 [39]
4	1a	3- $\text{OCH}_3\text{C}_6\text{H}_4$	2d 	3d 4.30'	72	223-227, 223-227 [39]
5	1a	2- $\text{OCH}_3\text{C}_6\text{H}_4$	2e 	3e 4.10'	65	133-135, 133-135 [30]
6	1a	4- $\text{N}(\text{CH}_3)_2\text{C}_6\text{H}_4$	2f 	3f 3.15'	84	292-294, 288-290 [40]
7	1a	3- OHC_6H_4	2g 	3g 3.15'	74	273-275, 277 [41]
8	1a	4- ClC_6H_4	2h 	3h 2.45'	83	283-285, 284-286 [29]
9	1a	4- BrC_6H_4	2i 	3i 3.20'	77	282-285, 283-284 [29]
10	1a	4- $\text{NO}_2\text{C}_6\text{H}_4$	2j 	3j 5.55'	75	318, 317 [41]
11	1a	3- $\text{NO}_2\text{C}_6\text{H}_4$	2k 	3k 5.25'	60	206-207, 207-208 [29]
12	1a	2-OH-5- BrC_6H_3	2l 	3l 2.20'	88	255-257, 256-257 [29]
13	1a	2-Naphthyl	2m 	3m 3.30'	71	217-219, 218-219 [42]
14	1a	3-Indolyl	2n 	3n 4.20'	69	195-197, 196-198 [24]

15	1a	Terephthalyl	2o		3o	4.20'	67	245-246, 245-247 [43]
16	1b	C_6H_5	2a		3p	3.10'	89	239-241, 240-242 [39]
17	1b	4- $\text{CH}_3\text{C}_6\text{H}_4$	2b		3q	2.55'	80	101-103, 100-104 [39]
18	1c	4- $\text{CH}_3\text{C}_6\text{H}_4$	2b		3r	2.15'	86	243-247
19	1c	4- ClC_6H_4	2h		3s	3.25'	75	260-264

^a Reference of known compounds; ^b The reaction was performed with **1a** (2 mmol) and HNO_3 @nano SiO_2 (0.02 g).



Scheme 2. Plausible mechanism for the synthesis of 2-aryl-1H-benzimidazoles using HNO_3 @nano SiO_2 .

In order to investigate the high efficacy of the nanocatalyst, in the next step the benzimidazoles were obtained *via* the reaction of *o*-phenylenediamine and carboxylic acids in the presence of 0.02 g of HNO_3 @nano SiO_2 at 100 °C under solvent-free conditions. Results are summarized at Table 3. Different types of organic benzoic acids condensed with *o*-phenylenediamine (entries 1-8). Acetic acid as an aliphatic candidate also successfully created the 2-methyl-1H-benzimidazole (**3v**) (entry 9). No significant substituent effect was observed. According to the data, the electron-donating substituents at para-position of benzoic acid, such as 4-methyl, 4-methoxy, and 4-hydroxy substituents carried out the condensation better than benzoic acid (entries 2-4); while the electron-withdrawing 4-nitrobenzoic acid performed the reaction in a longer period than benzoic acid (entry 6). Comparison of data in Tables 2 and 3, demonstrated that aldehydes are better candidates than carboxylic acids in the condensation with diamines.

Although the real reaction route is not obvious, a plausible mechanism for the synthesis of 2-aryl-1H-benzimidazoles was proposed *via* the condensation reaction of *o*-phenylenediamine with carboxylic acids in the presence of HNO_3 @nano SiO_2 (Scheme 2). The nucleophilic attack of *o*-phenylenediamine (**1a**) to activated carboxylic acid **A** produced the intermediate **B**, which by water release gave the imine-alcohol intermediate **C**. The intramolecular Michael addition of the amine group in **C** to C=N bond led to **D** which dehydrated to form the products **3**.

In the next step, to evaluate the best efficiency of the nanocatalyst, we report a simple, efficient and eco-friendly approach for the synthesis of 2-oxazolines, 2-imidazolines, and 2-thiazoline derivatives using HNO_3 @nano SiO_2 (Table 4). In each case a model reaction was chosen for screening the best reaction conditions. The results are summarized in Table 4.

Table 3. Synthesis of 2-aryl-1*H*-benzimidazoles via the reaction of carboxylic acids with *o*-phenylenediamine in the presence of HNO_3 @nano SiO_2 (0.02 g) at 100 °C under solvent-free conditions.

Entry	R	Product	Yield (%)	Time (h)	M.p., Ref. (°C) ^a
1	C ₆ H ₅		75	5	285-289, 286-288 [29]
2	4-CH ₃ C ₆ H ₄		82	4.45'	268-272, 269-273 [39]
3	4-CH ₃ C ₆ H ₄		78	4.20'	223-225, 224-225 [39]
4	4-OHC ₆ H ₄		81	4.35'	228-230, 229-230 [40]
5	3-OHC ₆ H ₄		73	5.10'	273-275, 277 [41]
6	4-NO ₂ C ₆ H ₄		74	8.10'	318, 317 [41]
7	3-NO ₂ C ₆ H ₄		65	8	206-207, 207-208 [29]
8	2-NO ₂ C ₆ H ₄		67	8.20'	264-265, 264-266 [29]
9	CH ₃		64	9	176-177, 176-178 [44]

^a Reference of known compounds.**Table 4.** Screening the reaction conditions for preparation of 2-phenyl-4,5-dihydro-1*H*-imidazole (**7a**), 2-phenyl-4,5-dihydro-1,3-oxazole (**9a**), and 2-phenyl-4,5-dihydro-1,3-thiazole (**11a**).

Entry	A			B			C		
	Solvent (5 mL)/ HNO_3 @nano SiO_2 (g)/ temperature (°C)/ 6 (mmol)	Time (h)	Yield (%)	Solvent (5 mL)/ HNO_3 @nano SiO_2 (g)/ temperature (°C)/ 8 (mmol)	Time (h)	Yield (%)	Solvent (5 mL)/ HNO_3 @nano SiO_2 (g)/ temperature (°C)/ 10 (mmol)	Time (h)	Yield (%)
1	-/ 0.006/ 100/ 4	4.30'	30	-/ 0.005/ 90/ 6	6.20'	30	-/ 0.005/ 100/ 3.5	4.30'	55
2	-/ 0.012/ 100/ 4	4.20'	60	-/ 0.01/ 90/ 6	5.20'	50	-/ 0.008/ 100/ 3.5	3.30'	70
3	-/ 0.015/ 100/ 4	3.30'	65	-/ 0.02/ 90/ 6	4.50'	60	-/ 0.01/ 100/ 3.5	3	75
4	-/ 0.02/ 100/ 4	3.30'	65	-/ 0.024/ 90/ 6	4	70	-/ 0.012/ 100/ 3.5	3	75
5	-/ 0.015/ r.t./ 4	12	-	-/ 0.02/ r.t./ 6	12	-	-/ 0.01/ r.t./ 3.5	12	-
6	-/ 0.015/ 90/ 4	3.45'	55	-/ 0.02/ 60/ 6	5.10'	50	-/ 0.01/ 80/ 3.5	4	65
8	-/ 0.015/ 110/ 4	3.30'	65	-/ 0.02/ 100/ 6	4	70	-/ 0.01/ 110/ 3.5	3	75
9	H ₂ O/ 0.015/ reflux/ 4	12	-	H ₂ O/ 0.02/ reflux/ 6	12	-	H ₂ O/ 0.01/ reflux/ 3.5	12	-
10	EtOH/ 0.015/ reflux/ 4	12	-	EtOH/ 0.02/ reflux/ 6	12	-	EtOH/ 0.01/ reflux/ 3.5	12	-
11	CH ₃ CN/ 0.015/ reflux/ 4	12	-	CH ₃ CN/ 0.02/ reflux/ 6	12	-	CH ₃ CN/ 0.01/ reflux/ 3.5	12	-
12	-/ 0.015/ 100/ 2	6.10'	52	-/ 0.02/ 90/ 3	6.20'	54	-/ 0.01/ 100/ 3	3.20'	63
13	-/ 0.015/ 100/ 5	3.30'	65	-/ 0.02/ 90/ 7	4	70	-/ 0.01/ 100/ 4	3	70

Various parameters such as catalyst amount, solvent, temperature, and substrates molar ratio was examined. The best results for 2-phenyl-4,5-dihydro-1*H*-imidazole (**7a**) synthesis were obtained in the presence of 0.015 g of nanocatalyst under solvent-free conditions at 100 °C using 4 mmol of ethylenediamine (Table 2, column A, entry 3). 2-Phenyl-4,5-dihydro-1,3-oxazole (**9a**) was prepared using 6 mmol of ethanolamine at 90 °C under solvent-free conditions using 0.02 g of HNO_3 @nano SiO_2 (Table 2, column B, entry 3). The data for entry 3 of column C confirmed that 2-phenyl-4,5-dihydro-1,3-thiazole (**11a**) was obtained at 100 °C in the presence of 0.01 g of nanocatalyst under solvent-free conditions *via* the reaction of 3.5 mmol of amino ethanethiol (**10**).

Under these optimized conditions, a variety of aromatic and heteroaromatic nitriles were reacted with ethylenediamine to generate the corresponding 2-imidazolines (Table 5, entries 1-8). According to the data in Table 5, electron-withdrawing nitriles such as 4-chloro and 4-bromo benzonitriles carried out the reaction in shorter duration than electron-donating nitriles such as 4-methyl and 4-methoxy derivatives. 2-Cyanopyridine (**5f**), as a heteroaromatic nitrile, gave the 2-(4,5-dihydro-1*H*-imidazol-2-yl) pyridine very successfully (entry 6). Another interesting observation was with isophthalonitrile (**5g**) where using **5g/6** with the molar ratio 1/4 in the presence of 0.015 g of

nanocatalyst gave 3-(4,5-dihydro-1*H*-imidazol-2-yl)benzonitrile as the only product. No bis-cyclization was seen under these conditions.

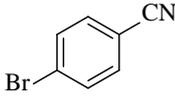
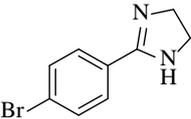
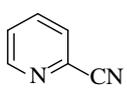
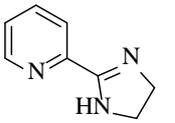
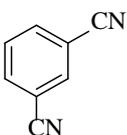
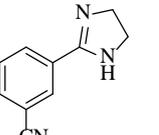
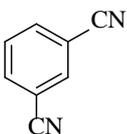
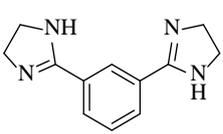
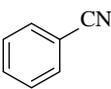
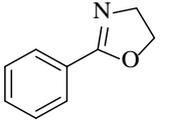
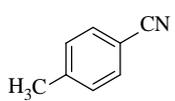
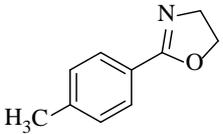
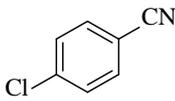
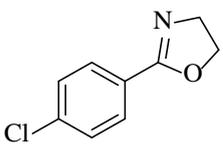
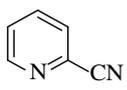
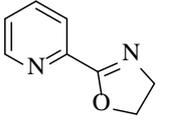
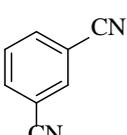
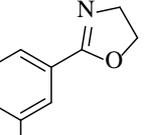
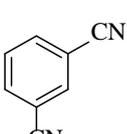
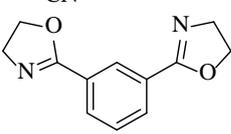
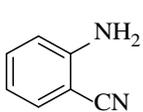
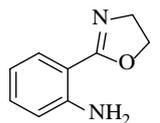
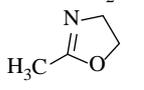
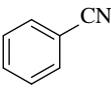
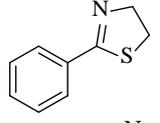
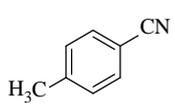
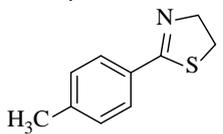
Changing the molar ratio of **5g/6** to 1/8 in the presence of 0.03 g of HNO_3 @ nano SiO_2 yielded the 1,3-bis(4,5-dihydro-1*H*-imidazol-2-yl) benzene as the only product. Based on these facts, the chemoselectivity of the procedure was confirmed. Under the optimized reaction conditions different oxazolines and thiazolines were also prepared. Manufacturing of mono- and bis-oxazolines (entries 13 and 14) and bis-thiazoline (entry 23) also validated the chemoselectivity of the procedure. The suggested mechanism for the synthesis of 2-imidazolines, 2-oxazolines, and 2-thiazolines is given in Scheme 3. The nanocatalyst activated the nitrile **5** to form the activated analogue **A**. The nucleophilic attack of **6**, **8**, **10** to **A** generated **B**. Intramolecular attack of NH_2 to $\text{C}=\text{N}$ bond gave **C** which released NH_3 to produce the desired products **7**, **9** and **11**. In order to show the efficient activity of the nanocatalyst, the reaction of *o*-phenylenediamine and benzaldehyde in a molar ratio of 1/1 was chosen as a model. After completion of the reaction (2.50', Table 2, entry 1), methanol (10 mL) was added to the mixture and the catalyst was filtered. The filtrate was washed with methanol (5 mL). The residue was heated at 100 °C for 30 min and used for another run. The catalyst could be recovered and reused for 4 runs without activity loss (Fig. 3).

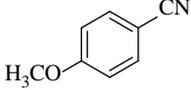
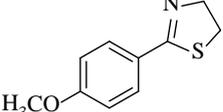
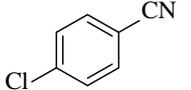
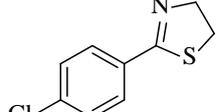
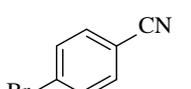
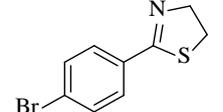
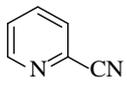
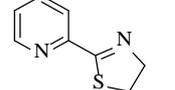
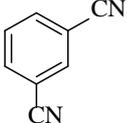
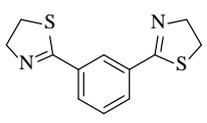
Table 5. Synthesis of imidazolines, oxazolines, and thiazolines in the presence of HNO_3 @nano SiO_2 .

$\text{R}-\text{C}_6\text{H}_4-\text{X}-\text{CN} + \text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{NH}_2 \xrightarrow{\text{HNO}_3 @ \text{nano SiO}_2} \text{R}-\text{C}_6\text{H}_4-\text{X}-\text{Imidazole}$

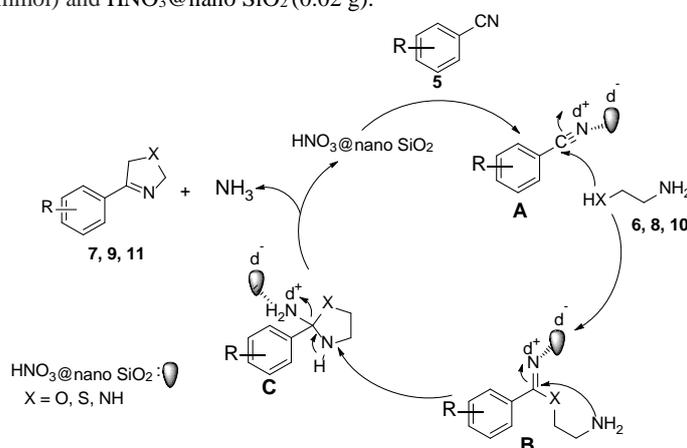
5: $\text{R}-\text{C}_6\text{H}_4-\text{X}-\text{CN}$
6: $\text{X} = \text{NH}_2$
8: $\text{X} = \text{OH}$
10: $\text{X} = \text{SH}$

Entry	Nitrile	Product	Time (h)	Yield (%)	M.p., Ref. (°C) ^a
1	5a	7a	3.30'	65	100-101, 100-101 [31]
2	5b	7b	9	67	176-179, 177-179 [31]
3	5c	7c	8	65	138-140, 139-140 [31]
4	5d	7d	6.30'	74	187-188, 186-188 [32]

5		5e		7e	4.10'	64	243-245, 242-246 [32]
6		5f		7f	2.50'	84	102-103, 101-102 [31]
7		5g		7g	3.25'	78	132-134, 133-134 [32]
8 ^b		5g		7h	4.30'	83	243-244, 242-243 [31]
9		5a		9a	4	70	Oil, Oil [32]
10		5b		9b	9	64	72-73, 71-73 [27]
11		5d		9c	5.45'	69	78-79, 77-79 [32]
12		5f		9d	4.30'	89	67-69, 68-69 [27]
13		5g		9e	4.30'	83	97-100, 98-100 [32]
14 ^c		5g		9f	5.30'	74	136-140, 137-139 [32]
15		5h		9g	9.10'	68	52-56, 53-55 [27]
16	CH_3CN	5i		9h	12	57	107-109, 108-109 [45]
17		5a		11a	3	70	126-129, 126-128 [32]
18		5b		11b	10	55	39-41, 40-41 [33]

19		5c		11c	8	56	52-54, 53-55 [32]
20		5d		11d	7	70	52-55, 53-55 [32]
21		5e		11e	8	75	59-61, 60-62 [32]
22		5f		11f	8	85	92-93, 92-94 [32]
23 ^d		5g		11g	4.45'	80	110-113, 111-113 [32]

^a Reference of known compounds; ^b Reaction conditions: ethylenediamine (8 mmol) and HNO₃@nano SiO₂ (0.03 g); ^c Reaction conditions: ethanolamine (12 mmol) and HNO₃@nano SiO₂ (0.02 g); ^d Reaction conditions: aminoethanthiol (7 mmol) and HNO₃@nano SiO₂ (0.02 g).



Scheme 3. Suggested mechanism for the preparation of 2-imidazolines, 2-oxazolines, and 2-thiazolines.

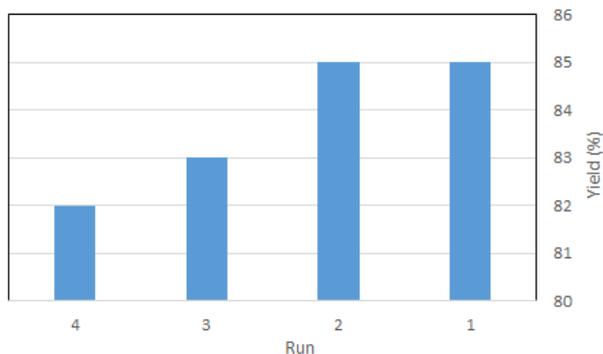


Fig. 3. Recovery and reusability of HNO₃@nano SiO₂ in the reaction of *o*-phenylenediamine and benzaldehyde.

EXPERIMENTAL

Materials and methods

All chemicals were purchased from Merck, Aldrich and Alfa Aesar and were used without further purification. The amorphous nano silica with

average particle size of 20-30 nm and specific surface area of 180-270 m²g⁻¹ was purchased from Tecnan Company. IR spectra were recorded in KBr disks using FT-IR Bruker Tensor 27 instrument. Melting points were determined on a Shimadzu DSC-50 thermal analyzer and are uncorrected. ¹H NMR spectra were recorded with a Bruker drx (400 MHz) machine. Elemental analyses were performed using a Thermo-Finnigan Flash EA 1112 Series. Progress of the reaction was monitored by thin layer chromatography (TLC) techniques using commercial available silica gel sheets. Preparative layer chromatography (PLC) was carried out on 20×20 cm² plates coated with a 1 mm layer of Merck silica gel PF₂₅₄, by applying the silica as slurry and drying in air. The products were characterized by their melting points, FT-IR, ¹H NMR, and CHN analysis.

Preparation of HNO_3 @nano SiO_2 [36]

In a round-bottom flask, concentrated HNO_3 (1 mL) was added to a mixture of commercial nano SiO_2 (2.5 g) in 10 mL of dry CHCl_3 and stirred at room temperature for 180 min. CHCl_3 was evaporated at atmospheric pressure and the obtained solid was placed in an oven for 2 h at 100°C to get the HNO_3 @nano SiO_2 as pale yellow solid.

General procedure for synthesis of benzimidazoles **3a-s** via the reaction of diamines and aldehydes

A mixture of diamines **1a-c** (1 mmol) and aldehydes **2a-o** (1 mmol) in the presence of HNO_3 @nano SiO_2 (0.01 g) at 90°C was stirred for appropriate time (Table 2, 2.15'-5.55'). The progress of the reaction was monitored by TLC. After completion, methanol (10 mL) was added to the mixture. The nanocatalyst was filtered and the filtrate was washed with methanol (5 mL). The crude products were purified by PLC (eluent: *n*-hexane/ethyl acetate, 2/1) to obtain **3a-s** in 60-89 %.

General procedure for synthesis of benzimidazoles via the reaction of *o*-phenylenediamine and carboxylic acids

A mixture of *o*-phenylenediamine (**1a**) (1 mmol) and carboxylic acids **4a-i** (1 mmol) in the presence of HNO_3 @nano SiO_2 (0.02g) at 100°C was stirred for appropriate time (Table 3, 4.20'-9 h). The progress of the reaction was monitored by TLC. After completion, methanol (10 mL) was added to the mixture. The nanocatalyst was filtered and the filtrate was washed with methanol (5 mL). The crude products were purified by PLC (eluent: *n*-hexane/ethyl acetate, 2/1) to obtain the corresponding benzimidazoles in 64-82 %.

General procedure for synthesis of 2-substituted imidazolines **7a-h**

A mixture of the nitriles **5a-h** (1 mmol), ethylenediamine (**6**) (4 mmol), and HNO_3 @nano SiO_2 (0.015 g) was stirred at 100°C under solvent-free conditions for appropriate time monitored by TLC (Table 5, 2.50'-9 h). After completion, methanol (10 mL) was added to the mixture. The nanocatalyst was filtered and the filtrate was washed with methanol (5 mL). The crude products were purified by PLC (eluent: *n*-hexane/ethyl acetate, 2/1) to obtain the corresponding imidazolines (Table 5, entries 1-8) in 64-84 %.

General procedure for synthesis of 2-substituted oxazolines **9a-h**

A mixture of a nitrile (1 mmol), ethanolamine (**8**) (6 mmol), and HNO_3 @nano SiO_2 (0.01 g) was

stirred at 90°C under solvent-free conditions for appropriate time monitored by TLC (Table 5, 4-12 h). After completion, methanol (10 mL) was added to the mixture. The nanocatalyst was filtered and the filtrate was washed with methanol (5 mL). The crude products were purified by PLC (eluent: *n*-hexane/ethyl acetate, 2/1) to obtain the pure products **9a-h** (Table 5, entries 9-16) in 57-89 %.

General procedure for synthesis of 2-substituted thiazolines **11a-g**

A mixture of nitriles **5a-g** (1 mmol), aminoethanethiol (**10**) (3.5 mmol), and HNO_3 @ nano SiO_2 (0.01 g) was stirred at 100°C under solvent-free conditions for appropriate time monitored by TLC (Table 5, 3-10 h). After completion, methanol (10 mL) was added to the mixture. The nanocatalyst was filtered and the filtrate was washed with methanol (5 mL). The crude products were purified by PLC (eluent: *n*-hexane/ethyl acetate, 2/1) to obtain the pure products **11a-g** (Table 5, entries 17-23) in 55-85 %.

2-(4-Methylphenyl)-3H-imidazo[4,5-b]pyridine (**3r**): M.p. $243\text{-}247^\circ\text{C}$. IR (KBr) ν/cm^{-1} 3444, 3028, 2962, 1698, 1620, 1108, 648. ^1H NMR (DMSO- d_6) δ 2.48 (s, 3H, Me), 7.20 (dd, $J = 7.95$ Hz, $J = 4.76$ Hz, 1H), 7.36 (d, $J = 8.08$ Hz, 2H), 7.74 (d, $J = 7.65$ Hz, 1H), 7.96 (d, $J = 7.84$ Hz, 1H), 8.12 (d, $J = 8.08$ Hz, 2H), 8.29 (d, $J = 4.6$ Hz, 1H). Anal. calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_3$: C 74.62, H 5.29, N 20.08 %, found: C 74.43, H 5.16, N 19.96 %.

2-(4-Chlorophenyl)-3H-imidazo[4,5-b]pyridine (**3s**): M.p. $260\text{-}264^\circ\text{C}$. IR (KBr) ν/cm^{-1} 3469, 1613, 11452, 1082, 766, 672. ^1H NMR (DMSO- d_6) δ 6.56 (dd, $J = 7.57$ Hz, $J = 4.94$ Hz, 1H), 7.40 (d, $J = 7.5$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.84 (d, $J = 6.05$ Hz, 1H), 8.03 (d, $J = 8.44$ Hz, 2H), 8.69 (br s, 1H). Anal. calcd. for $\text{C}_{12}\text{H}_8\text{N}_3\text{Cl}$: C 62.75, H 3.51, N 18.29 %, found: C 62.55, H 3.41, N 18.07 %.

CONCLUSION

In conclusion, in this work we have synthesized a simple nanocatalyst *via* embedding HNO_3 on nano SiO_2 and characterized it by titration, FT-IR, and SEM techniques. Its catalytic activity was examined in the synthesis of benzimidazoles, imidazolines, oxazolines, and thiazolines under solvent-free conditions. The simple work-up procedure, the absence of hazardous and non-green solvents, good yields, mild reaction conditions, chemoselectivity, and recyclability of the catalyst are highlighted features of this new procedure.

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REFERENCES

1. B.S. Davidson, *Chem. Rev.*, **93**, 1771 (1993).
2. C. Dardonville, I. Rozas, *Med. Res. Rev.*, **24**, 639 (2004).
3. G.A. Head, S. L. Burke, C.K.S. Chan, *Clin. Exp. Hypertens.*, **19**, 591 (1997).
4. E.S. Vizi, *Med. Res. Rev.*, **6**, 431 (1986).
5. H.Y. Li, S. Drummond, I. Delucca, G.A. Boswell, *Tetrahedron*, **52**, 11153 (1996).
6. L. Crane, M. Anastassiadou, S. El Hage, J.L. Stigliani, G. Baziard-Mouysset, M. Payard, J.M. Leger, J.G. Bizot-Espiard, A. Ktorza, D.H. Caignard, P. Renard, *Bioorg. Med. Chem.*, **14**, 7419 (2006).
7. L.T. Vassilev, B.T. Vu, B. Graves, D. Carvajal, F. Podlaski, Z. Filipovic, N. Kong, U. Kammloft, C. Lukacs, C. Klein, N. Fotouhi, E.A. Liu, *Science*, **303**, 844 (2004).
8. M. Ueno, K. Imaizumi, T. Sugita, I. Takata, M. Takeshita, *Int. J. Immunopharmacol.*, **17**, 597 (1995).
9. T.G. Gant, A.I. Meyers, *Tetrahedron*, **50**, 2297 (1994).
10. A. Cwik, Z. Hell, A. Hegedus, Z. Finta, Z. Horvath, *Tetrahedron Lett.*, **43**, 3985 (2002).
11. P. Zhou, J.E. Blubaum, C.T. Burns, N.R. Natale, *Tetrahedron Lett.*, **38**, 7019 (1997).
12. I. Mohammadpoor-Baltork, A.R. Khosropour, S.F. Hojati, *Synlett.*, **18**, 2747 (2005).
13. V. Mirkhani, M. Moghadam, S. Tangestaninejad, H. Kargar, *Tetrahedron Lett.*, **47**, 2129 (2006).
14. C.T. Brain, A. Hallett, S.Y. Ko, *Tetrahedron Lett.*, **39**, 127 (1998).
15. M.K. Ghorai, K. Ghosh, K. Das, *Tetrahedron Lett.*, **47**, 5399 (2006).
16. H. Fujioka, K. Murai, O. Kubo, Y. Ohba, Y. Kita, *Tetrahedron*, **63**, 638 (2007).
17. T. Roth, M.L. Morningstar, P.L. Boyer, S.H. Hughes, R.W. Buckheit, C.J. Michejda, *J. Med. Chem.*, **40**, 4199 (1997).
18. J.S. Kim, B. Gatto, Ch.Yu, A. Liu, L.F. Liu, E.J. LaVoie, *J. Med. Chem.*, **39**, 992 (1996).
19. L.I. Kruse, D.L. Ladd, P.B. Harrsch, F.L. McCabe, S.M. Mong, L. Faucette, R. Johnson, *J. Med. Chem.*, **32**, 409 (1989).
20. L. Veerakumari, N. Munuswamy, *Vet. Parasitol.*, **91**, 129 (2000).
21. W.K.R. Mederski, D. Dorsch, S. Anzali, J. Gleitz, B. Cezanne, C. Tsaklakidis, *Bioorg. Med. Chem. Lett.*, **14**, 3763 (2004).
22. C.C. McGowan, T.L. Cover, M.J. Blaser, *Gastroenterol.*, **107**, 1573 (1994).
23. K.L. Brown, *Chem. Rev.*, **105**, 2075 (2005).
24. M.A. Chari, D. Shobha, T. Sasaki, *Tetrahedron Lett.*, **52**, 5577 (2011).
25. S. Salahuddin, M. Shaharyar, A. Mazumder, M.J. Ahsan, *Arab. J. Chem.*, **7**, 418 (2014).
26. B. Karami, Sh. Nikoseresht, S. Khodabakhshi, *Chinese J. Catal.*, **33**, 298 (2012).
27. H. Ge, P. Liu, X. Li, W. Sun, J. Li, B. Yang, Zh. Shi, *Tetrahedron*, **69**, 6591 (2013).
28. N. Irvani, N. Safikhani Mohammadzade, Kh. Niknam, *Chinese Chem. Lett.*, **22**, 1151 (2011).
29. A. Mobinikhaledi, N. Foroughifar, M. Zendehtdel, M. Jabbarpour, *Synth. React. Inorg.*, **38**, 390 (2008).
30. H. Eshghi, M. Rahimizadeh, A. Shiri, P. Sedaghat, *Bull. Korean Chem. Soc.*, **33**, 515 (2012).
31. M.N-Esfahani, M. Montazerzohori, M. Moghadam, P. Akhlaghi, *ARKIVOC*, **X**, 97 (2010).
32. S.F. Hojati, S.A. Nezhadhosiny, *J. Serb. Chem. Soc.*, **77**, 1181 (2012).
33. L. Wu, *E. J. Chem.*, **9**, 1035 (2012).
34. Kh. Ghanbari, K. Nikoofar, *Monatsh. Chem.*, **145**, 1867 (2014).
35. K. Nikoofar, Kh. Ghanbari, *Monatsh. Chem.*, **146**, 2021 (2015).
36. K. Nikoofar, Sh. Moazzez Dizgarani, *J. Saudi Chem. Soc.*, **21**, 787 (2017).
37. K. Nikoofar, S. Gorji, *J. Sulfur Chem.*, **36**, 178 (2015).
38. M. Haghighi, K. Nikoofar, *J. Saudi Chem. Soc.*, **20**, 101 (2016).
39. F. K. Behbahani, A. Lotfi, *Eur. Chem. Bull.*, **2**, 694 (2013).
40. V. Prabhakar, K.S. Babu, L.K. Ravindranath, J. Latha, *World J. Pharm. Phar. Sci.*, **4**, 553 (2015).
41. A.T. Khan, T. Parvin, L.H. Choudhury, *Synth. Commun.*, **39**, 2339 (2009).
42. Y. Venkateswarlu, S.R. Kumar, P. Leelavath, *Org. Med. Chem. Lett.*, **3**, 7 (2013).
43. V.A.S. Sontakke, P.P. Ghosh, B.A. Lawande, V.S. Shinde, *Org. Chem.*, **45**, 3682 (2013).
44. H. Thakuria, G. Das, *RKIVOC*, **XV**, 321 (2008).
45. Aldrich, Catalog Handbook of Fine Chemicals, 1988-1989. P 1038.

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ННО₃ ИМОБИЛИЗИРАНА ВЪРХУ НАНО СИО₂: НОВА ЕФЕКТИВНА ХЕТЕРОГЕННА КАТАЛИТИЧНА СИСТЕМА ЗА СИНТЕЗ НА 2-ЗАМЕСТЕНИ ОКСАЗОЛИНИ, ИМИДАЗОЛИНИ, ТИАЗОЛИНИ И 2-АРИЛ-1H-БЕНЗИМИДАЗОЛИ В ОТСЪСТВИЕ НА РАЗТВОРИТЕЛ

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(Резюме)

ННО₃ имобилизирана върху нано SiO₂ (ННО₃@нано SiO₂) е изследвана за синтез на 2-заместени производни на оксазолини, имидазолини, тиазолини и 2-арил-1H-безцимидазол в отсъствие на разтворител. Резултатите потвърждават отличната ефективност на катализатора за получаване на споменатите хетероцикли. Доказано е, че синтезираният нанокатализатор е ефективен в широка област от трансформации на субстрата, даващи съответните продукти с добри добиви. Възстановяването и повторната употреба на катализатора са изследвани в 4 цикъла без загуба на активността. Предложен е механизъм на трансформациите.