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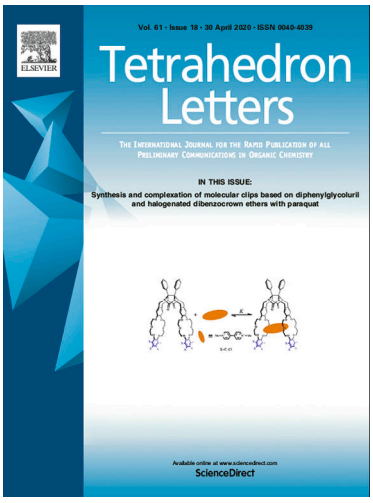

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A Transition Metal-free Cascade Reaction Using Heterogeneous Tin(IV)oxide Catalyzed and Iodine Promoted Synthesis of *3*-Aroylimidazo[*1,2*-a]pyridines

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Abstract:

The cascade synthesis of *3*-aroylimidazo[*1,2*-a]pyridines using chalcones and *2*-aminopyridine was achieved over the SnO_2/I_2 catalytic system in toluene at ambient air atmosphere. The catalyst shows high activity towards the broad substrate scope of the various aromatic and heterocyclic chalcones with *2*-aminopyridine, *4*-methyl *2*-aminopyridine, and *5*-methyl *2*-aminopyridine in good yields during the synthesis of *3*-aroylimidazo[1,2-a]pyridines. The methodology was further extended for the one-pot three-component synthesis of *3*-aroylimidazo[*1,2*-a]pyridines using acetophenone, benzaldehyde, and *2*-aminopyridine derivatives. The present protocol describes the easy purification methodology in the synthesis of *3*-aroylimidazo[*1,2*-a]pyridines

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Keywords: Acidity, *3*-aroylimidazo[*1,2*-a]pyridines, Cascade reaction, Heterogeneous catalyst, SnO_2/I_2

Introduction

Imidazo[*1,2-a*]pyridines, nitrogen-fused azole heterocycles are one of the biologically active candidates contributing to both natural products as well as synthetic organic chemistry.[1] These N-heterocyclic scaffolds are a key intermediate in the synthesis of optoelectronics, organometallics, material science, and also in the medicinal chemistry.[2] The imidazo[*1,2-a*]pyridine derivatives display a wide range of biological activities such as antifungal, anthelmintic, antiviral, antiprotozoal, antiulcer, antiepileptic, antibacterial, antituberculosis, anticancer, anti-inflammatory, anticonvulsant, antipyretic, analgesic and anxioselective.[3] In addition, they were studied as GABAA and benzodiazepine receptor agonists, MCH1R antagonists, histamine H_3 receptor antagonists, cardiotonic agents, *5*-lipoxygenase inhibitors, cyclin-dependent kinase inhibitors, β-amyloid detecting ligands, HIF-1α prolyl hydroxylase inhibitors, and p38 MAP kinase inhibitors as reported in the literature.[4] Similarly, the *2*-aryl-*3*-aroylimidazo[1,2-*a*]pyridine is one of the imidazo[*1,2-a*]pyridine derivatives also possess numerous biological activities such as anticancer and calcium channel blocking property.[5] Moreover, a number of commercially available drugs such as alpidem, zolpidem, saripidem, necopidem, olprinone, miroprofen, DS-1, zolimidine, GSK812397, minodronic acid contains imidazo[*1,2-a*]pyridine motifs.

Considering the application of imidazo[*1,2*-a]pyridine, the continuous efforts have been directed to develop a various synthetic methodology for the synthesis of imidazo[*1,2*-a]pyridines.[6] Currently, the number of reports are available for the imidazo[1,2-a]pyridine synthesis such as condensations, multicomponent synthesis, oxidative coupling reactions, oxidative cyclization's, tandem reactions, amino-oxygenation reactions, hydro-amination reactions, Vilsmmeier type cyclization's and Groebke–Blackburn–Bienayme (GBB) reactions using various starting materials.[7]

After the detailed literature survey of the biologically active and chemical application of *2*-aryl-*3*-aroylimidazo[*1*,*2*-*a*]pyridine, it is observed that the very few synthetic methodologies have been reported using homogeneous and heterogeneously catalyzed methods from *2*-aminopyridine and chalcones. Further, it is also reported that the *3*-aroylimidazo[*1*,*2*-*a*]pyridine motifs achieved successfully using one-pot three-component reaction of acetophenone, benzaldehyde and *2*-aminopyridine via in-situ chalcone formation.[8]

The homogeneously catalyzed methods have drawbacks such as the use of stoichiometric reagents/catalysts, and critical work-up during the quenching of reagents,[9] expensive metal like ruthenium[10] and ligand based catalysts,[11] non-reusability of the catalyst,[9-12] which leads to environmental pollution. Furthermore, the drawbacks associated with reported heterogeneous catalysts during the synthesis of *2*-aryl-*3*-aroylimidazo[*1*,*2*-*a*]pyridine are use of toxic solvents like DCM/AcOH and catalyst leaching which cause loss of catalytic activity, [13] low yields[14] and limited substrate scope.[15] To overcome from all these limitations, there is a scope for the design of an efficient, recyclable, and environmental friendly approach.

Since the last few decades, a researcher paid extensive attention to the development of nanomaterial-based heterogeneous catalysts having a wide range of textural and microscopic properties for their applications in organic synthetic chemistry.[16] However, a study revealed that SnO_2 is one of the metal oxide NPs act as a heterogeneous catalyst in several organic transformations to the synthesis of industrially valuable products such as imidazoles, spirooxindoles, *2*H-indazolo[*2*,*1*-β]phthalazine-triones, polyhydroquinoline, and the styrene hydrogenation.[17] Further, the molecular iodine (I_2)

is cheap, low toxic, non-hazardous than the transition metal-based catalysts. Thus, iodine is an ideal candidate as a catalyst in environment-friendly processes.[18]

Herein, a simple and efficient protocol of SnO_2/I_2 catalyzed *3*-aroylimidazo[*1*,*2*-*a*]pyridines synthesis using *2*-aminopyridine and chalcones in the presence of solvent toluene has been reported. The present protocol shows a broad substrate scope for the aromatic and heterocyclic chalcones with various *2*-aminopyridine derivatives in moderate to good yields. Furthermore, an additional advantage is the environment-friendly reaction work-up and easy separation as well as purification of the product.

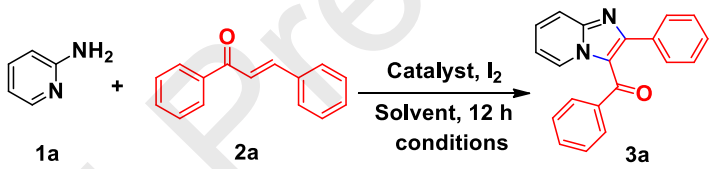
Result and Discussion

Catalyst activity testing and optimization of the reaction conditions

The catalyst activity, catalyst concentrations, I_2 amount, solvents screening, and temperature effects were studied for the *2*-aryl-*3*-aroylimidazo[*1*,*2*-a]pyridine synthesis using a mixture of 2-aminopyridine (**1a**, 1 mmol), and *1*,*3*-diphenyl-*2*-propen-*1*-one (**2a**, 1 mmol) as a model reaction and the results are presented in **Table 1**. No reaction was observed when the reaction mixture was refluxed without catalyst in toluene for longer reaction time under ambient conditions. (**Table 1, Entry 1**). But, when the reaction was performed using I_2 (0.5 equiv.), the poor yield (10%) of the desired product was obtained (**Table 1, Entry 2**). Further, the various metal oxides as solid acid catalysts were screened for the reaction along with the molecular iodine. The preliminary results on the screening of various metal oxide catalysts showed that SnO_2 was the most active catalyst for the cyclization reaction and gave an 84% yield of the desired product **3a** in the short reaction of time (**Table 1, Entry 3**). The other solid catalysts, such as ZnO, TiO_2, ZrO_2, and SiO_2 gave the lower yield (20-64%) of the product **3a** over 18 h (**Table 1, Entries 4-7**). The various solvents were optimized for the synthesis of *3*-aroylimidazo[*1*,*2*-a]pyridine such as chlorobenzene, 1,4-dioxane, THF, ethanol,

dichloromethane, and DMF but these were not as effective as toluene (**Table 1, Entries 3 and 8-13**). A series of reactions were also studied with varying concentrations of SnO_2 and I_2 to determine the most optimal reaction conditions in the tandem cyclization, and the highest yield was obtained with 10 mol% of SnO_2 and 0.5 equivalents of I_2 in toluene (**Table 1, Entries 3 and 14-18**). Moreover, the reaction which was performed at room temperature could not furnish the desired product even though in long reaction time (**Table 1, Entry 19**). The best yield of the product **3a** (84%) was obtained from the reaction of **1a** (1 mmol), **2a** (1 mmol), SnO_2 (10 mol %) and molecular iodine (0.5 mmol), in toluene (6 mL) refluxing for 12 h in ambient conditions.

Table 1 Catalyst screening and optimization of the reaction conditions.



Entry	Catalyst (mol %)	I_2 (Equiv.)	Solvent	Temp (^{O}C)	Time (h)	Yield (%)
1	Nil	Nil	Toluene	110	24	Nil
2	Nil	0.5	Toluene	110	24	10
3	**SnO_2 (10)**	**0.5**	Toluene	110	**12**	**84**
4	TiO_2 (10)	0.5	Toluene	110	18	52
5	ZrO_2 (10)	0.5	Toluene	110	18	64
6	ZnO (10)	0.5	Toluene	110	18	45
7	SiO_2 (10)	0.5	Toluene	110	18	15
8	SnO_2 (10)	0.5	PhCl	130	12	76
9	SnO_2 (10)	0.5	1,4-dioxane	100	12	24

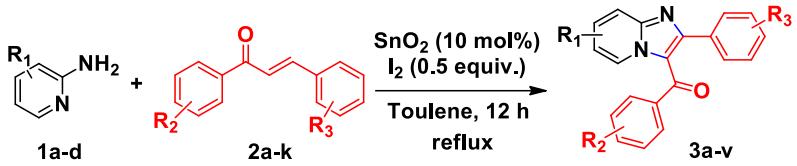
10	SnO_2 (10)	0.5	THF	65	12	10
11	SnO_2 (10)	0.5	EtOH	80	12	18
12	SnO_2 (10)	0.5	DCM	40	12	15
13	SnO_2 (10)	0.5	DMF	150	12	54
14	SnO_2 (15)	0.5	Toluene	110	12	84
15	SnO_2 (5)	0.5	Toluene	110	18	52
16	SnO_2 (10)	Nil	Toluene	110	24	Nil
17	SnO_2 (10)	0.25	Toluene	110	12	65
18	SnO_2 (10)	0.75	Toluene	110	12	84
19	SnO_2 (10)	0.5	Toluene	RT	24	Nil

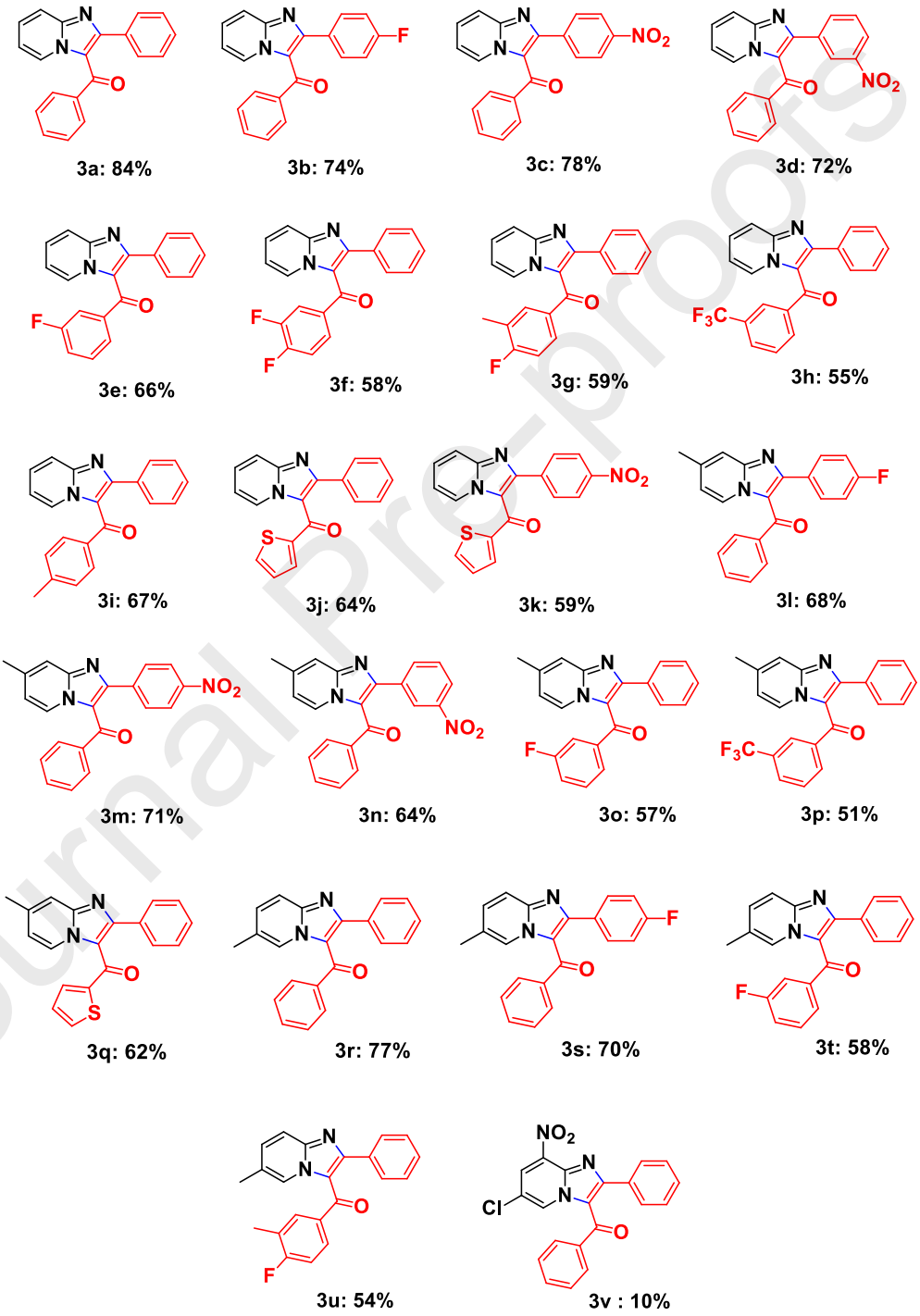
Reaction conditions: *2*-aminopyridine (**1a**, 1 mmol), and *1,3*-diphenyl-*2*-propen-*1*-one (**2a**, 1 mmol), amount of SnO_2 and I_2, solvent, time specified as given, isolated yields*.

Substrate scope

Using the optimized reaction conditions, this cyclization reaction was successfully carried out using the SnO_2/I_2 catalytic system with different substituted chalcones exerting electronic effects with *2*-aminopyridine derivatives to give the *2*-aryl-*3*-aroylimidazo[*1,2*-a]pyridines in moderate to good yields (51-84%) (**Table 2**). Initially, *2*-aminopyridine reacted smoothly with various substituted chalcones under optimized reaction conditions. Chalcone derivatives bearing substituents like fluoro, nitro, methyl and trifluoromethyl group present at the ortho, meta and para positions on both *2*-aryl as well as *3*-aroyl rings are well tolerated and yields the desired products (55-84%) (**Table 2, Entries 3a-3i**). Furthermore, the electronic effects, both electron-withdrawing and electron-rich substituents groups on chalcones show similar reactivity patterns and afforded good yields. Moreover, hetero-aryl chalcone like *2*-thienyl reacted smoothly

Table 2 Substrate scope for the synthesis of *2*-aryl-*3*-aroylimidazo[*1*,*2*-a]pyridines.



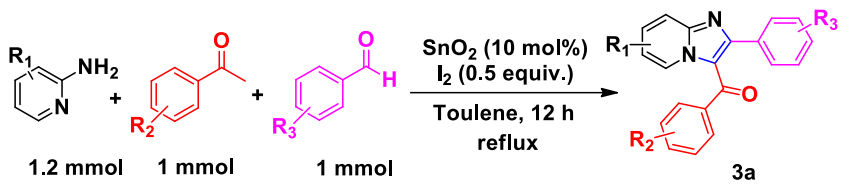


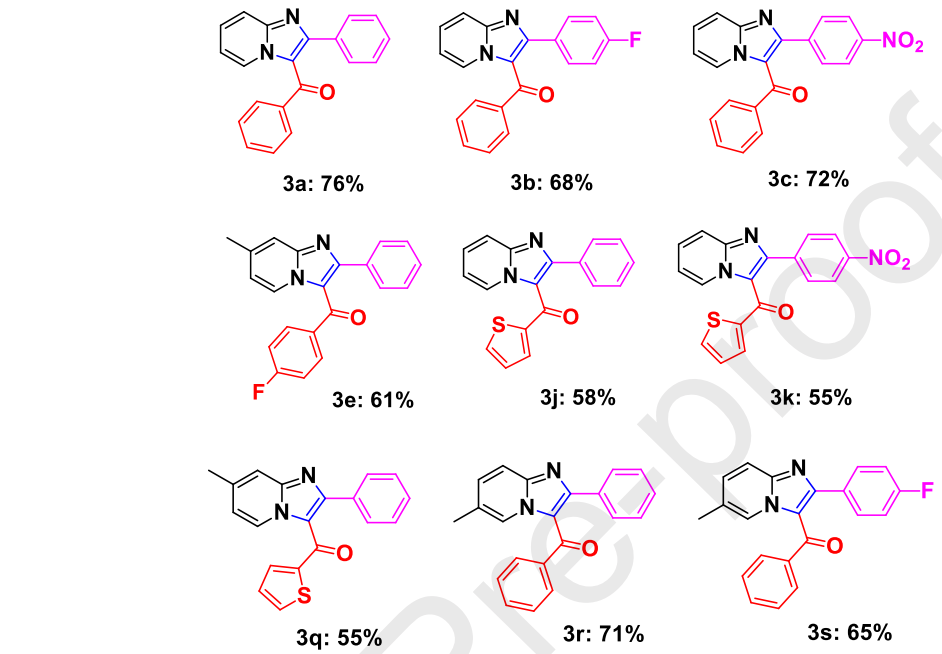
Reaction conditions: *2*-aminopyridine derivatives (**1a-d**) (1 mmol), chalcones (**2a-k**) (1 mmol), SnO_2 (10 mol %), I_2 (0.5 equiv.), toluene (6 mL), 110 ^{O}C, air, Isolated yields*.

with *2*-aminopyridine to the desired products in a 59-64% yield (**Table 2, Entries 3j and 3k**). Further, the different substituted *2*-aminopyridines were investigated to produce desired products with good yields. *2*-amino-4-methylpyridine as well as *2*-amino-*5*-methylpyridine also reacted efficiently with chalcones bearing halogen, electron-donating and electron-withdrawing group and hetero-aroyl chalcones (**Table 2, Entries 3l and 3u)** to give corresponding products in 51-77% yields. Whereas the *2*-amino-*3*-nitro-*5*-chloro-pyridine on reaction with chalcone (**2a**) gives traces of the corresponding product (**3v**) due to the strong deactivating -R and -I effect of -nitro as well as -Cl group on the *2*-aminopyridine. In the present work, synthesis of fluorine and fluorine-containing substituents were focused due to the vast scope in the drug industry because of the 20-30% drug contain organo-fluorine compounds.[19] The above substrate scope study reveals that the SnO_2/I_2 catalytic system demonstrated better catalytic activity in the synthesis of *2*-aryl-*3*-aroylimidazo[*1*,*2*-a]pyridines using a wide range of the chalcones and *2*-aminopyridine.

One-pot synthesis of *3*-aroylimidazo[1,2-a]pyridines

From the point of view of minimizing the number of steps and achieving the atom economy, the synthesis of *3*-aroylimidazo[1,2-a]pyridines was planned as a one-pot three-component tandem-cyclization reaction using acetophenone (1 mmol), benzaldehyde (1.2 mmol) and *2*-aminopyridine (1 mmol) using the same SnO_2/I_2 catalyst which yields *3*-aroylimidazo[1,2-a]pyridines in 55–76% yields without using any additives (**Scheme 1**).

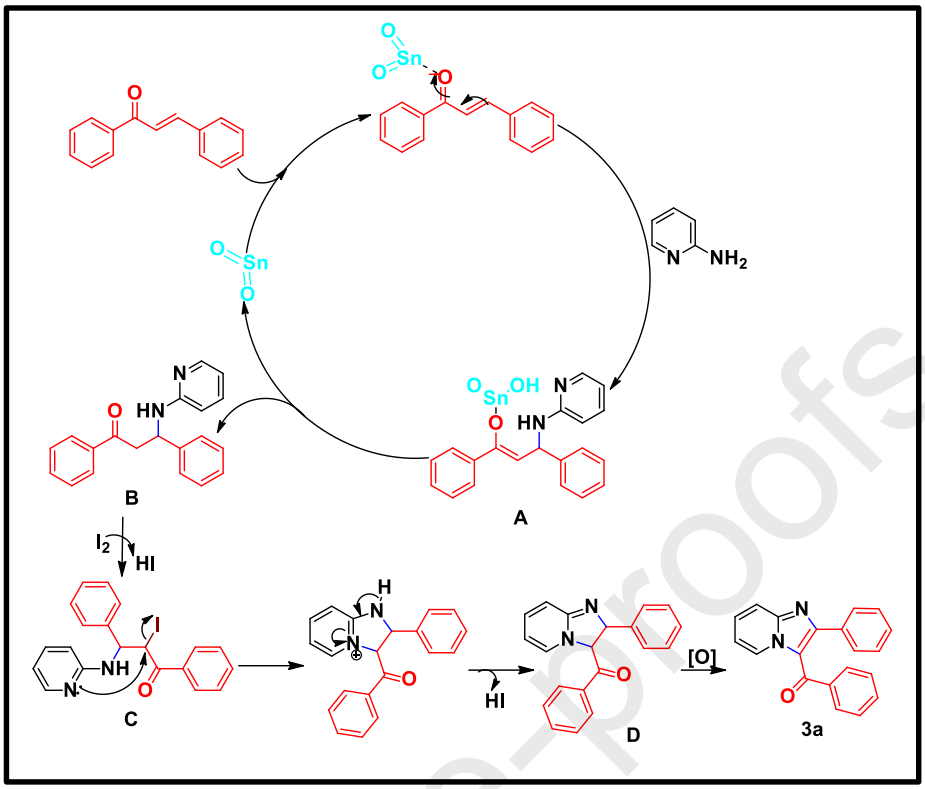




Scheme 1 One-pot synthesis of *3*-aroylimidazo[*1*,*2*-a]pyridines from ketone, aldehyde and *2*-aminopyridine

Plausible reaction mechanism

The plausible reaction mechanism for the synthesis of imidazo[*1*,*2*-a]pyridines using chalcone and *2*-aminopyridine through cyclization, represented in **scheme 2,** the mechanism for the reaction is assumed to be the same as previously reported.[8, 11] Initially, the chalcone gets activated by SnO_2, and then Michael addition of *2*-aminopyridine to activated chalcone takes place to form an enolate **A**, next the key intermediate **B** (**4a**) is formed with the release of catalyst SnO_2. Then **B** reacts with I_2 to produce intermediate **C,** followed by subsequently intra-molecular cyclization to form intermediate **D,** which leads to product *2*-aryl-*3*-aroylimidazo[*1*,*2*-a]pyridines **3a** under aerobic conditions.



Scheme 2 plausible mechanism *3*-aroylimidazo[*1*,*2*-a]pyridines synthesis using chalcone and *2*-aminopyridine promoted by SnO_2/I_2 catalytic system.

Catalyst recycles study

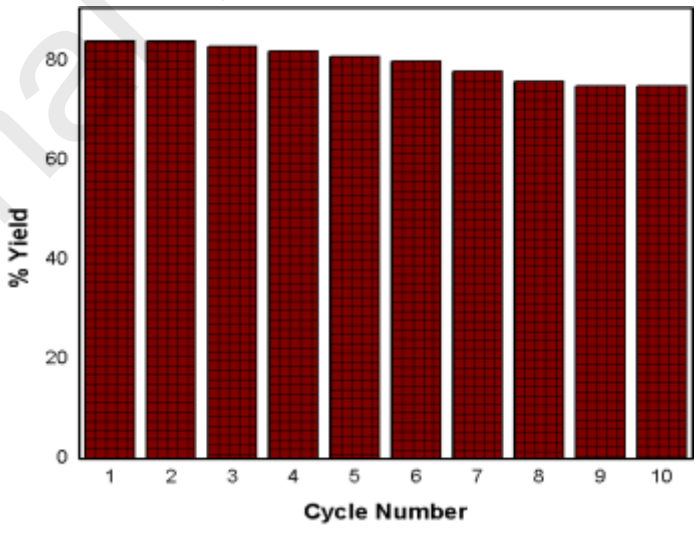


Figure 1 Recyclability study of SnO_2 for tandem cyclization reaction.

The recycle study of the SnO_2 NPs was studied for the reaction between chalcone and *2*-aminopyridine under the optimized reaction conditions up to ten cycles (**Figure 1**). After completion of the reaction, the reaction mixture was centrifuged. Then, the upper

solvent layer was separated and then the catalyst was washed with toluene for 2 to 3 times. The recycled catalyst was further used for the reaction along with the addition of 0.5 equivalents Iodine. The experimental results revealed that the catalytic activity of SnO_2 NPs displayed only a marginal decrease in yield (84 to75%) after ten catalytic cycles. The XRD pattern of the recycled SnO_2 catalyst was studied after the ten catalytic cycles (**Figure 2**), and was found to be indistinguishable from those of the fresh catalyst. This observation recommends the high chemical stability of the catalyst.

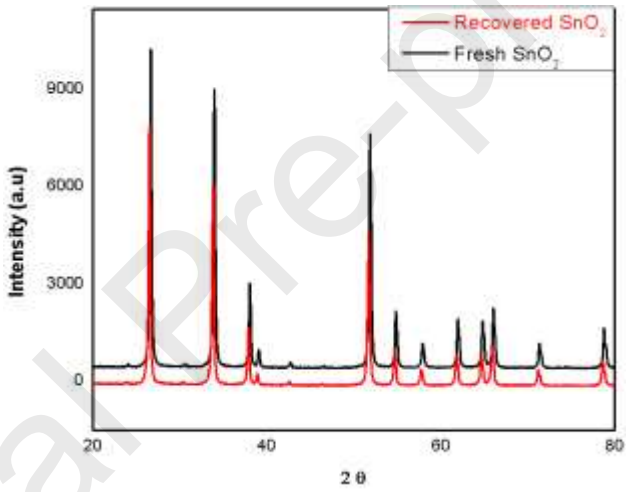


Figure 2 XRD spectra of fresh and recovered SnO_2 catalyst.

Conclusion

Cascade synthesis of *3*-aroylimidazo[1,2-a]pyridines was achieved successfully from chalcones and *2*-aminopyridine using the SnO_2/I_2 catalytic system in toluene at ambient conditions. SnO_2 catalyzed in situ Michael addition of chalcone and *2*-aminopyridine, followed by the addition of I_2, catalyzed intramolecular oxidative C-N bond formation. The efficiency of this tandem cyclization protocol was established by a broad substrate scope involving various 2-aminopyridine with aromatic and heterocyclic chalcones to give good yields (51-84%) of *3*-aroylimidazo[1,2-a]pyridines. Under similar reaction

conditions, One-pot three-component synthesis of *3*-aroylimidazo[1,2-a]pyridines was achieved successfully using acetophenone, benzaldehyde, and *2*-aminopyridine derivatives. Further, the SnO_2 NPs recycled several times without losing their activities and stability of the catalyst was studied by XRD of fresh and reused catalyst.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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- Heterogeneous SnO_2 catalyst
- Cost effective and non-hazardous Iodine
- Aerobic oxidation
- Green process
- Broad substrate scope
- One-pot synthesis
- Gram-scale synthesis
- Easy purification

Highlights

- The SnO_2/I_2 system investigated in the synthesis of *3*-aroylimidazo[*1,2*-a]pyridines
- The Py-FTIR of the SnO_2 shows both the Lewis and Brønsted types of acidic sites
- One-pot three-component synthesis of *3*-aroylimidazo[1,2-a]pyridines
- The SnO_2 NPs recycled successfully and showed high chemical stability