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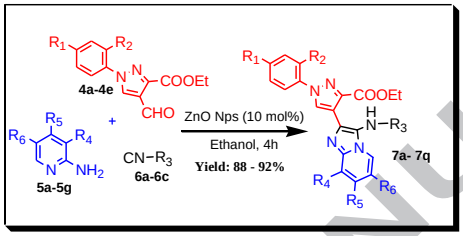

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ABSTRACT

An efficient, simple, environmentally benign synthetic protocol is developed for synthesis of biologically and medicinally relevant pyrazole coupled imidazo[1,2-*a*]pyridine derivatives via three component reaction of alkyl-4-formyl-1-phenyl-1*H*-pyrazole-3-carboxylate, 2-aminopyridine and isocyanide in presence of nano-crystalline ZnO in ethanol through one pot chemical operation. The present synthetic protocol provides several advantages like operational simplicity, short reaction time, reusable catalyst and easy work-up procedure.

Multicomponent reactions are well established synthetic tool for designing chemical reactions those are capable of providing complex target molecules with structural diversity.[1] Multicomponent reactions combined with eco-compatibility offer elegance of atom and step economy, multiple bonds forming efficiency, environmentally benign, milder reaction conditions and lesser reaction time in a single chemical operation.[2] The isocyanides based multicomponent reactions have emerged as a highly efficient and diversity oriented synthetic methodology for synthesis of complex drug like molecule having wide range of medicinal and biological activities.[3] Moreover, the development of new synthetic protocols involving use of low cost, readily available and reusable catalysts which minimize the consumption of auxiliary substances, energy, time required in achieving separation can result the synthetic method environmentally and economically viable. Catalysis by nanoparticles seems to be an attractive approach in organic transformations due to their larger reactive surface to volume ratio with higher potential for selectivity.[4] Moreover, possibility of reusing the catalyst, milder reaction conditions and easier isolation of product are additional advantages of nanoparticle catalyzed multicomponent reactions.[5] The metal oxide nanoparticles are well known to exhibit both Lewis base-Lewis acid and redox properties on their surfaces.[6] Among the others, zinc oxide nanoparticles are well established for having Lewis acidic sites at their surfaces[7a] which have been extensively employed as inexpensive heterogeneous catalyst to promote acid catalyzed organic transformations.[7b-i]

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Imidazole fused polyheterocycles containing ring junction nitrogen have attracted considerable interest in medicinal chemistry in view of their uses as anti-inflammatory,[8] anti-cancer,[9] anti-bacterial,[10] and anti-tuberculosis[11] agents. The importance of imidazo[1,2-*a*]pyridine is evident from the fact that it is prevalent in several marketed drugs such as Olprinone (cardio tonic agent),[12] Zolpidem (hypnotic),[13] Levamisole (anticancer),[14] Alpidem (a nonsedative anxiolytic),[15] Zolimidine (anti-inflammatory)[16] (Figure 1). They are also used in molecular recognition and bio-imaging probes due to their structural characteristics.[17] On the other hand, pyrazole is also considered as privileged heterocyclic system because of their wide range of biological and pharmaceutical activities such as anti-microbial,[18a-b] anti-inflammatory,[18c] anti-tubercular,[18d] anti-parasitic,[18e] anti-tumor[18f] and anti-fungal[18g] activities. In addition, aryl pyrazole and its derivatives have been reported recently to

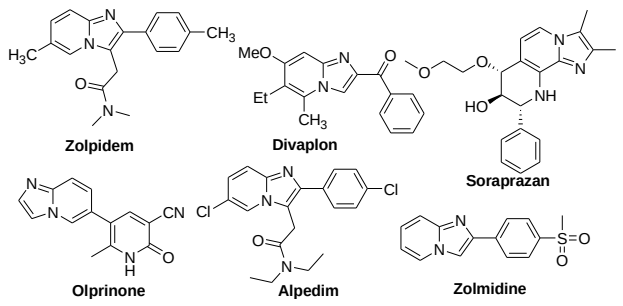
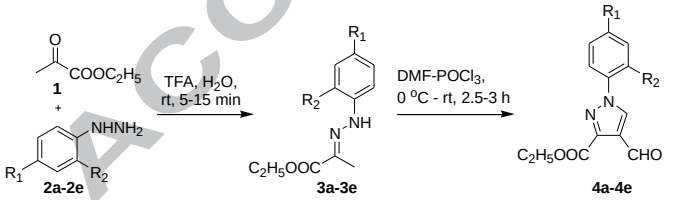


Figure 1. Representative example of imidazo[1,2-*a*]pyridine containing pharmaceutically important molecules.

exhibit high affinity towards A_{2b} adenosine receptor antagonist, non-nucleoside HIV-1 reverse transcriptase inhibitory activity

and many other applications.[19] Due to the prevalence of imidazo[1,2-*a*]pyridine and pyrazole in the numerous medicinally valuable chemical agents,[20,21] we are attracted by the possibility of coupling both entities via covalent linkage to provide valuable pyrazole coupled imidazo fused polyheterocyclic systems for useful bio-pharmaceutical applications because of their structural characteristics involving four nitrogens in condensed heterocyclic system integrated with secondary amine and ester functionality for non-covalent interactions. To achieve target molecules, our studies involved isocyanide based Groebke-Blackburn-Bienayme[3c-e] three component reactions in which aldehyde, 2-aminopyridine and isocyanide are condensed in presence of acid catalyst. Different methodology have been reported for this type of condensation reactions such as $Sc(OTf)_3$,[22a] $ZnCl_2$,[22b] $MgCl_2$,[22c] $ZrCl_4$,[22d] $SnCl_2.2H_2O$,[22e] $HClO_4$,[3d] AcOH,[3e] *p*-TSA,[22f] montmorillonite K-10,[22g] cellulose sulfuric acid,[3c] catalyst free and solvent free reaction conditions.[23] Most of these methods have many limitations in terms of lower product yields, toxicity, longer reaction time, higher energetic reaction conditions or use of hazardous and volatile organic solvents like acetonitrile, toluene, chloroform *etc*. Moreover, most of those catalysts are not reusable. Thus, in view of existing synthetic methods for imidazo[1,2-*a*]pyridine derivatives and related compounds, development of environmentally benign, efficient and high-yielding synthetic protocol is highly desirable with high convergence of products. In this paper, we report a straight forward one pot three component method for the synthesis of pyrazole coupled imidazo[1,2-*a*]pyridine derivatives in excellent yield. To the best of our knowledge, this is the first report for the synthesis of pyrazole coupled imidazo[1,2-*a*]pyridine scaffolds using nanocrystalline ZnO as a heterogeneous catalyst in ethanol. Our primary objective is to develop a green synthetic protocol using recyclable and reusable heterogeneous catalyst with benign reaction condition.

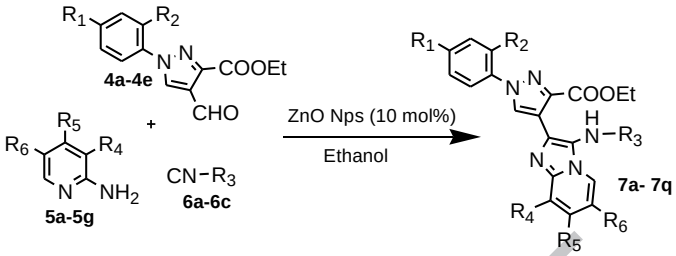
In our effort to prepare medicinally useful pyrazole coupled imidazo[1,2-*a*]pyridine heterocyclic system, first we prepared ethyl-4-formyl-1-substituted phenyl-1*H*-pyrazole-3-carboxylate derivatives **(4a-4e)** via two step synthetic protocol.[24] In the first step, ethylpyruvate (**1**) reacted with substituted phenyl hydrazine (**2a-2e**) in presence of trifluoroacetic acid in water for 5-15 minutes to give **3a-3e** in more than 95% yield. Reaction of **3a-3e** with DMF-$POCl_3$ afforded the desired product (**4a-4e**) in 92-97% yields (Scheme 1).



a: R_1= Br; R_2= H; **b**: R_1= Cl, R_2= H, **c**: R_1= Cl, R_2= Cl; **d**: R_1= H; R_2= CH_3; **e**: R_1= H, R_2= H

Scheme1. Synthesis of ethyl-4-formyl-1-substituted phenyl-1*H*-pyrazole-3-carboxylate derivatives.

Targeted pyrazole containing imidazo[1,2-*a*]pyridines derivatives (**7a-7q**) were synthesized via three component condensation reaction between alkyl-4-formyl-1-substituted phenyl-1*H*-pyrazole-3-carboxylate (**4a-4e**), 2-aminopyridines (**5a-5g**) and an isocyanide (**6a-6c**) in presence of reusable nano-crystalline ZnO as catalyst in ethanol (Scheme 2).



Scheme 2. Synthesis of pyrazole coupled imidazo[1,2-*a*]pyridines derivatives.

ZnO nanoparticles were prepared by reported literature.[25] The powder XRD analysis and SEM micrographs of synthesized ZnO indicated the high crystalline nature and nanometer range of materials respectively (see supporting information). TEM measurements further confirmed the nanostructure of ZnO with a mean diameter of 24 nm in semi-spherical nanoparticles as shown in Figure S2.

The optimization of reaction conditions was established using three model reactant ethyl-4-formyl-1-phenyl-1*H*-pyrazole-3-carboxylate (**4a**), 2-amino pyridine (**5a**) and ethylisocyanoacetate (**6b**). The efficiency of ZnO nanoparticles as catalyst over other catalysts and feasibility of present synthetic methodology using different solvents are also examined (Table 1). It was observed that, no product was formed in absence of catalyst at room temperature or refluxing temperature even after 24 h (Table 1, entry 1). However, when the model reaction was performed in presence of *p*-TSA (15 mol%) at 78˚C, the corresponding product was obtained in 55% yield (Table 1, entry 2). To improve the yield, various catalysts such as CH_3COOH, TFA, $Sc(OTf)_3$, $Bi(OTf)_3$, $Cu(OTf)_2$ were screened, but the desired product was obtained in moderate yield (Table 1. entries 3-8). To improve the yield, reaction was performed in presence of ZnO nanoparticles as catalyst (Table 1, entry 10). The result clearly indicated that higher yield was achieved in presence of ZnO nanoparticles with shorter reaction time in ethanol. The effect of catalyst loading on reaction was investigated by varying the loading amount (such as 5%, 10%, 15%, 20%) and maximum yield was obtained in presence of 10 mol% of ZnO nanoparticles (Table 1, entries 10-13). However, it was observed that reducing the amount the catalyst from 10 mol % to 5 mol %, reduced the yield while increasing the amount of catalyst have no significant effect on the yield of the product. The effect of solvent on reaction was also evaluated by employing various solvents (Table 1, entries 14-18). It was interesting to observe that maximum yield was obtained in ethanol.

Table 1. Optimization of reaction conditions[a,b]

S.no.	Catalyst (mol%)	Solvent[c]	Time (h)	Yield[d]
1.	Catalyst free	Ethanol	>24	No reaction
2.	p-TSA (15 mol%)	Ethanol	9	55%
3.	CH_3COOH (15 mol%)	Ethanol	9	58%
4.	TFA (15 mol%)	Ethanol	8	65%
5.	Boric acid (15 mol%)	Ethanol	8	55%
6.	$Sc(OTf)_3$(15 mol%)	Ethanol	7	70%
7.	$Bi(OTf)_3$(15 mol%)	Ethanol	6	70%
8.	$Cu(OTf)_2$ (15 mol%)	Ethanol	6	75%
9.	ZnO (15 mol%)	Ethanol	6	85%

10.	**ZnO Nps (10 mol%)**	**Ethanol**	**4**	**92%**
11.	ZnO Nps (5 mol%)	Ethanol	4	85%
12.	ZnO Nps (15 mol%)	Ethanol	4	92%
13.	ZnO Nps (20 mol%)	Ethanol	4	92%
14.	ZnO Nps (10 mol%)	1-propanol	4	90%
15.	ZnO Nps (10 mol%)	1,4-Dioxane	4.5	80%
16.	ZnONps (10 mol%)	Tetrahydrofuran	4.5	80%
17.	ZnO Nps (10 mol%)	Dichloromethane[e]	4	78%
18.	ZnO Nps (10 mol%)	Dimethylformamide	4	84%

[a]Bold row indicates the optimized reaction condition. [b]Ethyl 4-formyl-1-phenyl-1*H*-pyrazole-3-carboxylate (1 mmol), 2-amino pyridine (1 mmol) and ethylisocyanoacetate (1 mmol) were stirred at 78˚C till completion of reaction as indicated by TLC. [c]Solvents (4.0 mL). [d] Isolated yield after purification by recrystallization from EtOAc – n-hexane. [e] reaction was carried out at 40˚C.

In addition, it was observed that 78˚C was optimum temperature for maximum catalytic efficiency of ZnO nanoparticles (Table 2). Further, catalyst was easily recovered by filtration after completion of reaction, washed with ethanol and dried in vacuum followed by drying in hot air oven. Recovered ZnO nanoparticles could be used for at least eight times without any appreciable loss of its catalytic activity to provide structurally diverse pyrazole coupled imidazo[1,2-*a*]pyridine in excellent yield. It was found that after use of eight reaction cycles (Figure 3), the catalytic activity of ZnO nanoparticle decreased probably due to the aggregation of ZnO nanoparticles during the course of reaction. However, the post treatment of catalyst by calcination at 450˚C for 4 h restored its catalytic activity and then reused for five more reaction cycles.

Table 2. Effect of Temperature[a]

S. no.	Catalyst	Temp (˚C)	Time (h)	Yield[b] (%)
1.	ZnO NPs (10mol%)	r.t.	7-12	55
2.	ZnO NPs (10mol%)	45˚C	6	75
3.	ZnO NPs (10mol%)	60˚C	6	85
4.	ZnO NPs (10mol%)	70˚C	5	90
5.	ZnO NPs (10mol%)	78 ˚C	4	92

[a]Reaction conditions: Ethyl-4-formyl-1-phenyl-1*H*-pyrazole-3-carboxylate (1 mmol), 2-amino pyridine (1 mmol) and ethylisocyanoacetate (1 mmol); Catalyst: ZnO NPs (10 mol%); Solvent: ethanol. [b] Isolated yield after purification by recrystallization from EtOAc – n-hexane.

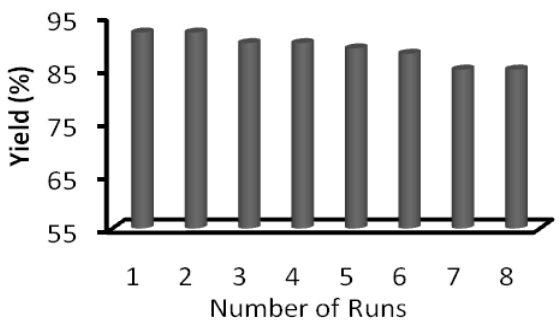
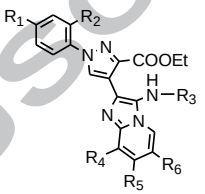


Figure 3. Recyclability and reusability of ZnO nanoparticles.

Under optimized reaction conditions, we turned to explore the generality of reaction by extending the methodology to different isocyanides and aminopyridines substituted with electron donating as well as electron withdrawing functional groups as depicted in Table 3. It was interesting to observe that 2-amino pyridine with electron donating and electron withdrawing functional groups (**5a-5g**) reacted successfully to furnish the products (**7a-7q**). In addition, a model reaction was also performed by taking reactants (**4a, 5a** and **6b**) in 100 fold excess concentrations which resulted the product (**7a**) in almost similar yield.[26] This result indicated that the reported protocol can be utilized for large scale synthesis. All the products were characterized by FT-IR, ^{1}H, ^{13}C NMR and mass spectroscopic analysis.

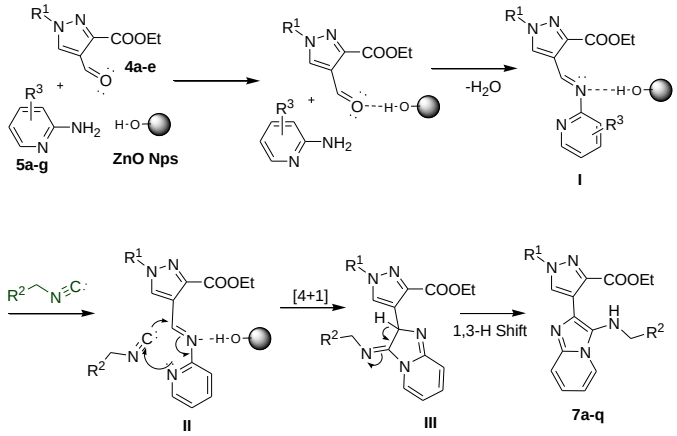
Table 3. Synthesis of pyrazole coupled imidazo[1,2-*a*] pyridine derivative



Entry	Product	R_1	R_2	R_3	R_4	R_5	R_6	Yield (%)
1	**7a**	Br	H	CH_2COOMe	H	H	H	90
2	**7b**	Br	H	CH_2COOEt	Br	H	H	92
3	**7c**	Br	H	CH_2COOEt	H	H	Br	92
4	**7d**	Br	H	CH_2COOEt	CH_3	H	H	92
5	**7e**	Br	H	CH_2COOEt	H	CH_3	H	90
6	**7f**	Br	H	CH_2COOEt	H	H	CH_3	91
7	**7g**	Br	H	CH_2COOEt	H	H	Cl	92
8	**7h**	Cl	H	CH_2COOMe	H	H	H	90
9	**7i**	H	CH_3	CH_2COOEt	H	H	H	90
10	**7j**	H	CH_3	CH_2COOMe	H	CH_3	H	88
11	**7k**	Cl	Cl	CH_2COOEt	H	H	H	90
12	**7l**	H	H	CH_2COOMe	H	H	Cl	92
13	**7m**	H	H	CH_2COOMe	H	H	Br	92
14	**7n**	H	H	CH_2COOMe	Br	H	H	90
15	**7o**	H	H	CH_2COOEt	H	H	Cl	91
16	**7p**	H	H	*tert*-butyl	H	H	H	90
17	**7q**	Br	H	*tert*-butyl	H	H	H	91

[a]Yields refer to isolated products after purification by recrystallization from EtOAc – n-hexane.

On the basis of results of studies, a plausible mechanism for the formation of pyrazole coupled imidazo[1,2-*a*]pyridine derivatives is depicted in Scheme 3. It is proposed that initially hydroxyl group present on surface of ZnO nanoparticles formed hydrogen bond with aldehyde oxygen, which activates carbonyl group to generate the carbonium ion, facilitating nucleophilic attack by aminopyridine resulting in imine formation. The resulting imine is further activated by ZnO nanoparticles to form electrophilic imine carbon (**I**) which is subsequently attacked by isocyanide followed by [4+1] cycloaddition to give cyclic adduct **III**. Finally, cyclic adduct (**III**) undergoes 1,3-H shift to furnish the desired product (**7a-q**).[27]



Scheme 3. Plausible mechanism for synthesis of imidazo[1,2-*a*] pyridine derivatives.

In conclusion, we have successfully developed an efficient and environmentally benign isocyanide based synthetic protocol for synthesis of biologically and medicinally relevant pyrazole coupled imidazo[1,2-*a*]pyridine derivatives involving three component reaction of alkyl-4-formyl-1-substitutedphenyl-1*H*-pyrazole-3-carboxylate, 2-aminopyridine and ethylisocyanoacetate/methylisocyanoacetate/*tert*-butyl isocyanide catalyzed by nanocrystalline ZnO in ethanol through one pot chemical operation. The present synthetic protocol offers several advantages such as environmentally benign, operational simplicity, wide functional group tolerance, short reaction time, reusable catalyst and easy work-up procedure. This methodology might prove as a better alternative to the existing literature methods.

Acknowledgments

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26. A mixture of **4a** (38.8 g, 120 mmol), **5a** (9.5 g, 100 mmol) and ZnO Nps (1.0 g, 10 mol%) was refluxed in ethanol (350 mL) for 10 min. Then, ethylisocyanoacetate (12 mL, 110 mmol) was added to the reaction mixture and the reaction mixture was stirred under refluxing. After the completion of reaction, as monitored by TLC, 150 mL of water was added to the reaction mixture and product was extracted with EtOAc (3 × 150 mL). The organic layers were combined and washed with 10% $NaHCO_3$ and brine 500 mL each. Organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to give desired product. The product was further purified with the help of recrystallization using EtOAc and n-hexane to afford the desired product in high purity with 90% yield.
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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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Graphical Abstract