

**Scheme 1.** Procedure for the preparation of ZPZn.

### 2.3. Recyclability studies of catalyst

To examine the recyclability of the catalyst, the used ZPZn was recovered from the reaction media and re-used. For recycling, after the first use, the catalyst was separated from the reaction mixture by centrifugation, washed sequentially with ethanol and water before being dried at 110 °C for 2h, and then activated at 450°C for 2 h.

## 3. Results and Discussion

### 3.1. Catalyst characterization

The ICP-OES analyses of ZP and ZPZn are shown in Table 1. The results obtained in the current study for ZPZn were compared with those reported previously in the literature [39-41]. Our results revealed that there was a negligible leach of zinc ions into the reaction media after the reaction (i.e., following the first use of the catalyst).

Pyridine has been verified to be an excellent FTIR spectroscopy probe to characterize the nature of the acid sites of the catalyst and the resulting IR spectrum is shown in Fig. 1. The main bands observed over the samples are assigned according to the literature data [24]. The origin of Brønsted acidity of the samples is due to the presence of P–OH groups. The pyridine-desorbed FTIR spectra of ZrP showed characteristic strong bands about 1446  $\text{cm}^{-1}$ , which are assigned to

the coordinated pyridine in Lewis acid sites. The pyridinium ions are formed by the transfer of protons from the P–OH groups in the ZrP to the organic base. The absorption peak about 1630 and 1541  $\text{cm}^{-1}$  are caused by pyridine adsorbed on Brønsted acid sites [23, 24]. Additionally, the band at 1488  $\text{cm}^{-1}$  indicates the combination band between those adjacent Lewis and Brønsted acid sites at 1541 and 1446  $\text{cm}^{-1}$  respectively [23].

It is obvious from the figure that the prepared ZrP shows a higher number of Brønsted acid sites accompanied by low amounts of Lewis acid sites.

The surface morphology of the ZP and ZPZn was studied by SEM (Fig. 2). The SEM image of ZP (Fig. 2(a)) revealed the presence of hexagonal plates with well-defined shapes and very smooth surfaces. Fig. 2(b) and (c) show the SEM images of ZPZn. These images revealed that the structure of ZPZn was less ordered than that of ZP and that the ZPZn particles had aggregated to form both sheets and spheres of different shapes and sizes [39,40,45].

Fig. 3 shows the TEM images of ZPZn. It shows that ZPZn catalyst retained the original morphology of ZP (layered structure) and that the particles were approximately 150 nm in size. These images also showed nanoparticles of different sizes on the smooth surface of the ZP.

**Table 1.** Element contents of ZPZn (atm.%) and physical properties of the catalysts before and after the reaction.

Entry	Sample	Zn	O	Zr	P	BET ( $\text{m}^2/\text{g}$ )	Total acidity ( $\text{mmol NH}_3/\text{g}$ )
1	ZP	-	65.3	12.4	22.3	118.2	2.5
2	ZPZn	12.1	54.1	12.3	21.5	102.4	1.6
3	ZPZn <sup>a</sup>	11.9	54.2	12.3	21.6	102.1	1.52
4	ZPZn <sup>b</sup>	4.5	63.6	12	19.9	86.4	0.78

<sup>a</sup>After the first cycle.

<sup>b</sup>After the 7th cycle.

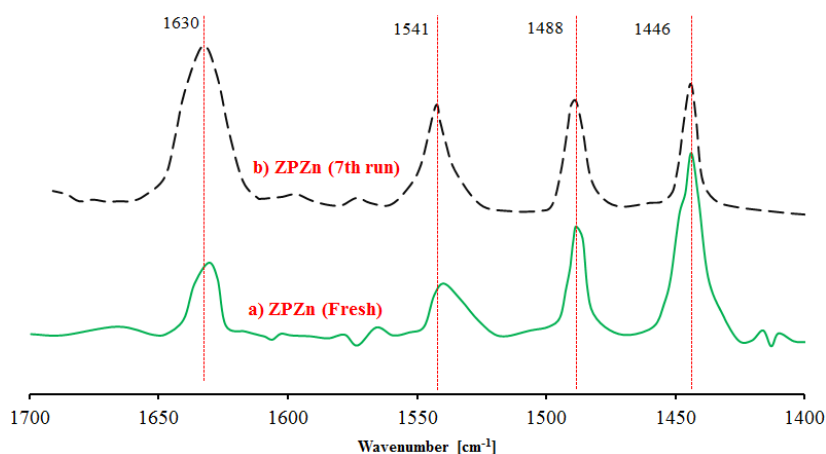


Fig. 1. Pyridine-desorbed FTIR spectra of ZPZn (Fresh and after the 7th run).

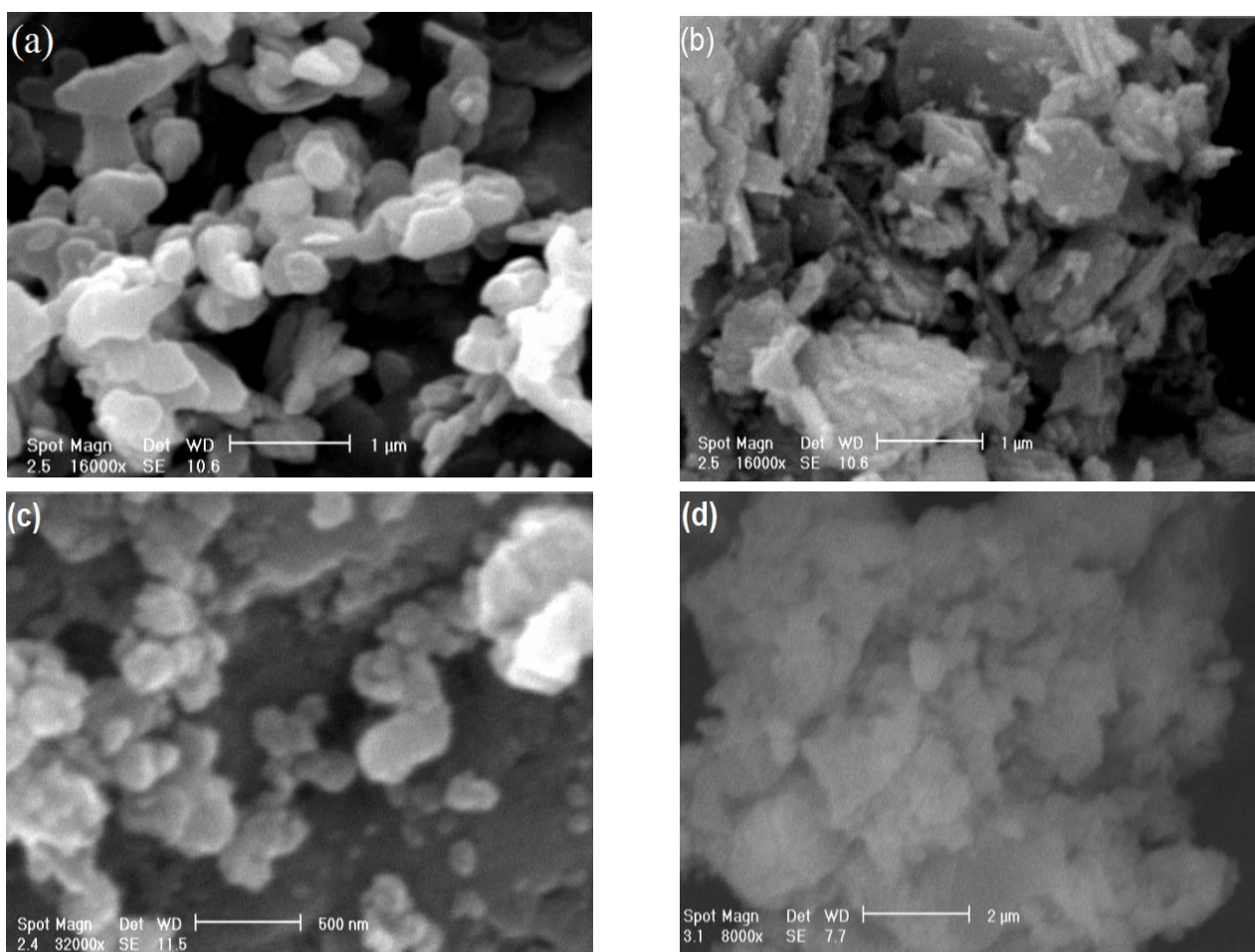
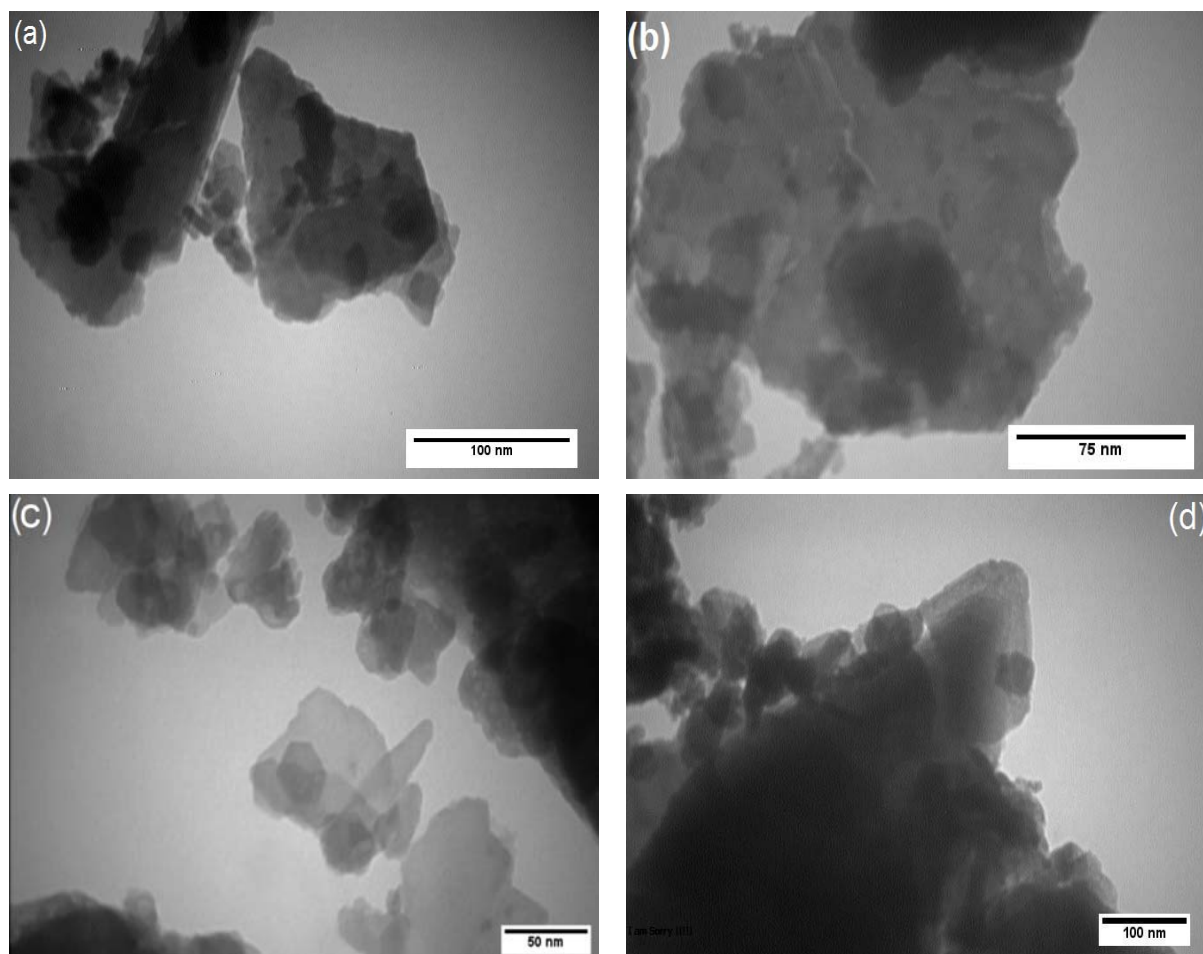


Fig. 2. SEM images of the regular morphology of prepared ZP (a), ZPZn fresh (b, c) and after the 7th run (d).

The presence of metallic crystal nanoparticles on the surface of ZP indicated that the zinc deposited on the surface of the ZP had agglomerated. Similar observations have also been reported for copper, zinc, and cerium with ZP [40,41]. Fig. 2(d) and 3(d) show the SEM and TEM images of the catalyst after several regenerations, respectively.

All these images showed that the sheets and particles had conglomerated to a much greater extent following the 7th run because of the process used to regenerate the catalyst. A detailed discussion about XRD, BET, and TPD-NH<sub>3</sub> of the catalyst is presented in the supplementary information (Pages S2-S6).

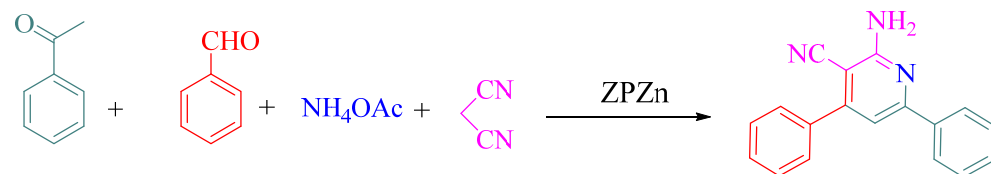


**Fig. 3.** TEM images of the regular morphology of prepared ZPZn fresh (a-c) (different magnification) and after the 7th run (d).

### 3.2. Synthesis of 2-amino-3-cyanopyridines

To find out the suitable conditions for the reaction, a series of experiments were performed for the synthesis of 2-amino-4,6-diphenylnicotinonitrile (**1a**) as a model compound (Table 2). The reaction was performed in various solvents to identify the best solvent condition. Several classic solvents such as EtOH, MeOH, CH<sub>3</sub>CN, H<sub>2</sub>O, DMF, n-hexane, CHCl<sub>3</sub>, THF, 1,4-Dioxane, toluene and also solvent-free conditions were examined. The experimental results showed that the yield of the product is higher under solvent-free conditions (Table 2, entry 11). In order to further improve the reaction yield, five experiments at different temperatures were performed (Table 2, entries 11-15). It was observed that the application of a lower temperature gave the corresponding product in lower yield. The reaction provided little amounts of product without the catalyst (Table 2 entry 20). The optimal conditions were determined as the reaction was catalyzed by 1.5 mol% of ZPZn under solvent-free

conditions at 60 °C in 60 min (Table 2 entry 11). To delineate the scope and generality of our new protocol, this methodology was examined by the reaction of several substituted aldehydes and acetophenones (Table 3). The reaction succeeded well, providing the corresponding 2-amino-4,6-diphenyl nicotinonitrile derivatives in fair to high yields, demonstrating the generality of the method and its good tolerance of both EW and ED substituents on the both aromatic rings. The electronic effect seemed to have a clear influence on the reaction since the EW groups on the different aromatic rings resulted in better yields than ED groups. We also studied this condensation reaction with 2-substituted benzaldehyde and found that the reaction time was longer and yields were somewhat lower than other aldehydes, which were possibly attributed to the steric hindrance (Table 3, entries 4,5). Surprisingly, the aliphatic aldehyde (hexanal) and the aliphatic ketone (acetone) gave no products. Obviously, the reactivity of aldehydes is the key factor for this one-pot transformation.

**Table 2.** Synthesis of 2-amino-4,6-diphenylnicotinonitrile (**1a**) under different conditions.<sup>a</sup>

Entry	Solvent	Catalyst (mol%)	Temp. (°C)	Time (min)	Yield (%) <sup>b</sup>
1	EtOH	1.5	Reflux	120	71
2	H <sub>2</sub> O	1.5	Reflux	120	Trace
3	MeOH	1.5	Reflux	120	66
4	CHCl <sub>3</sub>	1.5	Reflux	120	41
5	CH <sub>3</sub> CN	1.5	Reflux	120	45
6	THF	1.5	Reflux	120	53
7	DMF	1.5	100	120	61
8	n-hexane	1.5	Reflux	120	16
9	1,4-Dioxane	1.5	Reflux	120	32
10	Toluene	1.5	Reflux	120	22
11	Solvent-free	1.5	60	60	88
12	Solvent-free	1.5	R.T.	120	Trace
13	Solvent-free	1.5	40	120	46
14	Solvent-free	1.5	80	60	88
15	Solvent-free	1.5	100	60	89
16	Solvent-free	0.5	60	90	35
17	Solvent-free	1	60	60	58
18	Solvent-free	3	60	60	72
19	Solvent-free	5	60	60	88
20 <sup>c</sup>	Solvent-free	-	60	120	Trace

<sup>a</sup>The reaction was carried out in 5 ml of solvent.

<sup>b</sup>The yields refer to the isolated pure products.

<sup>c</sup>The reaction was carried out in the absence of ZPZn.

Based on previous research, a plausible mechanism for this condensation reaction was proposed. It is reasonable to suppose an initial activation of the carbonyl group of aldehyde by the Zn Lewis acid sites. Next, the carbonyl carbon was attacked by the nucleophilic malononitrile to form intermediate arylidene malononitrile. The subsequent Michael addition of ketone followed by cyclization afforded the desired final product (Scheme 2).

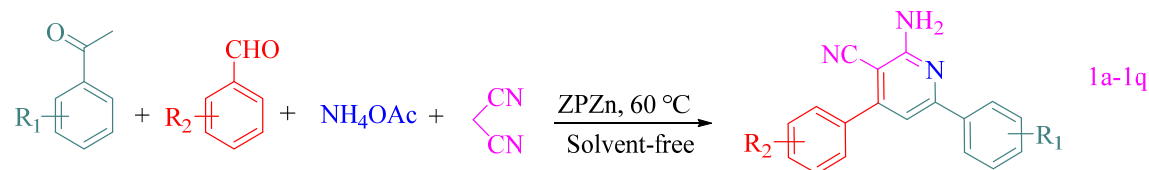
### 3.3. Reusability of the catalyst

The reusability of the ZPZn catalyst was investigated under the optimum reaction conditions for the synthesis of **1a**. The elemental composition of the catalyst remained largely unchanged following its 7th

run, although the amount of zinc in the catalyst was reduced by almost 60% compared with the first run (Table 1). The recycled ZPZn catalyst gave a similar product yield to the freshly prepared catalyst up until the sixth cycle. The yields for 7 runs were 90, 90, 90, 87, 83, 81 and 73%, respectively.

### 3.4. Comparison of activities of various catalysts

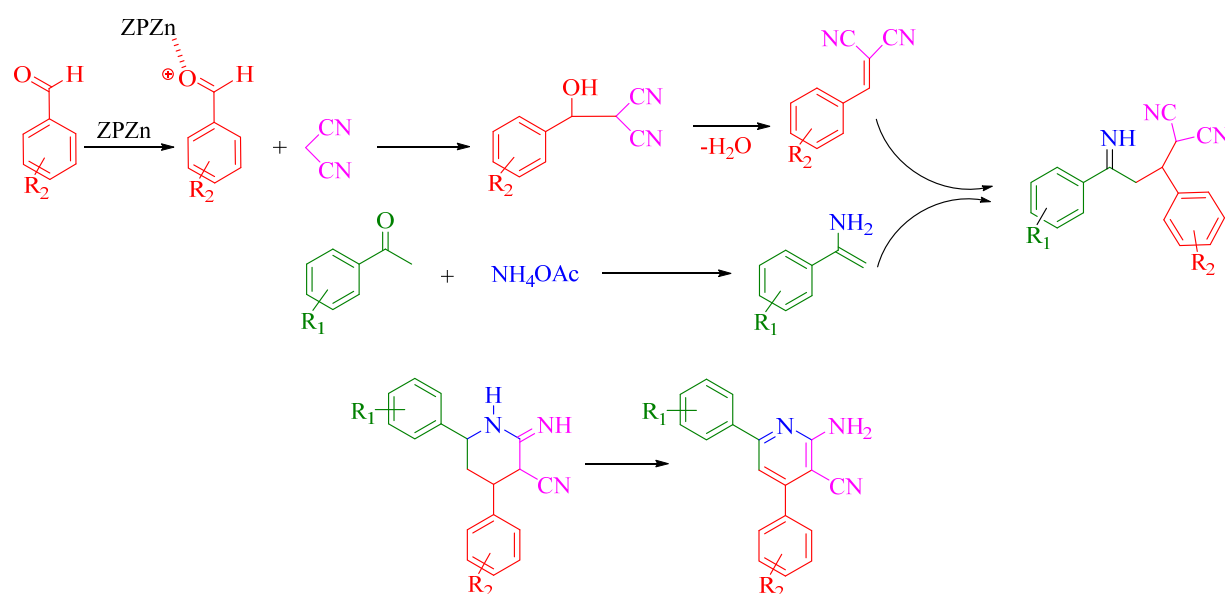
To show the value of the present work in comparison with reported results in the literature, the results of ZPZn catalyst for the synthesis of 2-amino-4,6-bis-(4-chlorophenyl)-nicotinonitrile (**1m**) was compared with results obtained by other groups (Table 4). As it can be seen from this Table, ZPZn acts as an effective catalyst with respect to reaction temperature, time, and yield.

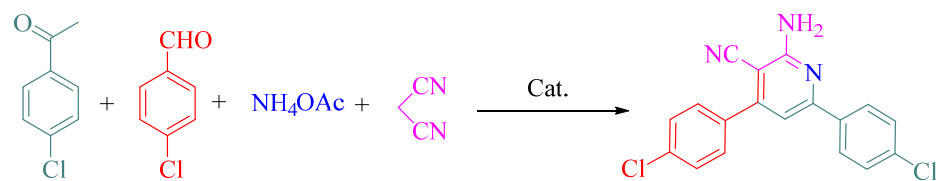
**Table 3.** Synthesis 2-amino-3-cyanopyridines using ZPZn under solvent-free conditions.<sup>a</sup>

Entry	Ketone	Aldehyde	Product	Time (min)	Yield (%)	m.p. (°C) <sup>b</sup>		Ref.
						Found	Reported	
1	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	1a	60	88	185-187	184-186	[13]
2	C <sub>6</sub> H <sub>5</sub>	4-Me-C <sub>6</sub> H <sub>4</sub>	1b	75	83	177-179	176-178	[13]
3	C <sub>6</sub> H <sub>5</sub>	4-MeO-C <sub>6</sub> H <sub>4</sub>	1c	75	80	179-181	180-182	[11]
4	C <sub>6</sub> H <sub>5</sub>	2-Cl-C <sub>6</sub> H <sub>4</sub>	1d	45	90	191-193	193-195	[12]
5	C <sub>6</sub> H <sub>5</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	1e	30	94	224-226	223-225	[13]
6	C <sub>6</sub> H <sub>5</sub>	4-Br-C <sub>6</sub> H <sub>4</sub>	1f	30	92	225-227	225-227	[16]
7	4-Me-C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	1g	90	85	177-179	178	[13]
8	4-MeO-C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	1h	90	82	179-181	177-179	[13]
9	4-Cl-C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	1i	45	91	240-242	241-242	[12]
10	4-Br-C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	1j	45	92	242-244	241-243	[16]
11	4-Cl-C <sub>6</sub> H <sub>4</sub>	4-Me-C <sub>6</sub> H <sub>4</sub>	1k	60	89	216-217	216-218	[11]
12	4-Cl-C <sub>6</sub> H <sub>4</sub>	4-MeO-C <sub>6</sub> H <sub>4</sub>	1l	60	86	203-203	204-205	[12]
13	4-Cl-C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	1m	20	94	231-233	230-231	[13]
14	4-Me-C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	1n	45	90	173-175	172-174	[16]
15	4-MeO-C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	1o	45	88	195-197	195-196	[14]
16	4-F-C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>	1p	20	95	217-219	219-220	[14]
17	4-MeO-C <sub>6</sub> H <sub>4</sub>	4-MeO-C <sub>6</sub> H <sub>4</sub>	1q	90	82	160-162	160-162	[14]

<sup>a</sup>All products were characterized by M.p, IR and <sup>1</sup>H NMR spectral data and comparison with those of authentic samples or reported data (Supplementary information Pages S7-S11).

<sup>b</sup>Isolated yield.

**Scheme 2.** A plausible reaction mechanism for the synthesis of 2-amino-3-cyanopyridine derivatives.

**Table 4.** Comparison of efficiency of various catalysts in the synthesis of **1m**.

Entry	Catalyst	Solvent	Temp. (°C)	Time (min)	Yield (%) <sup>a</sup>	Ref.
1	[EtNH <sub>3</sub> ]NO <sub>3</sub>	Solvent-free	60	150	90	[7]
2	MW <sup>b</sup>	Solvent-free	-	8	83	[11]
3	Yb(PFO) <sub>3</sub>	EtOH	Reflux	240	85	[12]
4	FePO <sub>4</sub>	EtOH	Reflux	240	93	[13]
5	TBBDA	Solvent-free	100	30	90	[14]
6	[Bmim][BF <sub>4</sub> ]	Solvent-free	60	300	88	[16]
7	Cellulose-SO <sub>3</sub> H	H <sub>2</sub> O	60	150	94	[17]
8	SBTETASA	Solvent-free	100	10	90	[20]
9	Trifluoroethanol	Solvent-free	Reflux	360	95	[21]
10	α-ZrP	Solvent-free	60	120	64	This Work
11	ZPZn	Solvent-free	60	60	88	This Work

<sup>a</sup>The yields refer to the isolated pure products.

<sup>b</sup>Microwave irradiation.

#### 4. Conclusions

In summary, we have reported the catalytic performance of water-insoluble ZPZn in an MCR. The catalyst was characterized by various methods and results showed good agreement with the literature. ZPZn showed outstanding catalytic performance with fair to excellent yields for all condensation reactions. These conditions are compatible with some acid-sensitive functional groups. The attractive features of these procedures are shorter reaction times, mild reaction conditions, high yields and no side reactions, ease of preparation and handling of the catalyst, green aspects by avoiding toxic catalysts and solvents, recyclability of the catalyst, and simple experimental procedure.

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