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ARTICLE TYPE

One-pot multicomponent synthesis of highly functionalized bio-active pyrano[2,3-*c*]pyrazole and benzylpyrazolyl coumarin derivatives using ZrO_2 nanoparticles as reusable catalyst

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A facile one-pot multicomponent protocol for the synthesis of bio-active pyrano[2,3-*c*]pyrazole and benzylpyrazolyl coumarin derivatives has been demonstrated using ZrO_2 nanoparticles as catalyst at room temperature. The reactions are very fast and high yielding. The catalytic activity and tetragonal plane of ZrO_2 nanoparticles remained unchanged after 10th cycle.

Over past decades, synthesis of complex biologically active scaffolds *via* one-pot multicomponent reactions (MCRs) has attracted considerable attention.[1] The synthetic utility of such protocol can be improved significantly by using green solvent and efficient heterogeneous catalyst.

The pyrano[2,3-*c*]pyrazole derivatives are one of the important biologically important scaffolds because of their wide applications in pharmaceutics[2,3] and in organic synthesis as essential intermediates.[4] These moieties have used as anti-cancer,[2a] anti-inflammatory,[2b] anti-microbial,[2c] inhibitors of human Chk1 kinase,[2d] fungicidal,[2e] insecticidal,[2f] molluscicidal,[2g] and analgestic.[2h] In addition, they can also act as hypoglycaemic,[3a] biodegradable agrochemicals,[3b] vasodilators and hypotensive.[3c]

On the other hand, 3-benzylsubstituted 4-hydroxycoumarin derivatives have been found in many natural products and exhibit various biological activities such as warfarin, phenprocoumene, coumatetralyl, carbochromen, bromadialone offering antibacterial, anti-HIV,[5a] antiviral,[5b] anticoagulant,[5c] antioxidant[5d] and anticancer activities (Fig. 1).[5e]

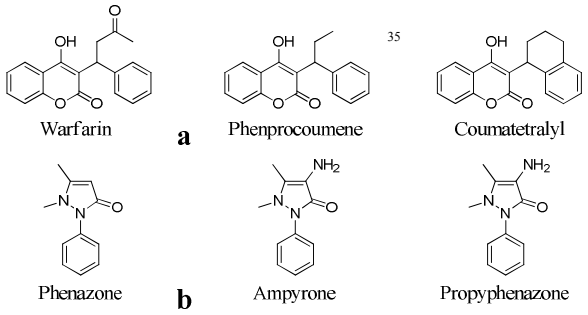


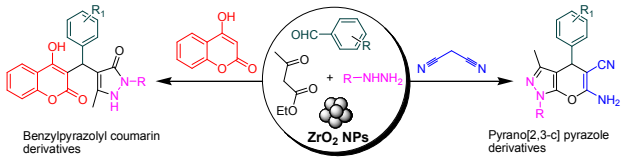
Figure 1 Few bioactive (a) coumarin and (b) pyrazolone derivatives.

Thus, integrated biological properties can be obtained from a single nucleus which contains 3-benzyl substituted coumarin and pyrazolone moieties. As a consequence synthesis of molecular scaffolds comprising both the nucleus will be beneficial form the biological point of view.

Generally, pyrano[2,3-*c*]pyrazoles have been synthesized *via* 2-component,[6a,b] 3-component,[6c-f] and more importantly 4-component reactions of aldehyde, ethyl acetoacetate, hydrazine hydrate and malononitrile.[6g,7] However, most of the protocols used homogeneous and nitrogenous based toxic catalysts e.g. triethylamine,[7a] piperidine,[7b] L-proline,[7c,d] per-6-amino-β-cyclodextrin,[7e] hexadecyl dimethyl benzyl ammonium chloride,[7f] basic ionic liquids,[7g,h] disulfonic acid imidazolium chloroaluminate,[7i] meglumine,[7j] sodium benzoate[7k] while only a few methods involving heterogeneous catalysts such as Amberlyst A21,[7l] γ-alumina,[7m] SnO_2 QDs[7n] and have been reported. Surprisingly, only one method is available for the synthesis of highly functionalized benzylpyrazolyl coumarin frameworks in presence of glacial acetic acid.[8] Thus, the development of general MCR protocol using a green catalyst leading to the pyrano[2,3-*c*] pyrazole derivatives and more interestingly highly functionalized benzylpyrazolyl coumarin frameworks is highly appreciated.

To the best of our knowledge there is no efficient general protocol for the synthesis of the above mentioned biologically active scaffolds using a green catalyst. The use of NPs could be more effective due to their large and reactive surface area. As a part of our interest to explore catalytic performance of nanoparticles (NPs), [9] here we sought to explore the activity of ZrO_2 NPs. The ZrO_2 NPs have been paid much attention in material science due to its specific optical and electrical properties (band gap ~ 5eV).[10] In catalysis, ZrO_2 NPs were mostly used as a solid support[11a,b] or as a photocatalyst[11c-i] and a few reports indicate the use as catalyst in the elementary organic transformations.[11j-n] However, ZrO_2 NPs have not been applied in MCRs leading to functionalized bio-active molecules.

Herein, for the first time we have reported a green and efficient protocol for the synthesis of biologically active pyrano[2,3-*c*] pyrazole and benzylpyrazolyl coumarin derivatives using tetragonal ZrO_2 NPs as a heterogeneous catalyst (Scheme 1).



Scheme 1 Synthesis of pyrano[2,3-*c*] pyrazole and benzylpyrazolyl coumarin derivatives using ZrO_2 NPs as catalyst.

Initially, we have prepared ZrO_2 NPs following a modified previously reported protocol.[12] Briefly, a solution of $ZrO_2Cl_2.8H_2O$ was condensed under basic medium (pH~10) at 0-5 ^oC and stirred the solution additionally for 24 hrs at 100 ^oC. The colloidal particles were recovered by centrifugation and washed several times with water, dried and finally NPs were calcined at 500 ^oC for 4 hrs (See ESI-1 for details). The formation of ZrO_2 NPs was confirmed by spectroscopic (FT-IR, UV-Vis) and analytical (XRD, FE-SEM, HR-TEM) techniques. In the UV-Vis spectrum (See S1, ESI-2) a maxima was observed at 261 nm which is equivalent to band gap of 4.76 eV.

The powder X-ray diffraction pattern of the catalyst (Fig. 2) indicates the formation of tetragonal ZrO_2 ($^tZrO_2$) NPs.[13] The peak at 2θ = 30.4, 51.01 and 59.30 are assigned for the (101), (112) and (103) reflection plane for tetragonal ZrO_2 and no peak was observed corresponding to monoclinic plane. Thus, the synthesized NPs were purely tetragonal in nature.

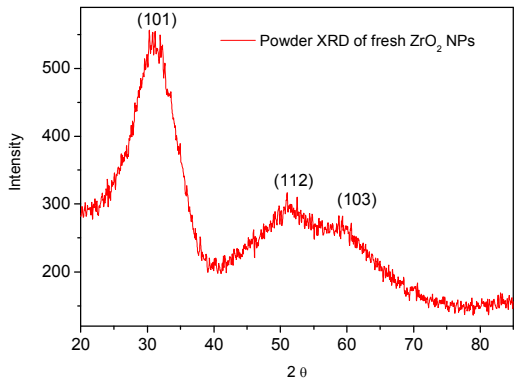


Figure 2 Powder X-ray diffraction patterns of fresh $^tZrO_2$ NPs.

The broadening of peaks indicates the formation of small sized NPs. The particle size of ZrO_2 NPs was determined to be 17 nm from the XRD spectra by the full-width at half-maximum calculation (FWHM) using Scherrer formula.[14]

The morphology of the NPs has been confirmed from Field emission scanning electron microscopic (FE-SEM) study. The FE-SEM image (Fig. 3) indicates the formation of spherical shaped and nearly uniform size ZrO_2 NPs with the average particle size of ~ 17 nm which are in good match with the values (~17 nm) obtained from powder XRD study. The morphology and uniformity of particle size of prepared ZrO_2 NPs were further confirmed by high resolution transmission electron microscopy (HR-TEM) study.

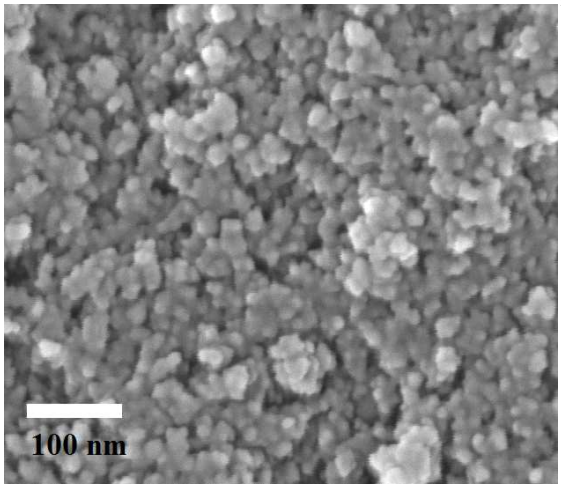


Figure 3 Field emission scanning electron microscopy image of ZrO_2 NPs.

The HR-TEM image (Fig. 4) clearly indicates that the particles have nearly uniform size and the size distribution of the particles was measured from TEM over 75 particles and average particle size of 16 nm obtained from a Gaussian plot (See Fig. S2, ESI-2). The uniform distribution of particles size can also be seen from Dynamic Light Scattering study (See Fig. S3, ESI-2).

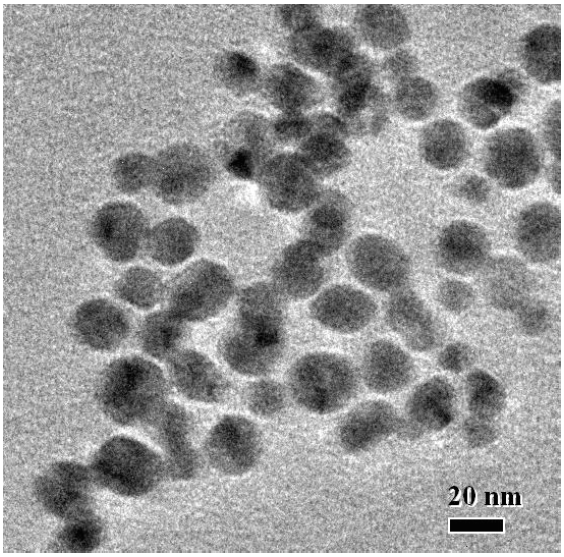


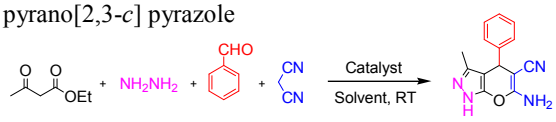
Figure 4 high resolution transmission electron microscopy image of ZrO_2 NPs.

The absorbance bands at 494 and 447 cm^{-1} in FT-IR spectrum were attributed to the Zr-O stretching corresponding to tetragonal ZrO_2 (FT-IR spectra of $^tZrO_2$ NPs is given in S4, ESI-2).[15]

Initially, to test the catalytic activity of ZrO_2 NPs in MCR, a four-component reaction of benzaldehyde, ethyl acetoacetate, hydrazine hydrate and malononitrile has been taken as a model reaction for the synthesis of 6-amino-3-methyl-4-phenyl-1,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile. When a mixture of benzaldehyde, ethyl acetoacetate, hydrazine hydrate, malononitrile and ZrO_2 NPs (10 mol %) was stirred in ethanol at room temperature the product was obtained in good yield (80%)

(entry 1, Table 1). On the other hand, no such product was obtained in absence of the ZrO_2 NPs even after 2 hours (entry 2, Table 1) stirring under same reaction conditions. To obtain better yield of product, next we have optimized the reaction conditions by changing different reaction parameters. The results were presented in Table 1. Next, screening of different solvents revealed that the ZrO_2 NPs are more effective in polar-protic solvents like ethanol, water compared to organic solvents (*e.g.* DCM, DMF, THF and CH_3CN etc). This is possibly due to the surface of the NPs more active in polar-protic solvents. It was observed that ethanol-water (6:1) mixture is the best among others tested in this study in terms of yield (95 %) and reaction time (5 min.) (Entry 3, Table 1).

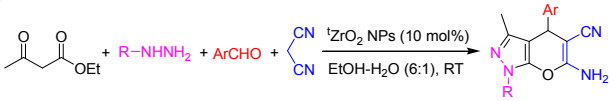
Table 1 Optimization of reaction conditions for the synthesis of pyrano[2,3-*c*] pyrazole



Entry	Catalyst	Solvent	Time (min)	Yield[a] (%)
1	$^{t}ZrO_2$ NPs	EtOH	15	80
2	No Catalyst	EtOH	120	-
3	$^{t}ZrO_2$ NPs	**EtOH-H_2O (6:1)**	**5**	**95**
4	$^{t}ZrO_2$ NPs	Solvent Free	30	50
5	ZrO_2 powder	EtOH-H_2O (6:1)	30	30
6	$^{t}ZrO_2$ NPs	H_2O	30	60
7	$^{t}ZrO_2$ NPs	EtOH-H_2O (1:1)	15	86
8	$^{t}ZrO_2$ NPs	DCM	30	40
9	$^{t}ZrO_2$ NPs	DMF	30	50
10	$^{t}ZrO_2$ NPs	THF	30	40
11	$^{t}ZrO_2$ NPs	CH_3CN	30	45
12	SiO_2-ZrO_2Cl_2	EtOH-H_2O (6:1)	60	40
13	$^{t}ZrO_2$ NPs	EtOH-H_2O (6:1)	10	65
14	$^{t}ZrO_2$ NPs	EtOH-H_2O (6:1)	5	95
15	$^{m}ZrO_2$ NPs	EtOH-H_2O (6:1)	30	40

Reaction conditions: ethyl acetoacetate (1 mmol), hydrazine hydrate (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol), catalyst (10 mol%) and solvent (2 ml) with continuous stirring at room temparature. [a] Isolated yield. [b] 5 mol% catalyst. [c] 15 mol% catalyst.$^{t}ZrO_2$ represents tetragonal ZrO_2 and $^{m}ZrO_2$ represents monoclinic ZrO_2.

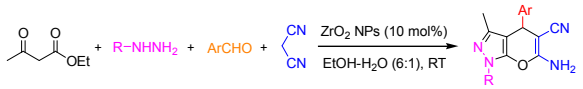
In contrast, only 50% of yield was obtained under solvent-free reaction condition (entry 4, Table 1). A further decrease in yield was observed when the reaction was carried out with bulk ZrO_2 powder (entry 5, Table 1) or monoclinic ZrO_2 (entry 15, Table 1). On the other hand, SiO_2-ZrO_2Cl_2 produced 40% yield of product (entry 12, Table 1). Similar yield was obtained when catalyst loading was increased to 15 mol% (entry 14, table 1). However, the size of the NPs did not alter the yields of the products significantly in this reaction (see ESI-3). Thus, 10 mol% of catalyst in 6:1 ethanol-water mixture proved to be the best conditions for this MCR (Scheme 2).

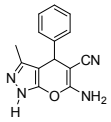
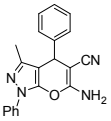
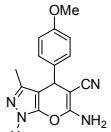
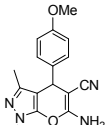
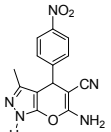
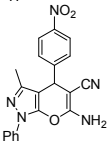
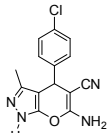
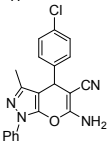
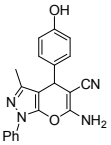
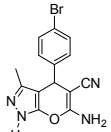
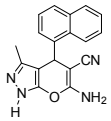


Scheme 2 One-pot multi-component synthesis of pyrano[2,3-*c*] pyrazole derivatives using ZrO_2 NPs as catalyst.

To explore the scope and generality of this MCR, next we have tried to construct a library of pyrano[2,3-*c*]pyrazole derivatives using the optimized reaction conditions.

Table 2 Synthesis of pyrano[2,3-*c*]pyrazole derivatives using ZrO_2 NPs as catalyst



Entry	R	Time (min)	Product	Yield[a] (%)	M.P. °C[b] (Lit.[Ref.])
1	H	5		95	243-245 (242-244[7n])
2	Ph	8		92	168-170 (170-172[7n])
3	H	3		98	210-212 (210-212[7n])
4	H	10		94	172-173 (172-174[7m])
5	H	2		98	250-252 (249-250[7n])
6	Ph	6		95	188-190 (189-191[7k])
7	H	4		95	232-234 (230-232[7k])
8	Ph	7		92	171-172 (173-174[7k])
9	Ph	10		90	211-212 (211-213[7k])
10	H	5		94	180-181 (178-180[7n])
11	H	5		98	222-224 (223-224[7j])

[a] Yields of isolated products. [b] Melting points were determined from pure recrystallized products.

The experimental procedure is simple[16] (See ESI-4 for details) and a variety of aryl aldehydes containing different substituent (*e.g.* $-NO_2$, –Cl, –Br, –OH, –OMe) participated in this MCR to provide the excellent yields (92-98%) of products within very short time period (2-10 min) and electronic effect of the substituent was not observed. The same MCR also proceeds with phenyl hydrazine in place of hydrazine. The results were listed in Table 2. Relatively low yields of the products were observed in case of phenyl hydrazine. This could be due to the delocalisation of lone pair of one nitrogen atom to the phenyl ring. The formation of pyrano[2,3-*c*] pyrazole derivatives was confirmed primarily by determination of melting points (See Table 2). Further, all the compounds were characterized by FT-IR and ^{1}H NMR spectroscopic data.

In general all the reactions listed in Table 4 are very fast (2-10 min.) and high yielding (92-98%). In addition, the reactions were performed in non-hazardous solvent (EtOH-H_2O) and finally, products were recrystallized from ethanol and thus purification by column chromatography has been avoided in this protocol. The catalyst, ZrO_2 NPs is non-toxic and reusable in nature. Thus, the present protocol fulfilled the criteria for green synthesis.

Next, the robustness of ZrO_2 NPs for the synthesis of pyrano[2,3-c]pyrazole was tested by investigating the effect of phase and its reusability by consulting the previous study of synergic stability and reactivity of a catalyst.[17] When the synthesis of pyrano[2,3-c]pyrazole was carried out using monoclinic-ZrO_2, (for powder XRD pattern See S5, ESI-2)[11m] a significant role of phase of the NPs was observed with marked decrease in the yield (entry 15, Table 1). The higher reactivity of tetragonal phase compared to monoclinic was also previously reported in the literature[11n,p] and observed higher activity of tetragonal phase was possibly due presence of oxygen vacancies, which are responsible for stability and higher surface activity for pure tetragonal ZrO_2.[11n-p] Finally, catalyst stability was investigated by checking reusability. After each cycle the ^{t}ZrO_2 NPs were recovered by centrifugation, washed with hot methanol, dried and reused for subsequent reactions. The results were presented in Fig. 5. It was observed that even after 10th cycle the catalytic efficiency was intact and marginal (15 %) loss in activity was observed.

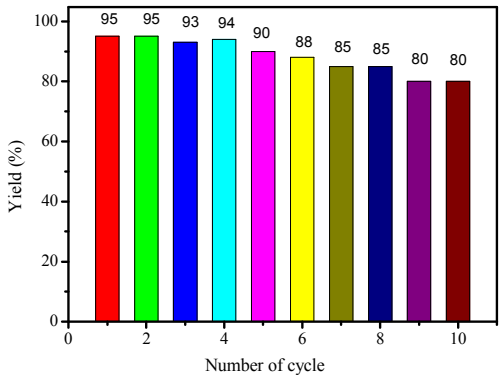


Figure 5 Reusability of ZrO_2 NPs for the synthesis of 6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile as model reaction.

This loss of catalytic activity is possibly due the deactivation of the active surface -OH groups of ZrO_2 NPs. To realize this speculation of catalyst deactivation, FT-IR spectra of fresh and reused ZrO_2 NPs have been recorded and a significant decrease in intensity of peaks corresponding to surface hydroxyl groups were observed in the FT-IR spectra of reused ZrO_2 NPs compared to fresh one (see Fig. S8, ESI-7). However, powder XRD study of reused ZrO_2 NPs reveals that the tetragonal phase of the NPs remained intact which was confirmed (See Fig. S6, ESI-6).

In order to compare the catalytic activity of ZrO_2 NPs for this MCR, a comparative study of catalytic performance is presented in Table 3 for the synthesis of 6-amino-3-methyl-4-phenyl-1,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile.

Table 3 Comparative results of catalysts for the synthesis of pyrano[2,3-*c*]pyrazole derivatives

Entry	Catalyst[Ref.]	Reaction conditions	Time (min)	Yield (%)
1	**ZrO_2 NPs[a]**	**10 mol%; EtOH-H_2O (6:1); rt**	**5**	**95**
2	Et_3N[7a]	20 mol%; EtOH; reflux	15	65
3	Piperidine[7b]	5 mol%; H_2O; rt	10	83
4	L-Proline[7d]	10 mol%; H_2O; reflux	10	90
5	Meglumine[7j]	10 mol%; EtOH-H_2O (9:1), rt	15	95
6	γ-Alumina[7m]	30 mol%; H_2O; reflux	50	80
7	[Bmim]OH[7g]	20 mol%; 50-60^{o}C	10	88
8	[Dsim]$AlCl_4$[7i]	7 mol%; neat; 80^{o}C	1	90
9	SnO_2 QDs[7n]	8 mol%; H_2O; rt	150	93

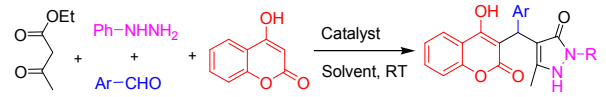
[a] Present work

As demonstrated in Table 3, most of the catalysts are able to produce satisfactory yield but some of them required drastic reaction conditions (*e.g.* refluxing or high temperature). Moreover, many of the catalysts are toxic *N*-containing bases (entry 2-5, 7 and 8, Table 3) and are not reusable in nature (entry 2 and 3) creating the synthetic protocols more environmentally malignant and expensive. Thus, the present ZrO_2 NPs is better alternative to the previously reported catalysts in the perspective of reaction time, yield of product and of course green chemistry point of view for the construction of biologically important pyrano[2,3-*c*]pyrazole scaffold.

The excellent catalytic efficiency of tetragonal ZrO_2 NPs in the synthesis of pyrano[2,3-*c*]pyrazoles motivated us to explore its efficacy for the synthesis of bio-active highly functionalized benzylpyrazolyl coumarin derivatives. We found that ZrO_2 NPs provided excellent yield of benzylpyrazolyl coumarin, 4-[(4-hydroxy-2-oxo-2H-chromen-3-yl)-phenyl-methyl]-5-methyl-2-phenyl-1,2-dihydro-pyrazol-3-one (Table 5, entry 1) by the one-pot MCRs of benzaldehyde, phenyl hydrazine, ethylacetoacetate and 4-hydroxycumarin within practical time. The results for the optimization of reaction conditions for the synthesis 4-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-phenyl-methyl]-5-methyl-2-phenyl-1,2-dihydro-pyrazol-3-one are given in Table 4. The optimized yield was obtained in ethanol-H_2O (1:1) medium and using 10 mol% ZrO_2 NPs (entry 2, Table 4). The reaction without ZrO_2 NPs has not provided the product even after 2 hrs under same conditions (entry 1, Table 4).

Using the optimized reaction conditions, in as simple experimental procedure[18] several benzylpyrazolyl coumarin derivatives were prepared and the results are presented in Table 5. After the reaction solid product was dissolved in hot ethanol and NPs were separated by centrifugation and crystalline product was obtained.

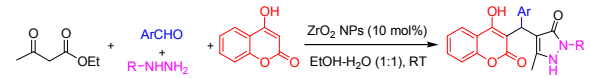
Table 4 Optimization of reaction conditions for the synthesis of benzylpyrazolyl coumarin using ZrO_2 NPs as catalyst

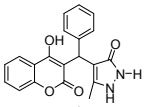
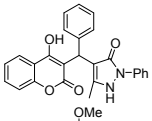
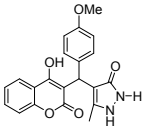
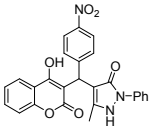
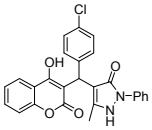
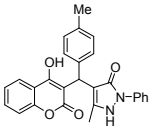


Entry	Catalyst	Solvent	Time (min)	Yield[a] (%)
1	No Catalyst	EtOH-H_2O (1:1)	120	-
2	**ZrO_2 NPs**	**EtOH-H_2O (1:1)**	**5**	**92**
3	ZrO_2 NPs	EtOH	15	76
4	ZrO_2 NPs	H_2O	20	80
5	ZrO_2 NPs	DCM	30	40
6	ZrO_2 NPs	DMF	30	44
7	ZrO_2 NPs	CH_3CN	30	52
8	ZrO_2 NPs	Solvent Free	10	61
9	ZrO_2 NPs[b]	EtOH-H_2O (1:1)	10	74
10	ZrO_2 NPs[c]	EtOH-H_2O (1:1)	5	87

Reaction conditions: ethyl acetoacetate (1 mmol), phenyl hydrazine (1 mmol), benzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), [t]ZrO_2 NPs (10 mol%) and solvent (2 ml) with continuous stirring at room temparature. [a] Isolated yield. [b] 5 mol% catalyst. [c]15 mol% catalyst.

Table 5 [t]ZrO_2 NPs catalyzed synthesis of benzylpyrazolyl coumarin derivatives

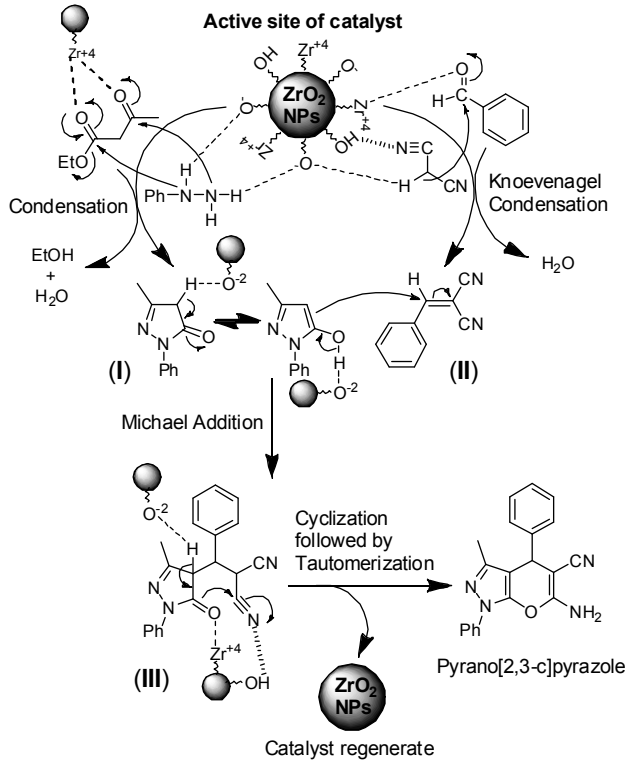


Entry	R	Time (min)	Product	Yield[a] (%)	M.P. [o]C[b] (Lit.[Ref.])
1	H	4		93	229-230 (231-233[8])
2	Ph	5		92	231-233 (232-234[8])
3	H	5		95	201-203 (202-204[8])
4	Ph	2		97	250-251 (248-250[8])
5	Ph	5		96	230-231 (227-229[8])
6	Ph	7		95	223-224 (224-224[8])

7[a] Yields of isolated products. [b] Melting points were determined for the pure recrystallized products.

The formation of products was initially confirmed by checking their melting points followed by spectroscopic (FT-IR, ^{1}H NMR) studies. This present protocol offered several advantages over its first report by Das *et al.*[8] using glacial acetic acid such as less reaction time (2-7 min.), use of non-toxic and heterogeneous ZrO_2 NPs as catalyst etc. Thus, this protocol using ZrO_2 NPs is better and green alternative to that of previous report using glacial acetic acid.

We speculated that the surface of ZrO_2 NPs plays an important role in this MCR for the synthesis of pyrano[2,3-*c*]pyrazoles. The surface of ZrO_2 NPs possibly contains active hydroxyl, oxide and Zr^{+4} which are well reported in the literature[11o] to act as Lewis acid-base. A plausible mechanism for the ZrO_2 NPs catalyzed synthesis of pyranopyrazole derivatives has been presented in Scheme 3. The formation of pyrano[2,3-*c*]pyrazole derivative, namely, 6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile proceeds *via* the simultaneous formation of two intermediates, pyrazolone (I) *via* cyclo-condensation and 2-phenylidene-malononitrile (II) by Knoevenagel reaction which were promoted by ZrO_2 NPs as shown in Scheme 3.



Scheme 3 Plausible mechanism for ZrO_2 NPs catalyzed synthesis of 6-amino-3-methyl-1,4-diphenyl-1,4-dihydro- pyrano[2,3-*c*]pyrazole-5-carbonitrile.

Subsequently, the intermediates I and II underwent Michael type addition to give enolate intermediate III *via* the activation of I by Lewis basic (O^-) site of NPs. Finally, the Lewis acidic and basic sites of NPs facilitated intra-molecular electrophilic cyclization followed by tautomerization affording the desired pyrano[2,3-c]pyrazole derivative. To establish the proposed mechanism, we have performed the synthesis of pyrano[2,3-*c*]pyrazole step by step using ZrO_2 NPs. In this context, separately, we have synthesized two intermediates I and II

separately from the respective starting materials using ZrO_2 NPs as catalyst. Finally, mixing of two intermediates in presence of ZrO_2 NPs produced desired pyrano[2,3-*c*]pyrazole derivative. The intermediates were confirmed by their melting point determination and UV-Vis spectroscopic studies. The melting point values are in well-accordance with those of reported values. The melting points of pyrazolone (I) was determined to be 128-129 °C (reported[17]: 127 °C) and intermediate II was 82-84 °C (reported[10n]: 85 °C). The formation of these intermediates was further confirmed by ^{1}H NMR (See ESI) and UV-Vis studies. The ^{1}H NMR data were consistent with reported values.[11n, 19] The UV-Vis spectra of two intermediates are given in Fig. 6. The observed λ_{max} value (246 nm) of pyrazolone (I) is also close to values reported in the literature.[19]

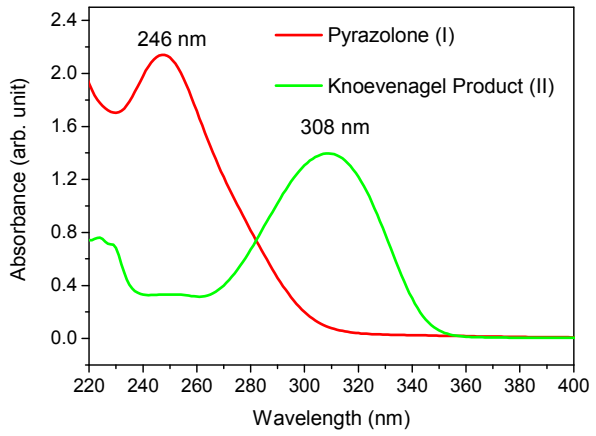


Figure 6 UV-Vis spectra of intermediate I and II.

Conclusions

In conclusion, a facile one-pot multicomponent protocol has been demonstrated for the synthesis of bio-active pyrano[2,3-*c*]pyrazole and highly functionalized benzylpyrazolyl coumarin derivatives at room temperature using ZrO_2 NPs as catalyst. The present work has several attractive features such as, (i) prepared uncapped ZrO_2 NPs are purely tetragonal in nature (size ~ 17 nm), (ii) ZrO_2 NPs showed superior catalytic performance with respect to reaction time (~10 min.) and high isolated yields of products (92-98%) in comparison to the literature reported catalysts, (iii) this is first report of synthesis of biologically important benzylpyrazolyl coumarin derivatives using a heterogeneous and green catalyst (the synthesis of this moiety was first reported by Das *et al.* using glacial acetic as catalyst[8]), (iv) the catalytic activity and tetragonal phase of ZrO_2 NPs remained unchanged even after 10th cycle, (v) the tetragonal ZrO_2 NPs were found to more active than monoclinic one and finally (vi) the present protocol is environment benign in nature as the catalyst is non-toxic and reusable, reactions were performed at room temperature in a green solvent (water-ethanol), products were purified by re-crystallization from ethanol and separation by column chromatography was not required by this method and thus use of volatile and hazardous solvents has been avoided. We hope that ZrO_2 NPs will find more applications in MCRs leading to biologically potent molecules in near future.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Preparation of catalyst, UV-Vis spectra of fresh ZrO_2 NPs, particle size distribution using DLS and TEM studies, powder XRD of monoclinic ZrO_2 NPs, General experimental procedure for the synthesis of pyrano[2,3-*c*]pyrazole and benzylpyrazolyl coumarin derivatives, effect of size on the yield of the reaction for the preparation of compounds pyrano[2,3-*c*]pyrazoles derivative, comparison of FT-IR spectra of fresh and reused ZrO_2 NPs, copies of ^{1}H NMR and FT-IR spectra of selected compounds are available in supplementary information]. See DOI: 10.1039/c000000x/

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16 *Representative experimental procedure for the preparation of 6-amino-3-methyl-4-(4-phenyl)-1,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile using ZrO_2 NPs as catalyst (entry 1, Table 3):* A mixture of hydrazine hydrate (1 mmol, 50 mg), ethyl acetoacetate (1 mmol, 130 mg), benzaldevhyde (1 mmol, 106 mg), malononitrile (1 mmol, 66 mg) and ZrO_2 NPs (10 mol%, 12.4 mg) in 2 ml ethanol-H_2O (6:1) was stirred at room temperature for 5 minutes until the reaction mixture solidified (monitored by TLC). After completion of the reaction, solvent was removed under reduced pressure from the reaction mixture sequentially the solid crude product was stirred with 5 ml methanol at 60 ^oC for 5 min followed by separation of the catalyst by centrifugation. Then methanol was removed under reduced pressure and the solid compound was purified by recrystallization from absolute ethanol without using any column chromatography to give pure 6-amino-3-methyl-4-(4-phenyl)-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile (yield 95%, 240 g). The compound was identified by checking melting point (observed m.p.-243-245^oC, reported m.p. 242-244 ^oC[7n]) and then further characterized by FT-IR and ^1H NMR studies.

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18 *Representative experimental procedure for synthesis of 4-((4-chlorophenyl)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-1,2 dihydro-5-methyl-2-phenylpyrazol-3-one (entry 5, Table 5):* A mixture of phenyl hydrazine (1 mmol, 108 mg), ethyl acetoacetate (1 mmol, 130 mg), 4-chlorobenzaldehyde (1 mmol, 141 mg), 4-hydroxycoumarin (1 mmol, 163 mg) and ZrO_2 NPs (10 mol%, 12.4 mg) in 2 ml ethanol-H_2O (1:1) was stirred at room temperature for 5 min. until the reaction mixture solidified (monitored by TLC). After completion of the reaction, solvent was removed under reduced pressure from the reaction mixture sequentially the solid crude product was stirred with 5 ml methanol at 60 ^oC for 5 min. followed

by the catalyst was separated by simple filtration. Then methanol was removed under reduced pressure and the solid compound was purified by recrystallization from absolute ethanol without using any column chromatography to give pure 4-((4-chlorophenyl)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-1,2-dihydro-5-methyl-2-phenylpyrazol-3-one (yield 96%, 441 mg). The product was identified by melting point determination (observed: 230-231^{o}C, reported: 227-229 ^{o}C[8]) and then further characterized by FT-IR and ^{1}H NMR studies.

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Graphical Abstract

One-pot multicomponent synthesis of highly functionalized bio-active pyrano[2,3-c]pyrazole and benzylpyrazolyl coumarin derivatives using ZrO_2 nanoparticles as reusable catalyst †

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Here, a facile one-pot multicomponent protocol for the synthesis of biologically important pyrano[2,3-c]pyrazole and benzylpyrazolyl coumarin derivatives has been demonstrated using ZrO_2 nanoparticles as catalyst at room temperature. The reactions are very fast and high yielding. The catalytic activity and tetragonal plane of ZrO_2 nanoparticles remained unchanged after 10^{th} cycle.