

Rapid Four-component Synthesis of Dihydropyrano[2,3-c]pyrazoles using Nano-egg Shell/Ti(IV) as a Highly Compatible Natural Based Catalyst

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Abstract

Nano-egg shell/Ti(IV) (NEST) as a novel naturally based catalyst was prepared, characterized and applied for the synthesis of dihydropyrano[2,3-*c*]pyrazole [DHPP] derivatives. The characterization of NEST was performed using Fourier Transform Infrared (FT-IR) spectroscopy, X-ray Diffraction (XRD), Field Emission Scanning Electron Microscopy (FESEM), Energy-Dispersive X-ray Spectroscopy (EDX), and Thermo Gravimetric Analysis (TGA). DHPPs were synthesized in the presence of NEST *via* a four component reaction of aldehydes, ethyl acetoacetate, malononitrile and hydrazine hydrate at room temperature under solvent free conditions. The principal affairs of this procedure are easy work-up, high yields of pure products without the use of any toxic organic solvents, mild condition and short reaction times.

Introduction

One key-step toward green chemistry concerns on chemical transformations under solvent-free conditions [1, 2]. Solvent free conditions often lead to a decrease reaction time, increased yields and easy work-up [3, 4]. Combining this condition with Multi-component reactions (MCRs) disclosed a particular opportunity to architecting of heterocyclic molecules in a short time [5, 6]. MCRs play an essential role in combinatorial chemistry due to one-pot synthesis of various complex molecules, atom economy and effectiveness compared with single step reaction [7, 8]. For economic reasons and preventing environmental pollution, solvent free reactions were demonstrated to be an efficient method for the synthesis of chemical product in a clean and safe condition [9–11]. Dihydropyrano[2,3-*c*]pyrazole [DHPP] are important class of heterocycle compounds because of their wide application in medicinal and pharmaceutical chemistry [12]. Many of these properties are known for their antimicrobial [13], anti-inflammatory [14], anticancer [15], bactericidal [16], molluscicida [17] and kinase inhibitory [18] activities. In the first report, DHPP was synthesized from the reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene [19]. Recently, DHPPs have been synthesized *via* the reaction of hydrazine hydrate, ethyl acetoacetate, malononitrile and aldehydes. Some catalysts have been used to developed this reaction such as γ -alumina [20], glycine [21], ionic liquids [22], L-proline [23], imidazole [24], I_2 [25] and triethylamine [26]. In recent years, heterogeneous catalysts, due to the high capability for recycling and reutilization, has surpassed homogeneous catalytic systems, despite their benefits such as high activity and selectivity [27]. Nowadays, nanocatalysts have been subject of immense interest, because of their potential applications in different fields. They have several important advantages as heterogeneous catalysts including high catalytic activity, readily available, simple separation, high degree of chemical stability, and reusability [28–31].

The egg shell is represented 11% of the total weight of the egg and composed predominantly of calcium carbonate (94%), calcium phosphate (1%), organic matter (4%) and magnesium carbonate (1%) [32].

In continuation of our previous works in solid acids [33–38], herein, we have reported an efficient one-pot four-component reaction protocol for the synthesis of DHPPs in the presence of NEST as a highly

effective nanocatalyst in good to excellent yields under mild conditions (Scheme 1).

Results And Discussion

Characterization of the nanocatalyst

NEST was prepared simply *via* addition of TiCl_4 to a suspension of egg-shell nanoparticles in CH_2Cl_2 (Scheme 2). The obtained catalyst was characterized using Fourier Transform Infrared (FT-IR) spectroscopy, X-ray Diffraction (XRD), Field Emission Scanning Electron Microscopy (FESEM), Energy-Dispersive X-ray (EDX) spectroscopy, and Thermo Gravimetric Analysis (TGA).

The FT-IR spectra of CaCO_3 [39, 40], nano-egg shell, and NEST are shown in Fig. 1. Distinct peaks can be observed at 711, 871 and 1391 cm^{-1} in all compared spectra show the presence high percent of CaCO_3 in egg-shell and NEST. For NEST (Fig. 1(c)), in addition to the egg shell absorption bands, stretching vibrations of C-O-Ti group at 916 cm^{-1} is appeared which is indicated that TiCl_4 functionalized on nano-egg shell successfully. The absorbed band at 1613 cm^{-1} is associated the bending vibration of H-O-H which show absorbed water on catalyst [41].

Figure 2 shows the XRD patterns of NEST, TiO_2 and CaCO_3 in the range of 10–70 $^\circ(2\theta)$. NEST (Fig. 2(c)), has shown diffraction peaks at $2\theta = 23^\circ, 29^\circ, 37^\circ, 40^\circ, 43^\circ, 47^\circ, 48^\circ, 56^\circ, 57^\circ, 61^\circ$ and 62° , which are quite matched with the structure of pure CaCO_3 . By comparison with Figs. 2a, 2b and 2c, we can conclude the absence of TiO_2 and presence of CaCO_3 in catalyst.

Surface morphology of NEST was observed using FESEM. This image indicates that NEST nanoparticles have a quasi-spherical shape with an average size about 40 nm (Fig. 3).

The existence of the expected elements in the structure of the NEST was approved by EDX analysis (Fig. 4). The EDX results clearly confirm the presence of C, O, Cl, Ca and Ti elements in the catalyst. According to this data, the weight percentages of the above mentioned elements are 14.48, 43.13, 7.16, 29.3 and 5.94, respectively.

For thermal stability investigation of the catalyst, TGA technique was done in a range of 45–813 $^\circ\text{C}$ (Fig. 5). According to the TGA curve, the initial weight loss at 70–130 $^\circ\text{C}$ is 4% with an endothermic process. The second weight decrease was occurred at 130–600 $^\circ\text{C}$ (exothermic effect 130–600 $^\circ\text{C}$, 16% weight loss). As the temperature increased to 800 $^\circ\text{C}$, the main mass loss could be associated with the decomposition of egg shell to CO_2 and CaO .

To optimize the conditions for the synthesis of the DHPPs in the presence of NEST, the condensation of 4-chlorobenzaldehyde, malononitrile, ethyl acetoacetate, and hydrazine hydrate in the molar ratio 1:1:1:2 was done under various conditions (Table 1). According to the obtained data, the best yield of 6-amino-4-

(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**5 h**) was achieved using 0.06 g of NEST at room temperature under solvent-free condition (Table 1, entry 12).

Table 1
Preparation of **5 h** in the presence of NEST under various conditions.^a

Entry	Conditions Solvent/Catalyst (g)/ Temp. (°C)	Time (min)	Yield ^b (%)
1	H ₂ O/ NEST (0.06)/ r.t.	180	55
2	H ₂ O/ NEST (0.06)/ Reflux	120	58
3	EtOH/ NEST (0.06) / r.t.	60	75
4	EtOH/ NEST (0.06)/ Reflux	60	80
5	H ₂ O:EtOH (1:1)/ NEST (0.06)/ r.t.	45	83
6	H ₂ O:EtOH (1:1)/ NEST (0.06)/ Reflux	30	85
7	-/ NEST (0.06)/ 35	90	77
8	-/ NEST (0.06)/ 60	150	70
9	-/ -/ r.t.	30	25
10	-/ NEST (0.02)/ r.t.	45	85
11	-/ NEST (0.04)/ r.t.	20	90
12	-/ NEST (0.06)/ r.t.	15	94
13	-/ NEST (0.1)/ r.t.	20	89
^a Reaction was performed with ethyl acetoacetate (1 mmol), 4-chlorobenzaldehyde (1 mmol), malononitrile (1 mmol), and hydrazine hydrate (2 mmol).			
^b Isolated yield.			

After optimization of the reaction conditions for preparation of DHPPs, various aromatic and heteroaromatic aldehydes were used for expansion of this protocol. The reactions were proceeded rapidly for all used aldehydes (Table 2). The desired products were isolated in good to excellent yields in very short reaction times without any by products.

Table 2
Synthesis of DHPPs 5(a-o) in the presence of NEST.

Entry	Ar	Product	Time (min)	Yield ^a (%)	Mp (°C)	Refs.
1	C ₆ H ₅	5a	10	92	242–244	[42]
2	2-OCH ₃ C ₆ H ₄	5b	15	89	226–228	[43]
3	3-O ₂ NC ₆ H ₄	5c	10	90	210–211	[43]
4	4-H ₃ CC ₆ H ₄	5d	18	87	204–206	[44]
5	4-O ₂ NC ₆ H ₄	5e	9	93	239–242	[43]
6	3-BrC ₆ H ₄	5f	15	94	223–224	[44]
7	4-BrC ₆ H ₄	5g	12	96	178–180	[43]
8	4-ClC ₆ H ₅	5h	10	94	230–232	[42]
9	4-OHC ₆ H ₄	5i	10	95	222–224	[44]
10	3,4-(OH)C ₆ H ₃	5j	10	91	225–227	[45]
11	2,4-(Cl)C ₆ H ₃	5k	20	90	223–225	[44]
12	3-OCH ₃ 4-OH, C ₆ H ₃	5l	15	92	234–236	[44]
13	4-FC ₆ H ₄	5m	8	96	212–214	[43]
14	2-Furyl	5n	10	91	228–230	[46]
15	1-Naphthyl	5o	25	88	206–208	[20]
^a Isolated yield.						

A acceptable mechanism for the synthesis of DHPPs catalyzed by NEST was shown in Scheme 3. Initially, condensation of hydrazine hydrate (**4**) and ethyl acetoacetate (**1**) was formed intermediate (**6**) in the presence of NEST as a Lewis acid. The Knoevenagel condensation of malononitrile (**3**) with aromatic aldehyde (**1**) produced the intermediate (**8**). Michael addition reaction of the intermediate (**8**) and (**7**) generates intermediate (**10**), followed by intramolecular cyclization and tautomerization to give the DHPP (**5**).

In order to investigation of the catalyst reusability, after completion of the reaction, the NEST was isolated by adding acetone to reaction mixture and then filtered. The recovered catalyst was washed with hot EtOH, acetone, and dried at room temperature. It was observed that the recovered nanocatalyst could be used at least four times without significant loss of its catalytic activity (Fig. 6).

Finally, the catalytic performance of NEST was compared with that of other previously reported catalysts for the synthesis of 5a (Table 3). From the viewpoints of green chemistry and simplicity, our method is a good one.

Table 3
Catalytic performances of NEST versus some other catalysts for synthesis of 5a.

Entry	Catalyst	Solvent	Temp (°C)	Time (min)	Yield ^a (%) ^{Ref}
1	I ₂	H ₂ O	r.t.	10	90 ⁴⁷
2	Isonicotinic acid	-	80	10	92 ⁴⁸
3	piperidine	H ₂ O	r.t.	5–10	89 ⁴⁹
4	γ-Alumina	H ₂ O	reflux	35	90 ²⁰
5	Et ₃ N	EtOH	reflux	15	72 ²⁶
6	NEST ^b	-	r.t.	10	92
^a Isolated yield.					
^b This work.					

Conclusion

In this work, we have synthesized the NEST and characterized it as a novel heterogeneous natural nanocatalyst. This catalyst was used for the synthesis of DHPPs at room temperature under solvent free condition *via* condensation of hydrazine hydrate, ethyl acetoacetate, malononitrile and aromatic aldehydes. This method includes some main advantages such as solvent-free condition, good to excellent yields, room temperature, short reaction time, easy work-up and reusability of catalyst.

Experimental Section

Chemicals and apparatus

All chemicals were commercial products. FT-IR spectra were run on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 Avance) NMR was used to record the ¹H and ¹³C NMR spectra. The morphology of the particles was observed by scanning electron microscopy (SEM) under acceleration voltage of 120 kV. The XRD pattern was obtained on a Philips Xpert MPD diffractometer (Cu Ka, radiation, k¼ 0.154056 nm).

Energy dispersive spectroscopy (EDS) was obtained using a Phenom pro X instrument. Thermal gravimetric analysis (TGA) was conducted using STA 504 instrument.

Preparation of NEST

Firstly, the egg shell was heated in a boiling water for 30 minutes, dried in oven 150 °C and powdered. Then, 1 g of prepared nano-egg shell powder was stirred for 30 minutes in 10 mL of dried CH₂Cl₂. Titanium tetrachloride (4.36 mL) was slowly added dropwise to the mixture. After stirring at room temperature for 30 minutes, the resulting product filtered and washed with dichloromethane three times. Finally, the obtained NEST was dried at room temperature for 3 hours.

General procedure for the synthesis of DHPPs

In a 100 ml round bottom flask, a mixture of aldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (2 mmol), ethyl acetoacetate (1 mmol) and NEST (0.06 g) was stirred at room temperature. Progress of the reaction was monitored by TLC (*n*-hexane: EtOAc, 4:1). After completion of the reaction, the mixture was dissolved in acetone. Then, the catalyst was filtered off and the obtained solution was poured into cold water. The obtained solid product was filtered and purified by re-crystallization from ethanol and water (5:1). The obtained NEST catalyst was then washed with EtOH, dried and reused directly for four times in other fresh reactions with negligible decreasing of the yield.

Spectroscopic data for some products

6-Amino-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (Table 2, entry 3)

White solid. M.P. 210-211 °C. FT-IR (ATR)/ $\bar{\nu}$ (cm⁻¹): 3484, 3231, 3120, 2190, 1645, 1597, 1519, 1491, 1410, 1351, 733. ¹H NMR (400 MHz, DMSO-d₆)/ δ (ppm): 1.82 (s, 3H), 4.89 (s, 1H), 7.08 (s, 2H), 7.64-7.70 (m, 2H), 8.04 (s, 1H), 8.13-8.15 (d, *J* = 8 Hz, 1H), 12.23 (s, 1H).; ¹³C NMR (100 MHz, DMSO-d₆)/ δ ppm: 161.63, 155.17, 148.36, 147.32, 136.38, 134.88, 130.47, 122.33, 121.01, 97.15, 56.59, 36.11, 10.25.

6-Amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (Table 2, entry 5)

White solid. M.P. 239-242 °C. FT-IR (ATR)/ $\bar{\nu}$ (cm⁻¹): 3475, 3227, 3106, 2195, 1646, 1592, 1513, 1399, 1348, 1163, 1109, 810, 744.; ¹H NMR(400 MHz, Acetone-d₆)/ δ ppm: 2 (s, 3H), 4.88 (s, 1H), 6.30 (br s, 2H), 7.55

(d, $J = 8$ Hz, 2H), 8.23 (d, $J = 8$ Hz, 2H), 11.43 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6)/ δ ppm: 161.62, 155.15, 152.59, 146.85, 136.36, 132.19, 129.32, 124.38, 120.98, 97.04, 56.37, 36.36, 10.22.

6-Amino-4-(4-hydroxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, entry 9)

White solid. M.p. 222-224 °C. FT-IR (ATR)/ $\bar{\nu}(\text{cm}^{-1})$: 3372, 3304, 3127, 2173, 1645, 1594, 1510, 1489, 1441, 1404, 1189, 1166, 1041, 809. ^1H NMR (400 MHz, Acetone- d_6)/ $\delta(\text{ppm})$: 1.74 (s, 3H), 4.44 (s, 1H), 6.65 (dd, $J=7.5$ Hz, $J=3.7$ Hz, 2H), 6.76 (br s, 2H), 6.91 (dd, $J=7.5$ Hz, $J=3.7$ Hz, 2H), 9.27 (s, 1H), 12.02 (s, 1H).; ^{13}C NMR (100 MHz, DMSO- d_6)/ δ ppm: 161.10, 156.49, 155.22, 135.98, 135.24, 128.92, 121.40, 115.58, 98.54, 58.21, 35.95, 10.24.

6-Amino-4-(2,4-dichlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, entry 11)

Pale yellow solid. M.P. 223-225 °C. FT-IR (ATR)/ $\bar{\nu}(\text{cm}^{-1})$: 3482, 3243, 3115, 2186, 1638, 1587, 1491, 1408, 1100, 1052, 866, 741.; ^1H NMR (400 MHz, DMSO- d_6)/ δ ppm: 1.85 (s, 3H), 5.13 (s, 1H), 7.07 (s, 2H), 7.29 (d, $J = 8$ Hz, 1H), 7.47 (dd, $J = 8.4$ Hz, $J = 2$ Hz, 1H), 7.65 (d, $J = 2.4$ Hz, 1H), 12.23 (s, 1H).; ^{13}C NMR (100 MHz, DMSO- d_6)/ δ ppm: 161.30, 154.88, 140.07, 135.44, 132.81, 132.10, 128.83, 128.02, 120.25, 96.32, 55.21, 33.07, 9.53.

Abbreviations

NEST: Nano-egg shell/Ti(IV); MCR: multi-component reactions; EtOH: ethanol; FESEM: field emission scanning electron microscope; FT-IR: Fourier Transform Infrared; XRD: X-ray Diffraction; EDX: Energy Dispersive X-ray; TGA: Thermo Gravimetric Analysis; NMR: Nuclear Magnetic Resonance; TLC: Thin Layer Chromatography.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Availability of data and materials

All data generated or analysed during this study are included in this published article and Additional file 1.

Authors' contributions

ADT and BFM designed and performed the research, analyzed the data, interpreted the results and prepared the manuscript. ADT performed the assay, conducted the optimization, purification of compounds. AB and NS revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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References

1. Choudhary G, Peddinti RK (2011) An expeditious, highly efficient, catalyst-free and solvent-free synthesis of nitroamines and nitrosulfides by Michael addition. *Green Chem* 13:276–282
2. Jain SL, Singhal S, Sain B (2007) PEG-assisted solvent and catalyst free synthesis of 3, 4-dihydropyrimidinones under mild reaction conditions. *Green Chem* 9:740–741
3. Metzger JO (1998) Solvent-free organic syntheses. *Angew Chem Int Ed* 37:2975–2978
4. Tavakolian M, Vahdati-Khajeh S, Asgari S (2019) Recent advances in solvent-free asymmetric catalysis. *ChemCatChem* 11:2943–2977
5. Rahman M, Sarkar A, Ghosh M, Majee A, Hajra A (2014) Catalytic application of task specific ionic liquid on the synthesis of benzoquinazolinone derivatives by a multicomponent reaction.

Tetrahedron Lett 55:235–239.M

6. De Graaff C, Ruijter E, Orru RV (2012) Recent developments in asymmetric multicomponent reactions. *Chem Soc Rev* 41:3969–4009
7. Domling A, Wang W, Wang K (2012) Chemistry and biology of multicomponent reactions. *Chem Rev* 112:3083–3135
8. Hulme C, Chappeta S, Griffith C, Lee YS, Dietrich J (2009) An efficient solution phase synthesis of triazadibenzoazulenones: 'designer isonitrile free' methodology enabled by microwaves. *Tetrahedron Lett* 50:1939–1942
9. Trost BM (1991) The atom economy—a search for synthetic efficiency. *Science* 254:1471–1477
10. Shen ZL, Ji SJ (2009) Alkali salt of L-proline as an efficient and practical catalyst for the cyanosilylation of a wide variety of carbonyl compounds under solvent-free conditions. *Synth Commun* 39:775–791
11. Tanaka K, Toda F (2000) Solvent-free organic synthesis. *Chem Rev* 100:1025–1074
12. Das D, Banerjee R, Mitra A (2014) Bioactive and pharmacologically important pyrano [2, 3-*c*] pyrazoles. *J Chem Pharm Res* 6:108–116
13. Mandour A, El-Sawy E, Ebaid M, Hassan S (2012) Synthesis and potential biological activity of some novel 3-[(*N*-substituted indol-3-yl) methyleneamino]-6-amino-4-aryl-pyrano (2,3-*c*) pyrazole-5-carbonitriles and 3, 6-diamino-4-(*N*-substituted indol-3-yl) pyrano (2, 3-*c*) pyrazole-5-carbonitriles. *Acta Pharm* 62:15–30
14. Zaki ME, Soliman HA, Hiekal OA, Rashad AE (2006) Pyrazolopyranopyrimidines as a class of anti-inflammatory agents. *Z Naturforsch C* 61:1–5
15. Mohamed NR, Khaireldin NY, Fahmyb AF, El-Sayed AAF (2010) Facile synthesis of fused nitrogen containing heterocycles as anticancer agents. *Der Pharm Chem* 2:400–417
16. Nasr MN, Gineinah MM (2002) Pyrido [2, 3-*d*] pyrimidines and pyrimido [5', 4': 5, 6] pyrido [2,3-*d*] pyrimidines as new antiviral agents: synthesis and biological activity. *Arch Pharm Int J Pharm Med Chem* 335:289–295
17. Abdelrazek FM, Metz P, Metwally NH, El-Mahrouky SF (2006) Synthesis and molluscicidal activity of new cinnoline and pyrano [2,3-*c*] pyrazole derivatives. *Arch Pharm Int J Pharm Med Chem* 339:456–460
18. Foloppe N, Fisher LM, Howes R, Potter A, Robertson AG, Surgenor AE (2006) Identification of chemically diverse Chk1 inhibitors by receptor-based virtual screening. *Bioorg Med chem* 14:4792–4802
19. Junek H, Aigner H (1973) Synthesen mit nitrilen, XXXV. Reaktionen von tetracyanäthylen mit heterocyclen. *Chem Ber* 106:914–921
20. Mecadon H, Rohman MR, Rajbangshi M, Myrboh B (2011) γ -Alumina as a recyclable catalyst for the four-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2, 4-dihydropyrano [2, 3-*c*] pyrazole-5-carbonitriles in aqueous medium. *Tetrahedron Lett* 52:2523–2525

21. Reddy MM, Jayashankara VP, Pasha MA (2010) Glycine-catalyzed efficient synthesis of pyranopyrazoles *via* one-pot multicomponent reaction. *Synth Commun* 40:2930–2934
22. Ebrahimi J, Mohammadi A, Pakjoo V, Bahramzade E, Habibi A (2012) Highly efficient solvent-free synthesis of pyranopyrazoles by a Brønsted-acidic ionic liquid as a green and reusable catalyst. *J Chem Sci* 124:1013–1017
23. Mecadon H, Rohman MR, Kharbanger I, Laloo BM, Kharkongor I, Rajbangshi M, Myrboh B (2011) L-Proline as an efficient catalyst for the multi-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano [2,3-*c*] pyrazole-5-carbonitriles in water. *Tetrahedron Lett* 52:3228–3231
24. Siddekha A, Nizam A, Pasha MA (2011) An efficient and simple approach for the synthesis of pyranopyrazoles using imidazole (catalytic) in aqueous medium, and the vibrational spectroscopic studies on 6-amino-4-(4'-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano [2,3-*c*] pyrazole using density functional theory. *Spectrochim Acta A* 81:431–440
25. Reddy MB, Pasha MA (2012) One-pot, multicomponent synthesis of 4*H*-pyrano [2, 3-*c*] pyrazoles in water at 25 °C. *J Chem Sci* 134:537–541
26. Litvinov YM, Shestopalov AA, Rodinovskaya LA, Shestopalov AM (2009) New convenient four-component synthesis of 6-amino-2,4-dihydropyrano [2,3-*c*] pyrazol-5-carbonitriles and one-pot synthesis of 6'-aminospiro [(3*H*)-indol-3,4'-pyrano [2,3-*c*] pyrazol]-(1*H*)-2-on-5'-carbonitriles. *J Comb Chem* 11:914–919
27. Zolfigol MA, Yarie M (2017) Fe₃O₄@TiO₂@O₂PO₂(CH₂)NHSO₃H as a novel nanomagnetic catalyst: Application to the preparation of 2-amino-4,6-diphenylnicotinonitriles *via* anomeric-based oxidation. *Appl Organomet Chem* 31:e3598
28. Shokouhimehr M, Piao Y, Kim J, Jang Y, Hyeon T (2007) A magnetically recyclable nanocomposite catalyst for olefin epoxidation. *Angew Chem Int Ed* 46:7039–7043
29. Kwon SG, Hyeon T (2008) Colloidal chemical synthesis and formation kinetics of uniformly sized nanocrystals of metals, oxides and chalcogenides. *Acc Chem Res* 41:1696–1709
30. Cai X, Wang H, Zhang Q, Tong J, Lei Z (2014) Magnetically recyclable core–shell Fe₃O₄@chitosan-Schiff base complexes as efficient catalysts for aerobic oxidation of cyclohexene under mild conditions. *J Mol Catal A Chem* 383:217–224
31. Polshettiwar V, Varma RS (2010) Green chemistry by nano-catalysis. *Green Chem* 12:743–754
32. Krishna DSR, Siddharthan A, Seshadri SK, Kumar TS (2007) A novel route for synthesis of nanocrystalline hydroxyapatite from eggshell waste. *J Mater Sci Mater Med* 18:1735–1743
33. Mirjalili BF, Zolfigol MA, Bamoniri A, Hazar A (2005) Al(HSO₄)₃ as an efficient catalyst for acetalization of carbonyl compounds under heterogeneous or solvent-free conditions. *J Brazil Chem Soc* 16:877–880
34. Mirjalili BF, Hashemi MM, Sadeghi B, Emtiazi H (2009) SnCl₄/SiO₂: An Efficient heterogeneous alternative for one-pot synthesis of β-acetamidoketones. *J Chin Chem Soc* 56:386–391

35. Safajoo N, Mirjalili BF, Bamoniri A (2019) Fe_3O_4 @nano-cellulose/Cu(II): a bio-based and magnetically recoverable nano-catalyst for the synthesis of 4*H*-pyrimido [2, 1-*b*] benzothiazole derivatives. RSC Adv 9:1278–1283
36. Salehi N, Mirjalili BF (2017) Synthesis of highly substituted dihydro-2-oxopyrroles using Fe_3O_4 @nano-cellulose- OPO_3H as a novel bio-based magnetic nanocatalyst. RSC Adv 7:30303–30309
37. Azad S, Mirjalili BF (2016) Fe_3O_4 @nano-cellulose/TiCl: a bio-based and magnetically recoverable nano-catalyst for the synthesis of pyrimido [2,1-*b*] benzothiazole derivatives. RSC Adv 6:96928–96934
38. Mirjalili BF, Reshquiyea RZ (2015) BF_3 /nano-sawdust as a green, biodegradable and inexpensive catalyst for the synthesis of highly substituted dihydro-2-oxopyrroles. RSC Adv 5:15566–15571
39. Su C, Suarez DL (1995) Coordination of adsorbed boron: A FTIR spectroscopic study. Environ Sci Technol 29:302–311
40. Ahmad R, Kumar R, Haseeb S (2012) Adsorption of Cu^{2+} from aqueous solution onto iron oxide coated eggshell powder: Evaluation of equilibrium, isotherms, kinetics, and regeneration capacity. Arab J Chem 5:353–359
41. Keller OL (1963) Identification of complex ions of niobium (V) in hydrofluoric acid solutions by Raman and infrared spectroscopy. Inorg Chem 2:783–787
42. Aliabadi RS, Mahmoodi NO (2016) Green and efficient synthesis of pyranopyrazoles using [bmim] $[\text{OH}^-]$ as an ionic liquid catalyst in water under microwave irradiation and investigation of their antioxidant activity. RSC Adv 6:85877–85884
43. Moosavi-Zare AR, Zolfigol MA, Salehi-Moratab R, Noroozizadeh E (2016) Catalytic application of 1-(carboxymethyl) pyridinium iodide on the synthesis of pyranopyrazole derivatives. J Mol Catal A Chem 415:144–150
44. Huang X, Li Z, Wang D, Li Y (2016) Bovine serum albumin: An efficient and green biocatalyst for the one-pot four-component synthesis of pyrano [2,3-*c*] pyrazoles. Chin J Catal 37:1461–1467
45. Tameh FA, Safaei-Ghomi J, Mahmoudi-Hashemi M, Shahbazi-Alavi H (2016) One-pot multicomponent reaction synthesis of spirooxindoles promoted by guanidine-functionalized magnetic Fe_3O_4 nanoparticles. RSC Adv 6:74802–74811
46. Pore DM, Patil PB, Gaikwad DS, Hegade PG, Patil JD, Undale KA (2013) Green access to novel spiro pyranopyrazole derivatives. Tetrahedron Lett 54:5876–5878
47. Muramulla S, Zhao CG (2011) A new catalytic mode of the modularly designed organocatalysts (MDOs): Enantioselective synthesis of dihydropyrano [2, 3-*c*] pyrazoles. Tetrahedron Lett 52:3905–3908
48. Zolfigol MA, Tavasoli M, Moosavi-Zare AR, Moosavi P, Kruger HG, Shiri M, Khakyzadeh V (2013) Synthesis of pyranopyrazoles using isonicotinic acid as a dual and biological organocatalyst. RSC Adv 3:25681–25685

49. Vasuki G, Kumaravel K (2008) Rapid four-component reactions in water: synthesis of pyranopyrazoles. Tetrahedron Lett 49:5636–5638

Figures

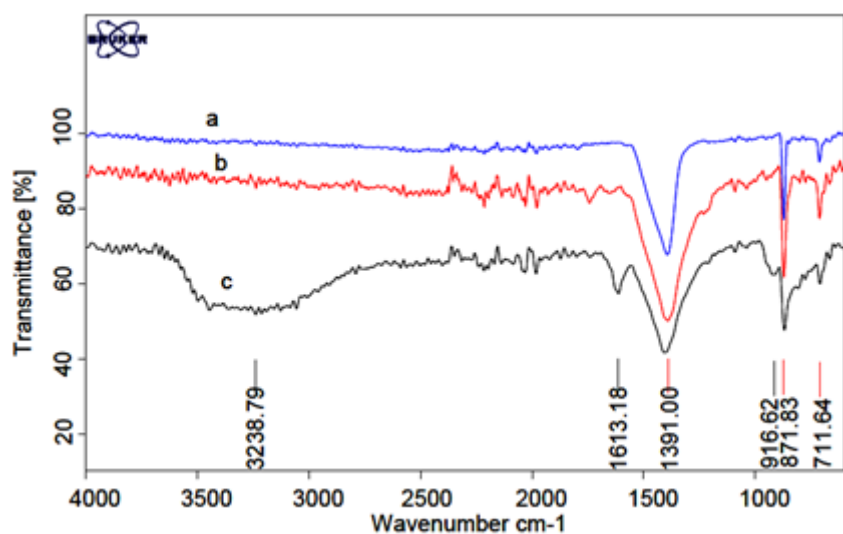


Figure 1

FT-IR spectra of (a) CaCO₃, (b) nano-egg shell, and (c) NEST

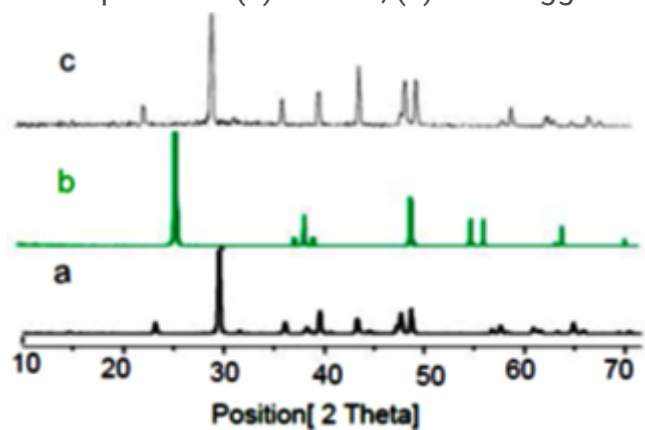


Figure 2

The XRD patterns of (a) CaCO₃, (b) TiO₂, and (c) NEST

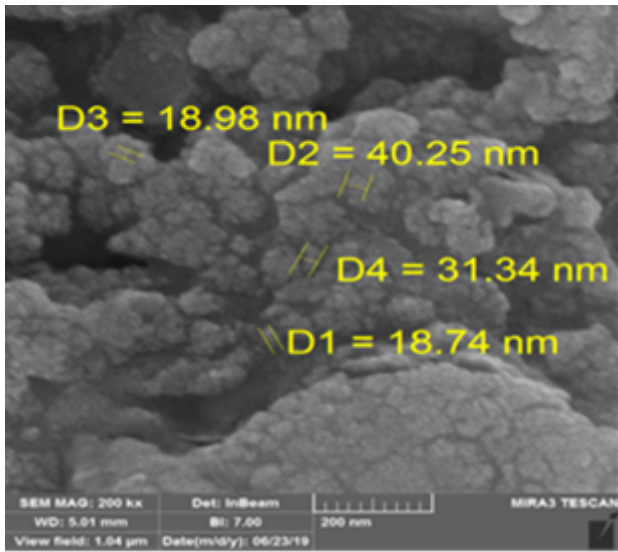


Figure 3

FESEM image of NEST

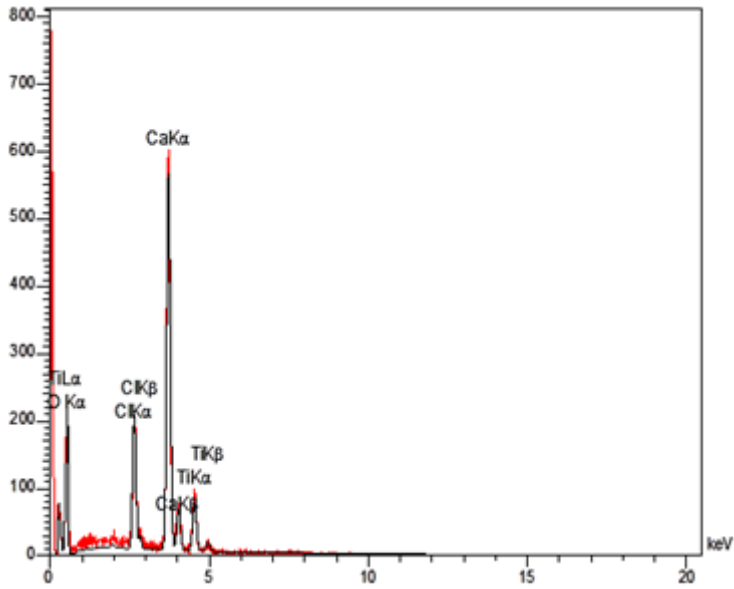


Figure 4

EDS analysis of NEST

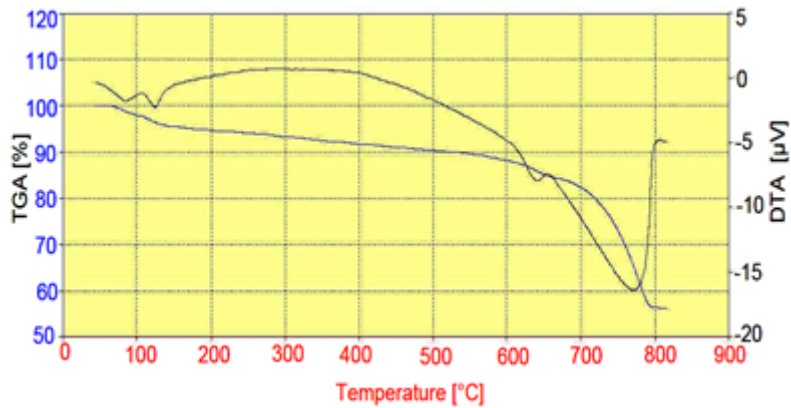


Figure 5

Thermal gravimetric analysis pattern of NEST

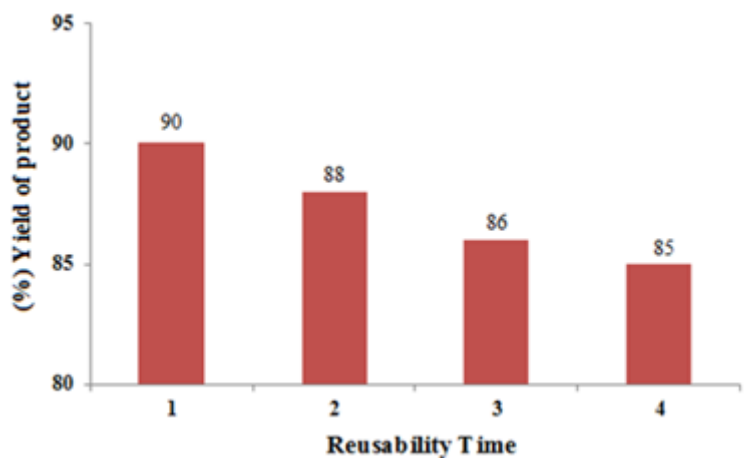


Figure 6

Reusability of NEST

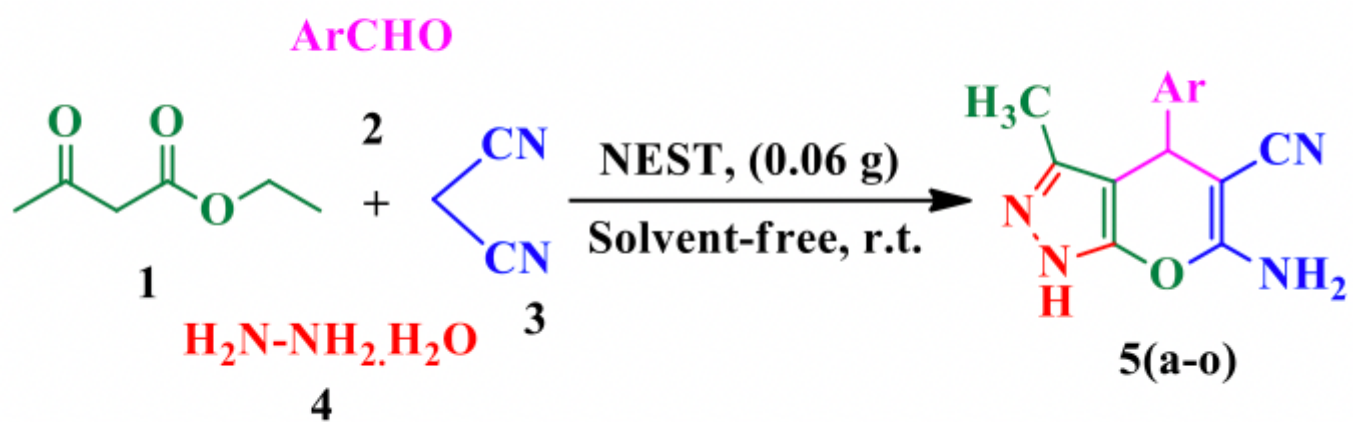


Figure 7

Scheme 1 synthesis of dihydropyrano[2,3-c]pyrazoles catalyzed by nano-egg shell/Ti(IV)

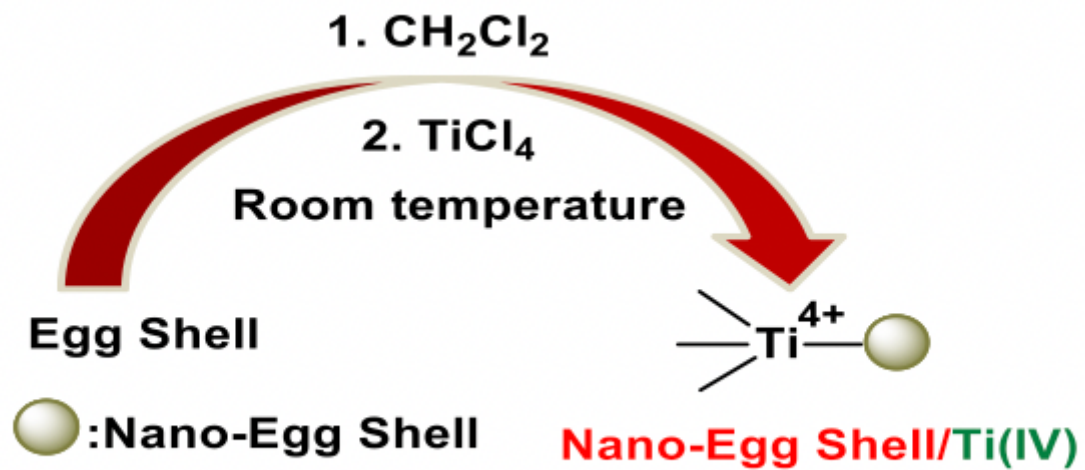


Figure 8

Scheme 2 Preparation of NEST

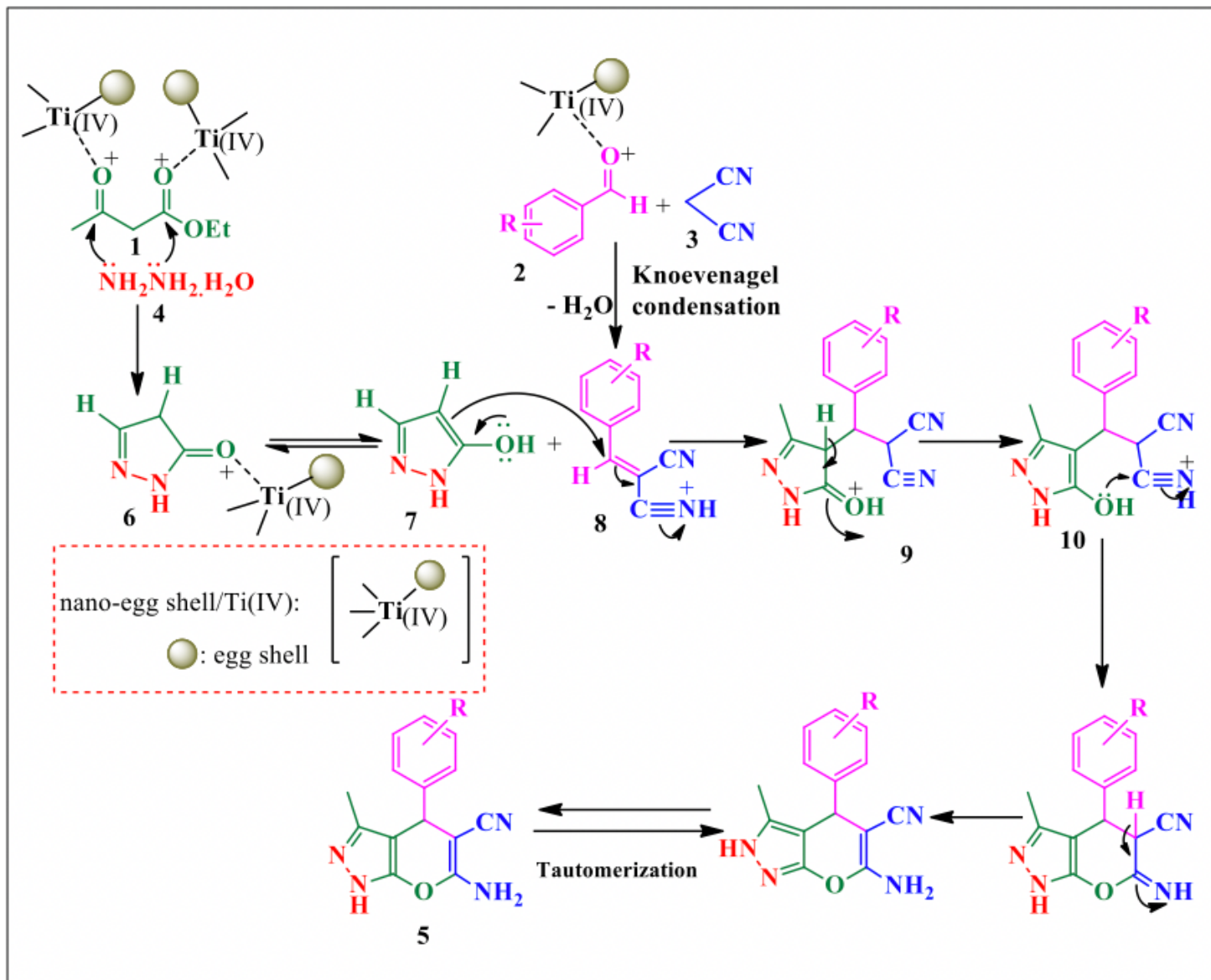


Figure 9

Scheme 3 A proposed mechanism for the synthesis of DHPPs.

Supplementary Files

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- [supplement1.jpg](#)