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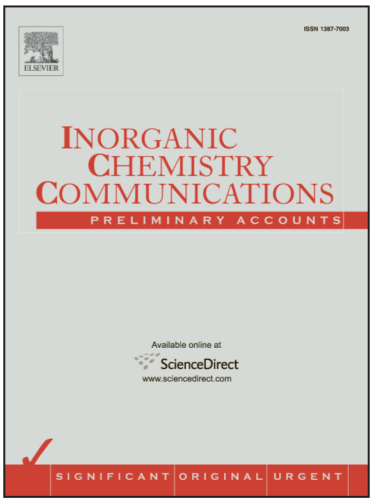

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MnO_2 on Hydroxyapatite: A green heterogeneous catalyst and Synthesis of pyran-carboxamide derivatives

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Abstract

Three different loadings of MnO_2 on hydroxyapatite (MnO_2/Hap) were synthesized and the hydroxyapatite supported MnO_2 materials were characterized by several analytical techniques including FT-IR, P-XRD, TEM and SEM analysis. 3% MnO_2/HAp material proved highly efficient catalyst for the synthesis of a series of ten pyran-carboxamide derivatives (yield 91-98 %) in aqueous medium at room temperature (RT) conditions, via one-pot multi-component reaction, of which nine were new moieties. The prominent features of the protocol are excellent yields, high atom efficiency, short reaction times (15 min), recyclable catalyst and no need for column separation.

Keywords: Hydroxyapatite; Reusable catalyst; Lewis acid sites; Multi component reaction; atom efficiency; Green synthesis.

Introduction

In recent years, the use of multicomponent reactions (MCRs) have gained prominence to synthesize compound collections in the field of biological, pharmaceutical and combinatorial chemistry [1-3], due to their proficiency to react three or more reactants, to achieve the target molecule in one-pot process. MCRs indicate a very potent process, from both cost and synthetic prospective [4]. Further, MCRs have many benefits such as green procedures, high atom efficacy

and easy to do drug discovery process [5]. Short reaction times, easy workup procedure, simple reaction conditions, efficient product selectivity and good to excellent yields are the other advantages of MCRs [6].

With increasing green perception in organic research and chemical industry, the challenges for viable benign and safe procedures that decrease or eradicate waste production and restrict the use of toxic solvents and reagents are growing [7, 8]. In recent past, significant growth was recorded in use of heterogeneous catalysts for different heterocyclic conversions in the MCRs and in green reaction protocols. This was mainly due to distinct chemical and physical properties of the catalyst materials, such as eco-friendliness, compatibility, cost-effectiveness, non-volatility, non-inflammability, good thermal stability, operational simplicity, mild reaction conditions, ease of isolation, reusability, non-hazardous and good activity [9, 10]. Calcium phosphate hydroxyapatite (HAp = $Ca_{10}(PO_4)_6(OH)_2$) is one of the effective materials, which displays good affinity and high stability, with variety of applications [11]. HAp draws attention because of its potential effectiveness in biomaterials, bio-ceramics, adsorbents, and ion-exchangers [11-13]. Recently, a new approach for the design of high-performance heterogeneous catalysts employing HAp as a macro-ligand for catalytically active centers was revealed [14]. HAp possesses many advantages such as (i) nonporous construction that can support to subdue the difficulties to mass alteration and (ii) weak acidic–basic possessions diminishing side-reactions influenced by the support. Here, we report the preparation of new hydroxyapatite supported metal catalysts and their utility in the synthesis of carbon–carbon bond developing reactions.

Ample attention has been paid to the preparation of different heterocyclic moieties [15-18]. Amongst the several heterocycles, the pyran ring structure received substantial attention because of its noticeable biological and pharmaceutical activity. Interestingly, the pyran and their derivative scaffolds gained importance in the field of drug discovery, due to their activity as efficient protein kinase inhibitors, which is one of the vital areas in the improvement of chemotherapeutic agents [19]. Further, pyrans exist as crucial subunits in various drug constituents, with a wide range of biological properties, including cytotoxic [20], anticancer [21], anti-inflammatory [22], analgesic [23], anticonvulsant [24], anti-proliferative [25], antifungal [26] and antimicrobial activities [27]. Thus, pyran scaffolds have established as privileged units in heterocyclic chemistry and also most essential pharmacophore in drug chemistry. In the recent years, several procedures have been developed for the preparation of this type of compounds. The

reported methods employed different catalysts, MgO [28], piperidine [29], nano SiO_2 [30], Mg/La metal oxides [31], D,L-proline [32], 4-(dimethylamino)-pyridine (DMAP) [33], tetrabutylammonium fluoride [34] etc. Although, these approaches are attractive, they suffer from one or more disadvantages such as inadequate availability of reagents, expensive, non-recyclable or toxic catalysts, need for high temperatures or prior purifications, low reaction rates, use of toxic solvents, low yields, and tedious work-ups. Therefore, taking into consideration the limitations in those reports, in this communication, we submit the scope of MnO_2 supported hydroxyapatite as an efficient recyclable catalyst for the synthesis of pyran-carboxamide derivatives at room temperature with water as solvent. As a part of our investigations to develop swift reactions under mild and green conditions, we earlier have reported various heterogeneous catalysts for synthesis of series of different heterocyclic moieties [35-39].

Experimental section

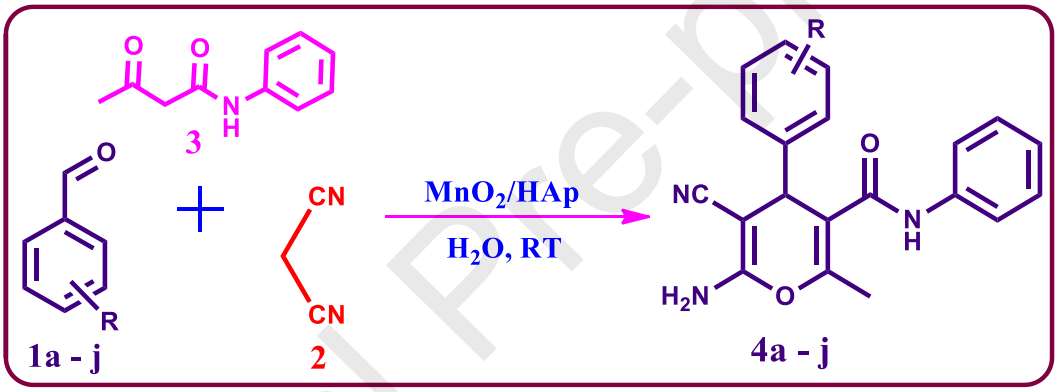
Catalyst Preparation:

A co-precipitation method was adopted to synthesize Ca-hydroxyapatite (HAp). In a typical procedure, the calcium nitrate tetra hydrate solution, $Ca(NO_3)_2.4H_2O$ (23.7 g) (0.167 mol) in 250 mL distilled water was adjusted to a pH 11 using concentrated ammonium solution. The pH of the diammonium hydrogen orthophosphate solution (5.6 g) (1.00 mol) was also adjusted to 11 with concentrated ammonia solution. Thereafter, both the solutions were separately diluted with 250 mL of distilled water. Under constant and vigorous stirring, a solution of diammonium hydrogen orthophosphate was drop-wise added to the $Ca(NO_3)_2.4H_2O$ solution over a period of 2 h and throughout the reaction, the mixture was maintained at pH 11 with help of ammonia solution. The obtained milky white gelatinous precipitate was heated for 40 min and the precipitate brought to room temperature. Afterwards, the white precipitate was filtered under vacuum and washed thoroughly with deionizer water and dried at hot air oven and calcined at 500°C for over six hours in presence of air. The prepared HAp metrical was characterized by XRD and FT-IR techniques (Figures S1 and S2 in supporting information, ESI). A wet impregnation technique was used for synthesis of the HAp supported metal catalysts. The required amount of prepared and calcined HAp was dispersed in 200 mL of distilled water under vigorous stirring. Afterwards, the desired amounts of manganese oxide (Sigma Aldrich, XRD in ESI) was added based on the requisite equivalent weight amounts. Then, the resultant slurry was evaporated under constant stirring and the mixture was dried at 100-120 °C for overnight in an oven. Materials with various weight

percentages (1, 3 and 5% w/w) of the MnO_2 on HAp were prepared and subsequently calcined at 450°C for five hours.

Synthesis of pyran-carboxamide derivatives: General Procedure

Aromatic aldehyde one equivalent, malononitrile 1.1 equivalent acetoacetanilide one equivalent and MnO_2/HAp (50 mg) were dissolved in 10 mL of aqueous solvent in a clean flask. Then the reaction mixture was stirred for 15-20 min at RT (scheme 1). Using TLC, the reaction progress was monitored. After completion of the reaction, the solid catalyst was separated from the mixture by simple filtration and washed with water, then dried for further reuse. To reaction product that extracted into ethyl acetate, anhydrous Na_2SO_4 was added for drying. Further, to obtain the pure target molecules, ethyl acetate was removed under reduced pressure (4a-j).



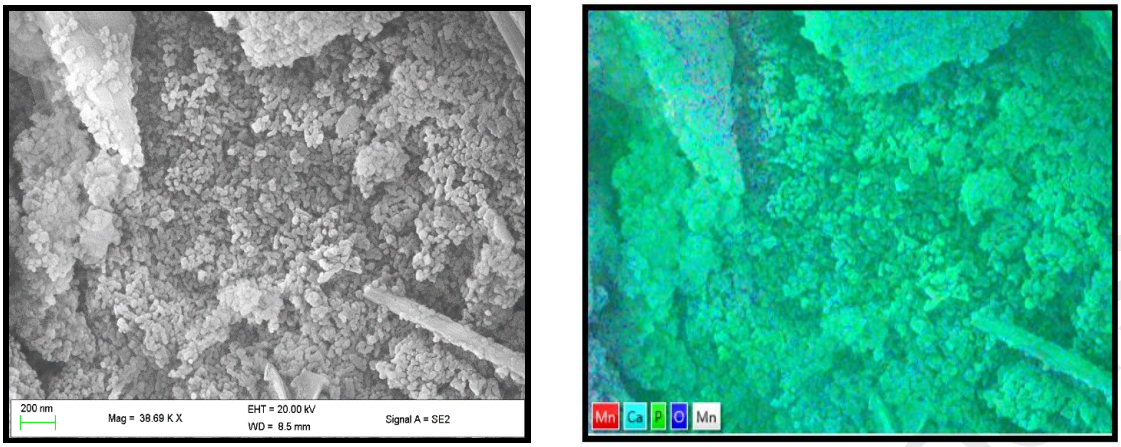
Scheme 1: Three-component green synthetic route for pyran carboxamide derivatives

Result and discussion

SEM & TEM analysis:

Fig. 1 and Fig. 2 illustrate the SEM and TEM morphological profiles respectively of 3% MnO_2/HAp calcined catalyst. An observation of the SEM (Fig. 1a and 1b) images reveal the unequal cube-like shapes of the catalyst material. Some agglomeration was detected, which probably owes to the manganese loading. Further, it can be observed that the dimensions of the average particles were of the order of 23 nm. SEM–EDX (Fig. 1c) image indicates that manganese was homogenously dispersed on the surface of the hydroxyapatites. The TEM micrograph shows black crystalline oval-shaped particles of dimension ranging from 45-59 nm (Fig 2) on the material surface. No extreme variation was perceived on the morphology of the used catalyst.

1 (a) 1(b)



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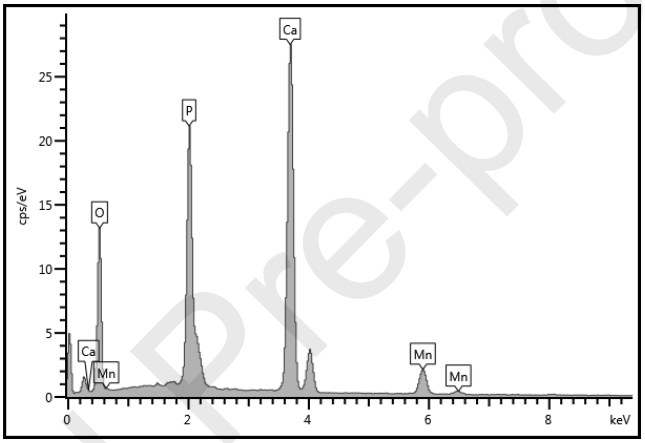


Figure 1: (a) SEM micrograph (b) elemental mapping and(c) EDS spectrum of of 3% MnO_2/HAp catalyst.

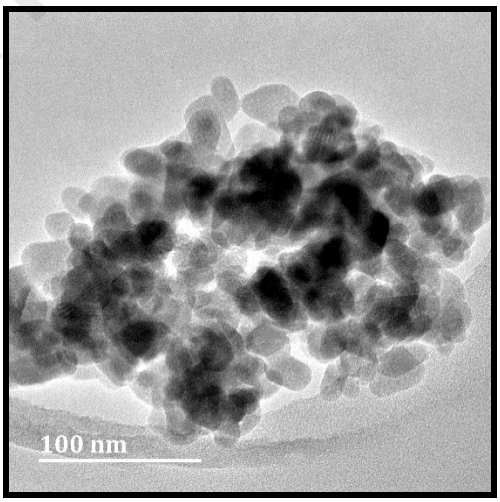


Figure 2: TEM micrograph of 3% MnO_2/HAp catalyst.

P-XRD study:

Figure 3 illustrates the XRD patterns of the MnO_2-HAp complex and the pure crystalline structure of the hydroxyapatite can be seen in the diffraction patterns. This diffraction patterns were correlated with the JCPDC file no. 09-432 for HAp and JCPDC file no. 44-0141 for MnO_2. The intensity planes (310), (300) and (002) were allotted to MnO_2 and other diffraction peaks were attributed to HAp. The higher intensity planes (002), (211), (300), (310), (222) and (213) altered significantly with the standard HAp phase. The additional MnO_2 concentration did not impact much distortion in HAp phase. This is attributed that the reactants proportions were well-interacted to afford the MnO_2-HAp composite.

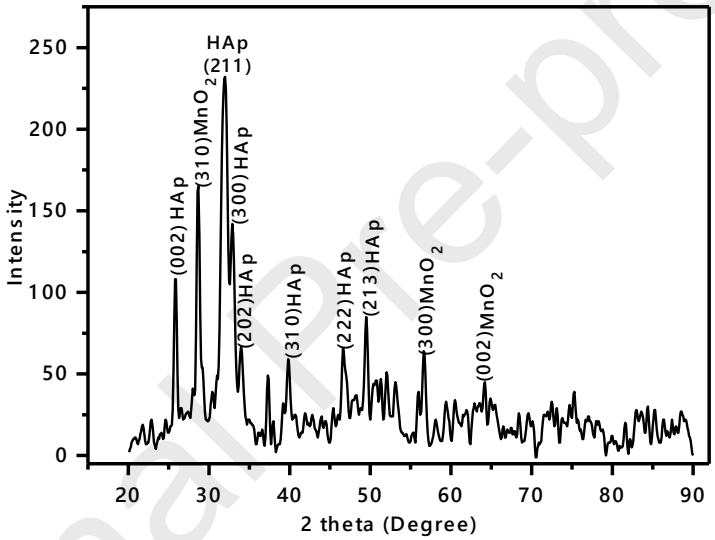


Figure 3. Powder XRD diffractogram of 3% MnO_2/HAp catalyst

Pyridine IR analysis

The nature of acidic sites on the prepared 3% MnO_2-HAP surface was examined by employing ex-situ pyridine FT-IR spectroscopy (Figure 4). The prominent band at 1448 cm^{-1} confirms the presence of Lewis acidic sites (L) on the surface of catalyst, suggesting that prepared material has Lewis acidic character. The Lewis acidic sites on the surface were due to the Ca^{2+} and phosphorous of PO_4 and the vacant metal orbitals, so that it is capable to attack the electron rich site to accept electron pairs.

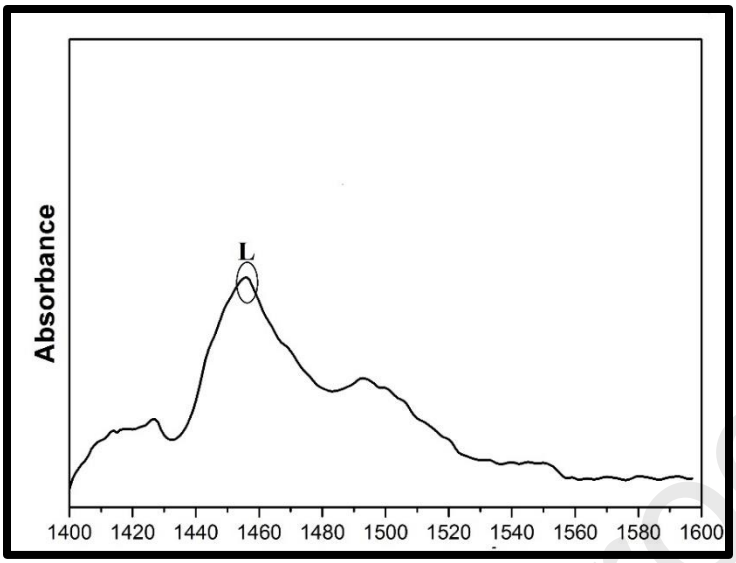


Figure 4: Pyridine IR spectrum of 3% MnO_2/HAp catalyst.

Optimization:

To achieve good efficiency in the production pyran-carboxamides, the title reaction was investigated under different reaction conditions including comparing the efficacy of different catalyst materials, solvents and temperature conditions.

To improve the reaction performance, a series of investigations were carried out using the model reaction of 2-methhoxybenzaldehyde, malononitrile and acetoacetanilide in absence and presence of catalysts, under varied temperatures and solvent systems. The results obtained are summaries in Table 1. In absence of any catalyst, no reaction was perceived for 24 h, under R.T. or reflex conditions (Table 1 entry 1 & 2). Using basic catalysts such as sodium hydroxide, pyridine, triethylamine, potassium carbonate and urea in aqueous media, no reaction occurred at R.T. event after 12 h (Table 1 entry 3-7). The presence of ionic liquid catalysts, such as 1-Butyl-3-methylimidazolium tetrafluoroborate and N-heterocyclic carbene gave a very small amount of the product at R.T. (Table 1, entries 8 & 9). By employing various acidic catalysts, namely, tetrafluoroboric acid, acetic acid and p-toluenesulfonic acid in aqueous solution at R.T. only low yields were perceived (Table 1, entries 10–12). Further, the model reaction was screened with various solid materials (MnO_2, SiO_2, Al_2O_3, HAp and hydrotalcites (HTAl) as catalysts in water, which showed moderate to good yields after 1 h (Table 1, entries 13-17). Among the various solid catalysts tested, MnO_2 and HAp offered better results with higher product yields. From the encouraging response with MnO_2 and Hap as catalysts, to enhance the reaction efficiency by

harvesting the synergic effect of the two, materials with different loadings of MnO_2 on HAP were prepared and efficacy of the 1% MnO_2/HAp, 3% MnO_2/HAp and 5% MnO_2/Hap materials as catalysts was assessed, and all the reactions gave excellent yields (89-98%) at R.T. in short reaction time of 15 min (Table 1, entries 18-20). Although, all the three mixed oxide catalysts offered small particle sizes, more surface than the single oxide homologues, among the three loadings of MnO_2, the 3% MnO_2/supported hydroxyapatite catalyst showed higher activity.

Table 1: Optimization for the synthesis of **4a** by 3% MnO_2/HAp catalyst[a]

Entry	Catalyst	Solvent	Condition	Time / h	Yield / %
1	--	--	RT	24	--
2	--	--	Reflux	24	--
3	NaOH,	H_2O	RT	12	--
4	pyridine	H_2O	RT	12	--
5	TEA	H_2O	RT	12	--
6	K_2CO_3	H_2O	RT	12	--
7	Urea	H_2O	RT	12	--
8	[Bmim][BF_4]	H_2O	RT	8.0	11
9	[NHC][BF_4]	H_2O	RT	10	09
10	HBF_4,	H_2O	RT	5.5	18
11	AcOH	H_2O	RT	4.5	22
12	PTSA	H_2O	RT	4.0	15
13	MnO_2	H_2O	RT	1.0	76
14	SiO_2	H_2O	RT	2.5	54
15	Al_2O_3	H_2O	RT	3.0	48
16	HAp	H_2O	RT	1.0	80
17	HTal	H_2O	RT	3.5	68
18	1% MnO_2/HAp	H_2O	RT	0.75	91
19	3% MnO_2/HAp	H_2O	RT	0.25	98
20	5% MnO_2/HAp	H_2O	RT	0.50	96

[a] All products were characterized by ^{1}H-NMR, ^{15}N NMR, ^{13}C-NMR and HRMS spectral analysis.
[b] Isolated yields.
-- No reaction

To optimize the solvent system for the reaction for target molecule (4a), reactions were investigated using THF, dioxane, CH_3CN, DCM, DMSO, CH_3OH, C_2H_5OH and H_2O as solvents in presence of 3 mol% MnO_2/HAp at R.T. The results compiled in Table 2 show that with non-polar solvent, n-hexane facilitated no reaction, however low yields were afforded using various other polar aprotic solvents like THF, dimethylformamide, CH_3CN and DCM (Table 2). Further, the reactions in CH_3OH and C_2H_5OH provided better yields than those with the other organic solvents, but best result was with H_2O.

Table 2: Optimization of different solvent conditions[a]

Entry	Solvent	Reaction time / min	Yield / %
1	n-Hexane	120	--
2	THF	60	23
3	Dioxane	60	27
4	CH_3CN	50	32
5	DCM	45	25
6	CH_3OH	30	72
7	C_2H_5OH	30	84
8	H_2O	15	98

[a]Reaction conditions: aromatic aldehyde one equivalent malononitrile one equivalent and acetoacetanilide one equivalent, catalyst (50 mg) and H_2O (10 mL) as solvent were stirred at R.T.

To improve the efficacy of the reaction, the optimized reaction was investigated with different amounts of the 3% MnO_2/HAp (Table 3). With lower amount of catalyst, the reaction times got prolonged and yields were lowered. An increase for catalyst amount from 20 mg to 50 mg not only reduced the reaction time, but also improved the product yield from 90% to 97%. However, the use of 60 mg of catalyst, reaction time remained unaffected, but the yield was marginally reduced to 95%. Therefore, 50 mg MnO_2/HAp was considered as ideal amount to catalyze the reaction under chosen conditions.

Table 3: Optimization of the amount of 3% MnO_2/HAp as catalyst in the model reaction[a]

Entry	Catalyst	Time (min)	Yield (%)
1	10	60	85
2	20	50	90
3	30	45	92
4	40	30	94
5	50	20	98
6	60	20	95

[a]Reaction conditions: aromatic aldehyde one equivalent malononitrile one equivalent and acetoacetanilide one equivalent catalyst and H_2O (10 mL) solvent were stirred at R.T.

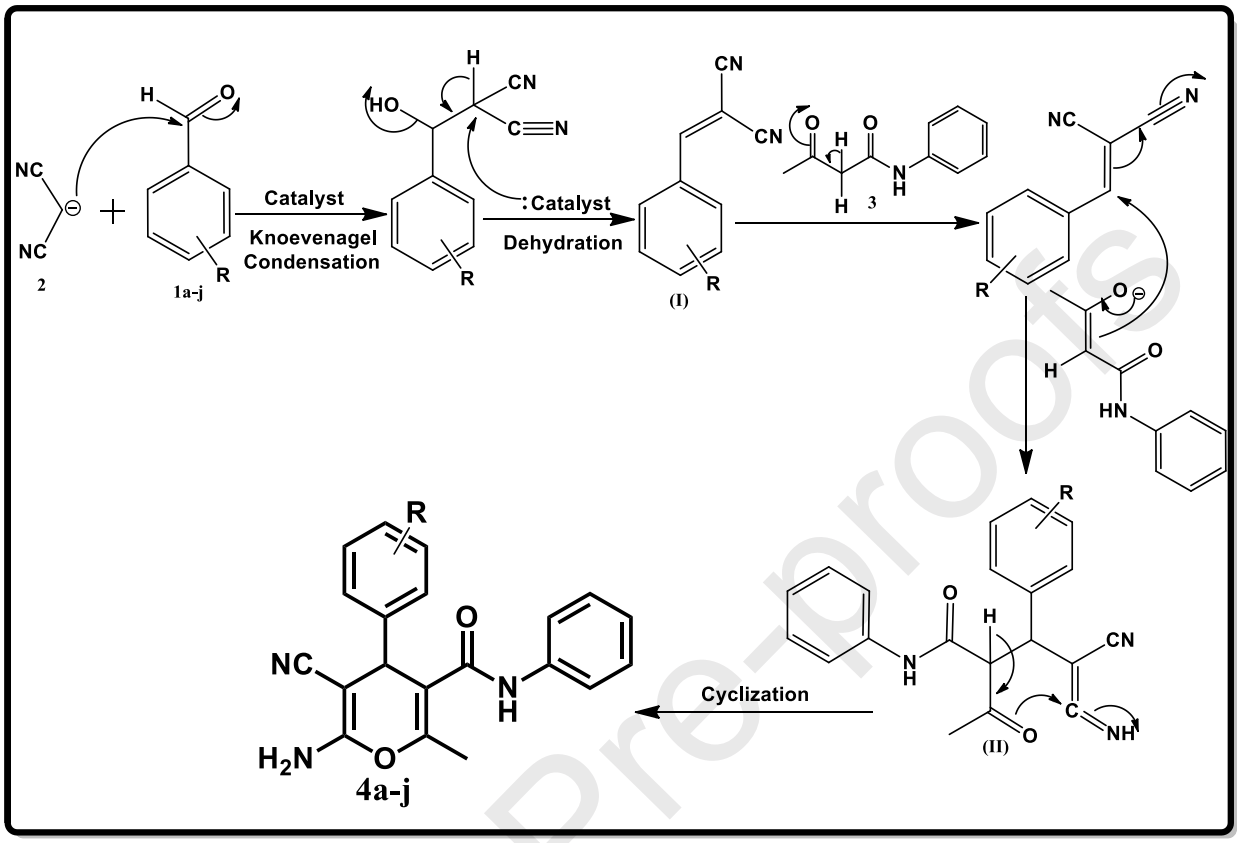
To broaden the scope of the title reaction, reactions were conducted using different aldehydes containing different electron donating and withdrawing substituents. Nine new derivatives (4a–j) were synthesized under otherwise similar reaction conditions as for 4a (Table 4). All the substituted aldehydes, both with electron-donating or electron-withdrawing groups reacted effectively to generate the corresponding target molecules with excellent yields. All structural assignments of these novel molecules were confirmed by ^{1}H NMR, ^{13}C NMR, ^{15}N NMR and HRMS spectral analysis. All the instrumentation and spectral details are incorporated in (ES1-II)

Table 4: Synthesis of pyran-carboxamides catalyzed by 3% MnO_2/HAp catalyst

Entry	R	Product	Yield (%)	Mp ºC
1	2-MeO	4a	98	159-161
2	2,3-$(OMe)_2$	4b	94	204-205
3	3-Br	4c	91	189-190
4	3-Cl	4d	90	221-223
5	2,5-$(OMe)_2$	4e	96	209-210
6	4-Et	4f	92	232-233
7	2,4,6-$(OMe)_3$	4g	92	197-198
8	3,4,5-$(OMe)_3$	4h	94	217-218
9	4-$N(Me)_2$	4i	96	199-201
10	3-Meo	4j	92	165-167

-- New compounds/no literature available.

A probable reaction mechanism for the generation of pyran-carboxamides is proposed as presented in Scheme 2. With primary condensation of aromatic aldehyde and malononitrile on the surface of MnO_2 loaded hydroxyapatite, leads to the formation benzylidenemalnonitrile intermediate (I). Further, the Michael addition of phenylbutnamide to the intermediate followed by intra-molecular cyclization, the second intermediate (II) is produced. Finally, the cyclization of (II) affords the final product, 6-amino-5-cyano-2-methyl-*N*,4-diphenyl-4H-pyran-3-carboxamide derivatives.



Scheme 2: Plausible reaction mechanism for the formation of pyran-carboxamide derivatives.

Recyclability

This is noteworthy to emphasize that recyclability of the catalyst is a significant feature of heterogeneous catalysis. The used Mn/HAp catalyst was separated from reaction mixture by filtration after each reaction. The recovered material washed with DCM several times, and dried in a vacuum oven at 80°C for period of two hours to reuse in consequent reactions. The collected catalyst was recycled at least six additional times in successive reactions without any significant loss in product yield.

Conclusion

In this communication, we reported a detailed mechanistic investigation for synthesis of novel pyran-carboxamide derivatives, through one-pot MCR using MnO_2/HAp as reusable catalyst with water as solvent at R.T. giving excellent yields. The attractive features of this protocol are high atom efficacy, short period of time, green solvent, cost-effective reagents, easy operational workup procedure, simple separation, higher yields and reusable catalyst. The above-mentioned

benefits make this procedure green and valid for industrial, pharmaceutical as well as other academic applications.

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Highlights

- 3% MnO_2/HAp as highly efficient heterogeneous catalyst
- Three component one-pot synthesis in water
- Nine new pyran-carboxamide derivatives
- Excellent yields (91-98%) in short reaction times (15 min).

MnO_2 on Hydroxyapatite: A green heterogeneous catalyst and Synthesis of pyran-carboxamide derivatives

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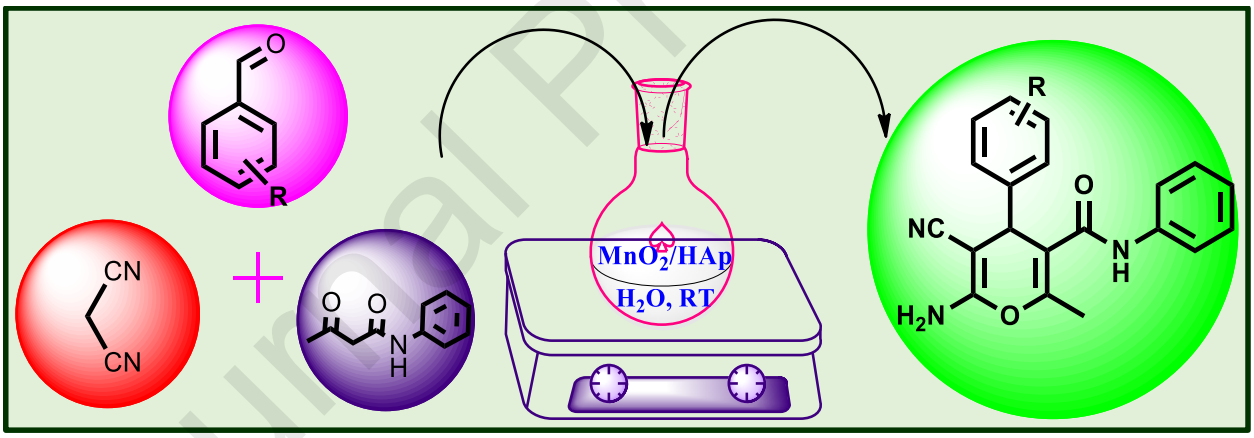

Conflict of interest statement

All the author hereby declare that we have no conflict of interest and no funding is received for this research. This work is unpublished and solely submitted to this journal

We here by certify that all authors have seen and approved the final version of the manuscript being submitted. This work is our original work, hasn't received prior publication and isn't under consideration for publication elsewhere.