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An Expeditious One-pot Synthesis of Imidazo[1,2-*a*] pyridines using $ZnCl_2.SiO_2$ as a Recyclable Heterogeneous Catalyst under Solvent-free Condition

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Abstract

Synthesis of imidazo[1,2-*a*]pyridines over several solid supported catalysts has been investigated. Among these catalysts, $ZnCl_2.SiO_2$ (silzic) showed excellent yields and short reaction times. The silzic catalyst could be recovered and reused in five reaction cycles. The present procedure offers several advantages such as short reaction time, simplicity of the reaction procedure, the elimination of solvents, simple workup, recovery and reusability of the catalyst.

Keywords: *Imidazo[1,2-a]pyridine, Silzic, Solvent-free, Rapid synthesis, Heterogeneous catalysts.*

Introduction

Heterocyclic compounds are in focus of intense investigations by academic and applied-oriented chemists because of the significant role in biological activities [1-4]. Among a large variety of nitrogen-containing heterocyclic compounds, imidazo[1,2-*a*] pyridine compound have received much attention toward to their diverse range of biological activities such as antimicrobial, potent ASK1 inhibitors, anti-rhinoviral, anti-epileptic and so on [5-8]. Recently more than a few synthetic methods for preparing these compounds based on multi component reactions have been reported [9-20]. Although, many of these methods have certain disadvantages such as long reaction time, complicated work-up, harsh reaction conditions, using of solvent and low yields.

Heterogeneous catalysts have gained significant attraction due to economic and environmental considerations [21-23].

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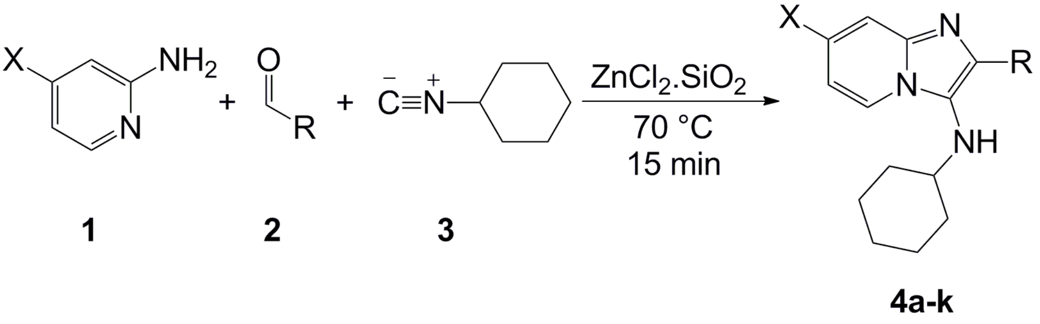
Immobilization of catalyst on porous solid supports has some advantages such as good dispersion of active reagent sites, cleaner reactions, easier work up and reducing in reaction times. Alumina, silica, and clays are of the most widely employed supports; however, silica is widely used as a supporting material [24-29], since it presents the advantages to be chemically inert towards many reactants which would reduce secondary reactions, to have surface hydroxyl groups which allow for ligand bonding, to present high specific surface areas and good thermal and mechanical stabilities. The aim of this study is therefore, to investigate the efficiency of supported heterogeneous catalysts for the synthesis of imidazo[1,2-*a*]pyridine derivatives. In connection with our previous work for the synthesis of imidazo[1,2-*a*] pyridines [30] and our interest in multi-component reactions (MCRs) [31-34], herein we wish to report rapid and efficient method for one-pot synthesis of imidazo[1,2-*a*] pyridines from aldehydes, 2-aminopyridines and isocyanide using silzic as reusable heterogeneous catalyst at 70 °C under solvent-free condition (Scheme 1).



Scheme 1. Synthesis of compounds 4a-k.

Experimental

All chemicals and reagents were obtained from Sigma–Aldrich or Merck and were used without further purification. The melting points of products were determined with an Electrothermal 9200 melting point apparatus. The FT-IR spectra were recorded on a Perkin-Elmer BX-II IR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were provided on Brucker DRX-400 Avance instruments in $CDCl_3$.

Preparation of catalyst ($ZnCl_2.SiO_2$)

Supported $ZnCl_2$ on silicagel was prepared according to the previous procedure [26]. Thus, 10% (w/w) $ZnCl_2$/silica gel (silzic 10%) was easily prepared by co-grinding of anhydrous zinc chloride (1 g) with dry silica gel (9 g) in an agate mortar at room temperature for 20-25 min. Careful mixing is required to attain uniform dispersion of $ZnCl_2$ over silica surface. This results in formation of homogenized, white free flowing powder which was further activated in vacuum at 80 °C for 2 h.

General procedure for the synthesis of imidazo[1,2-a]pyridines

A mixture of aldehyde (1 mmol), amidine (1 mmol), isocyanide (1 mmol) and silzic (0.05 g) was heated at 70 °C for an appropriate time as indicated by TLC. The mixture was filtered and washed with CH_2Cl_2 to separate catalyst. The solid residue was recrystallized from CH_3CN to obtain pure product in 99% yield. The synthesized compounds were identified by their melting point, IR, ^{1}H NMR and ^{13}C NMR spectral data. Spectroscopic data for the selected product is as follows:

*2-(4-chlorophenyl)-N-cyclohexylimidazo[1,2-a]pyridin-3-amine (**4a**, $C_{19}H_{20}ClN_3$)*

Light green crystal, (0.321 g, 99%); mp: 185-187 °C; IR (KBr, cm^{-1}): 3225 (NH), 2929 (CH), 1634 and 1469 (Ar). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.17–1.84 (10 H, m, 5 CH_2 of CyHex), 2.95 (1 H, m, CHN of CyHex), 3.35 (1H, s, NH), 6.87 (1 H, t, ^3J = 6.6, CH of Ar), 7.22 (1 H, t, ^3J= 7.8, CH of Ar), 7.41 (2 H, d, ^3J= 8.8, 2 CH of Ar), 7.61 (1 H, d, ^3J= 9.2, CH of Ar), 8.06 (2 H, d, ^3J= 8.4, 2 CH of Ar), 8.15 (1 H, d, ^3J= 6.8, CH of Ar). 13C NMR ($CDCl_3$, 100 MHz): δ = 24.81, 25.69, 34.19, 56.84, 111.82, 117.28, 122.72, 124.33, 124.92, 128.24, 128.64, 132.85, 133.00, 135.43, 141.53.

Results and discussion

By employing a reaction of 2-aminopyridine, 4-chlorobenzaldehyde, and cyclohexyl isocyanide, the reaction conditions were optimized. It is noticed that the reaction proceeded smoothly with 0.05 g silzic. Thus, after 15 min at 70 °C, the desired product was obtained in 99% yield under solvent-free condition. Initially, a comparative study was carried out with various catalysts in solvent-free condition (Table 1).

Table 1. Condensation reaction of 2-aminopyridine, 4-chlorobenzaldehyde and cyclohexylisocyanide in the presence of different loading of the catalyst under solvent-free conditions.

Entry	Catalyst	Catalyst loading (g)	Temperature(°C)	Time (min)	Yield^a (%)
1	-	-	70	120	Trace
2	SiO_2	0.05	70	120	<30
3	Al_2O_3	0.05	70	120	<30
4	TiO_2	0.05	70	120	<30
5	$FeCl_3.SiO_2$	0.05	70	15	85
6	$FeCl_3.Al_2O_3$	0.05	70	15	88
7	$KF.Al_2O_3$	0.05	70	120	50
8	$P_2O_5.SiO_2$	0.05	70	15	90
9	$P_2O_5.Al_2O_3$	0.05	70	15	83
10	$Na_2CO_3.SiO_2$	0.05	70	120	40
11	$NH_4OAc.Al_2O_3$	0.05	70	120	40
12	$H_3PO_4.Al_2O_3$	0.05	70	15	88
13	$ZnCl_2.SiO_2$	0.05	r.t	120	50
14	$ZnCl_2.SiO_2$	0.05	50	30	90
15	$ZnCl_2.SiO_2$	0.01	70	15	93
16	$ZnCl_2.SiO_2$	0.02	70	15	94
17	**$ZnCl_2.SiO_2$**	**0.05**	**70**	**15**	**99**
18	$ZnCl_2.SiO_2$	0.10	70	15	99
19	$ZnCl_2.SiO_2$	0.15	70	15	99

Conditions: 2-aminopyridine 1 mmol, 4-chlorobenzaldehyde 1 mmol and cyclohexylisocyanide 1 mmol.
^{a} Isolated yield.

The support catalysts showed very little activity to form the final product (Entry 2-4); however, their catalytic activities were increased intensely when they impregnate. Amongst the different supported catalysts tested, silzic [26] was found to be superior in terms of reaction time and yield. Moreover, the use of $FeCl_3.SiO_2$ [27], $FeCl_3.Al_2O_3$ [35], $KF.Al_2O_3$ [36], $P_2O_5.SiO_2$ [37], $P_2O_5.Al_2O_3$ [38], $H_3PO_4.Al_2O_3$ [38], $Na_2CO_3.SiO_2$ [39] and $NH_4OAc.Al_2O_3$ [39] catalysts afforded the desired products, albeit in longer reaction times, and lower yield. As can be seen acidic catalysts give higher yields comparing to basic catalysts; hence, it is evident that the presence of Lewis acidic site plays crucial role to obtain higher yields, also it is clarifying the plausible mechanism for this reaction. It is noteworthy that in the absence of catalyst a very low amount of the desired product was formed (Table 1, entry 1). Also taking reaction in the room temperature gave lower yield and higher reaction time (entry 14). The required quantity of catalyst was probed at five different silzic loadings. Effective catalysis was demonstrated down to 0.05 g of silzic (Table 1). The yield increased sharply when the temperature was raised from room temperature to 70 °C. Higher amounts of the catalyst up to 0.15 g and of the reaction temperature did not improve the results to a greater extent. To understand the role of solvent, we screened various solvent systems, such as CH_3CN, EtOH, MeOH, H_2O, $CHCl_3$, n-hexane, toluene and ethyl acetate (Table 2). The investigation of reaction medium for the process interestingly revealed that polar solvents such as CH_3CN, MeOH, EtOH, H O and ethyl acetate gave higher yields comparing to non-polar solvents. However, the rate of reaction and the amount of desired product was found to be greater in solvent-free condition.

Table 2. Initial solvent effect studies for synthesis of 3-aminoimidazo[1,2-*a*]pyridines with 0.05 g catalyst.

Entry	Solvent	Temp (°C)	Time (hr)	Yield (%)
1	CH_3CN	Reflux	24	93
2	EtOH	Reflux	24	93
3	MeOH	Reflux	24	80
4	H_2O	Reflux	24	74
5	$CHCl_3$	Reflux	24	65
6	*n*-Hexane	Reflux	24	50
7	Toluene	Reflux	24	50
8	Ethyl acetate	Reflux	24	98
9	**Solvent-free**	**70**	**0.4**	**99**

Conditions: aminopyridine (1 mmol), 4-chlorobenzaldehyde (1 mmol), cyclohexyl isocyanide (1 mmol) and 0.05 g silzic in 5 mL solvent, stirring

After optimizing the conditions, to demonstrate the diversity of the silzic catalyst and to explore the scope of the process, the optimized conditions were applied to reactions of 2-aminopyridine or 4-methyl-2-aminopyridine **1** and isocyanide **3** with various aromatic aldehydes **2** all desired products were formed as shown in (Table 3). We have found that the reactions of electron-withdrawing aldehydes have higher yields compared to the reactions of electron donating aldehydes. Averse the expectations, reactions of 4-methyl-2-aminopyridine have relatively lower yields comparing to 2-aminopyridine.

Table 3. Synthesis of various 3-aminoimidazo[1,2-*a*]pyridines in the presence of silzic.

Entry	X	R	Product	Yield* (%)	Time (min)	mp (°C)
1	H	4-Cl-C_6H_4	**4a**	99	15	185-187[30]
2	Me	4-Cl-C_6H_4	**4b**	98	15	208-209[30]
3	H	4-Br-C_6H_4	**4c**	99	15	176-178[30]
4	Me	4-Br-C_6H_4	**4d**	98	15	204-206[30]
5	H	2-Fluorenyl	**4e**	95	15	172-174[30]
6	Me	2-Fluorenyl	**4f**	95	15	200-201[30]
7	H	4-NMe_2-C_6H_4	**4g**	94	15	182-183[30]
8	Me	4-NMe_2-C_6H_4	**4h**	94	20	200-202 (dec)[30]
9	Me	Ph	**4i**	97	15	170-172[30]
10	Me	4-Me-C_6H_4	**4j**	96	20	191-192 (dec)[30]
11	Me	2,4-Me_2-C_6H_3	**4k**	95	20	198-199[30]

Conditions: aminopyridines (1 mmol), benzaldehydes (1 mmol), cyclohexylisocyanide (1 mmol) and 0.05 g silzic, stirring at 70 °C.
*Isolated yield.

The possibility to reuse the catalyst was tested in the synthesis of imidazo[1,2-*a*] pyridine (Figure 1) to check its capacity to provide the same catalytic activity. The solid catalyst was recovered after each run, washed with CH_2Cl_2 (3×5 mL) and subsequently dried at 50 °C to the reused. $ZnCl_2.SiO_2$ could be reused in subsequent reactions; there is slight loss of activity after each run, which may be due to some microscopic changes in the structure of the catalyst.

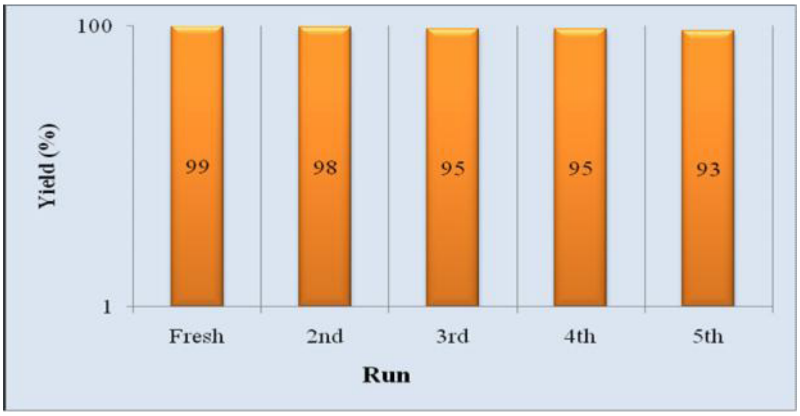
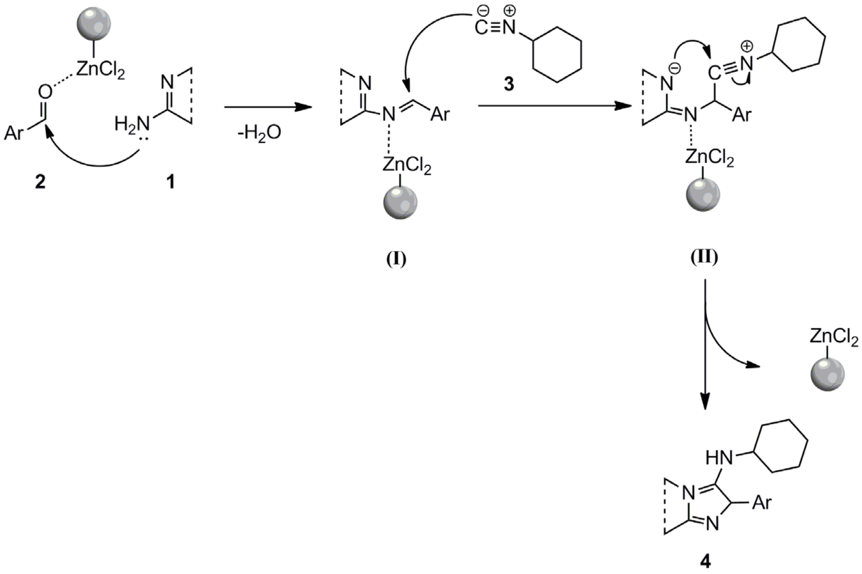


Figure 1. Yield refers to isolated products from the aminopyridines (1 mmol), 4-chlorobenzaldehyde (1 mmol), cyclohexylisocyanide (1 mmol) in the presence of 0.05 g silzic under solvent-free condition.

As reported in literature [9-11] and on the basis of the experimental observations, the possible mechanism for the formation of imidazo[1,2-*a*] pyridine over silzic demonstrated as follows (Scheme 2): Initially aromatic aldehyde **2** coordinates to the Lewis acidic site present at the catalyst. Then amidine **1** reacts with activated carbonyl of aldehyde to form imine (**I**) through elimination of the water, then it undergoes nucleophilic addition with the isocyanide **3** to form the isonitrilium intermediate (**II**), which cyclizes to form the final product **4** and regenerates the solid catalyst.



Scheme 2. Plausible mechanism for the synthesis of imidazo[1,2-*a*]pyridines using silzic.

Conclusion

In conclusion, we investigate the synthesis of imidazo[1,2-*a*]pyridines over several solid supported catalysts and we have developed a green and rapid methodology for synthesis of imidazo[1,2-*a*]pyridines using silzic as a reusable heterogeneous catalyst under solvent-free condition. The products were obtained in excellent yields and purities. This method has many advantages, such as short reaction time, low cost catalyst, excellent yields, solvent-free conditions, and reusability of catalyst; these attributes make silizic valuable and advantageous catalyst for synthesis of imidazo[1,2-*a*]pyridines.

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