



Original Research Article

Efficient Pseudo-Six-Component Synthesis of Tetrahydro-pyrazolopyridines Using [Zn-2BSMP]Cl₂Ahmad Reza Moosavi-Zare^{1,*}, Hamid Goudarziafshar¹, Zahra Jalilian², Fatemeh Hosseinabadi³¹Hamedan University of Technology, Hamedan, 65155, Iran²University of Kurdistan, Pasdaran Street, Sanandaj, 66177-15177, Iran³Sayyed Jamaledin Asadabadi University, Hamedan, Iran

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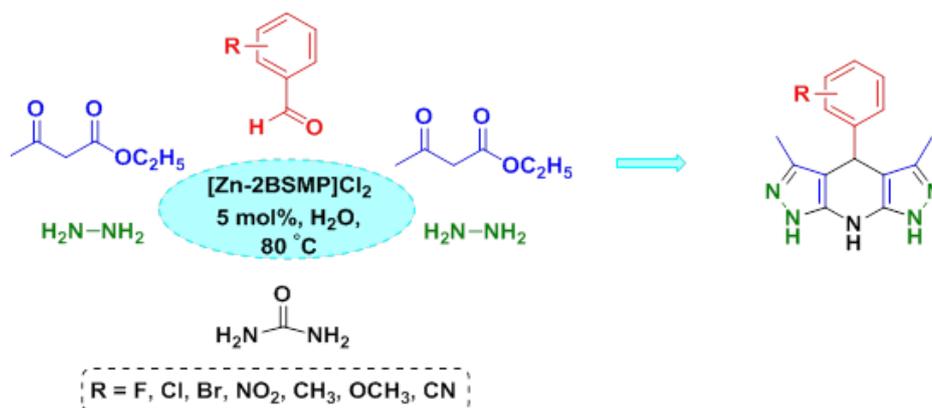
Tetrahydro-pyrazolopyridine

Multi-component reaction

ABSTRACT

Zn-[2-boromophenyl-salicylaldehyde-methylpyranopyrazole]Cl₂ {[Zn-2BSMP]Cl₂}, as a Schiff base complex, efficiently catalyzed the pseudo-six-component synthesis of tetrahydrodipyrazolopyridines by the condensation reaction of aryl aldehyde, hydrazine hydrate, ethyl acetoacetate and urea at 80 °C. Urea was used instead of ammonium salts as a source of ammonia by *in situ* generation of ammonia, in the presence of a little amount of water.

GRAPHICAL ABSTRACT



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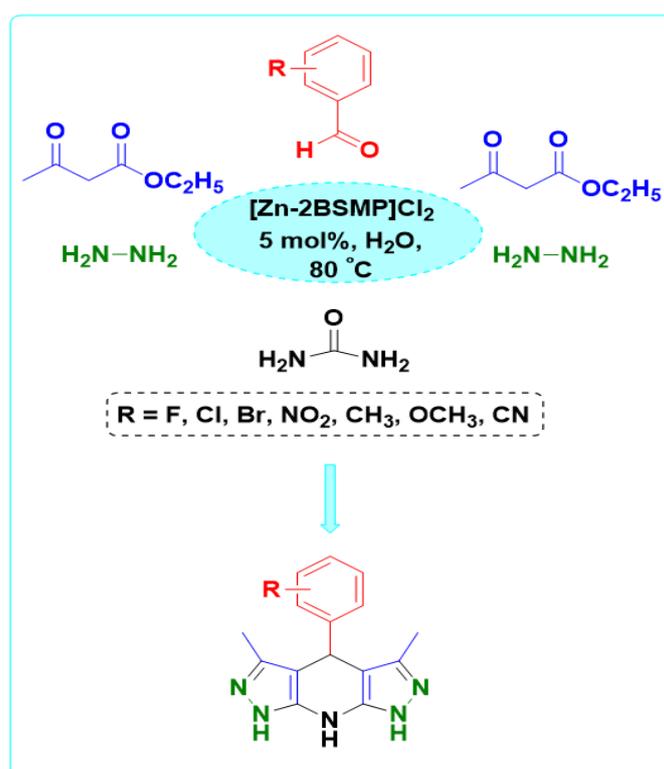
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Introduction

Pyrazolopyridines as an important biological group of organic compounds show pharmacological activities such as antiviral [1, 2], antimicrobial [3, 4], antileishmanial [5], antitumor [6], hypoglycemic [7], anxiolytic [8], anti-inflammatory [9], antiherpetic [10], antileishmania [11] and antiallergic [12]. Also, they act as protein kinase inhibitors [13, 14]. Pseudo-six-component synthesis of tetrahydrodipyrzolo-pyridines, by the condensation reaction of aryl aldehyde, hydrazine hydrate, ethyl acetoacetate and ammonium acetate, is an important strategy for the synthesis of the mentioned compounds [13]. Multi-component reactions are important protocol in organic synthesis due to their implementation in one step without the production of by-products. Saving the energy, time, solvent and chemical materials and reducing the production of chemical waste are some other advantages of these reactions [15-20]. The synthesis of tetrahydrodipyrzolo-pyridines (THPPs) by the condensation reaction of aldehyde, hydrazine

hydrate, alkyl acetoacetate and ammonium acetate were reported by different catalysts including triethanolamine-sodium acetate [13], nano-CdZr₄(PO₄)₆ [21], CuFe₂O₄@HNTs nanocomposite [22], (Fe₃O₄/KCC-1/IL/HPW) [23], nano-Fe₃O₄@SiO₂-SO₃H [24], nano-FeNi₃ [25], CuFe₂O₄@HNTs [26], nano-ovalbumin [27]. In the mentioned reports ammonium salts were used for the synthesis of THPPs by *in situ* generation of ammonia in the reaction. But limited methods were reported for the preparation of THPPs which urea used as a source of ammonia in the reaction.

According to the above facts and based on our previous works which have done in the use of Schiff base complex as a catalyst in the synthesis of organic compounds [28-36], we have applied Zn-[2-boromophenyl-salicylaldimine-methylpyranopyrazole]Cl₂ {[Zn-2BSMP]Cl₂} as an efficient catalyst for the preparation of 3,5-dimethyl-4-aryl-1,4,7,8-tetrahydrodipyrzolo[3,4-b:4',3'-e]pyridines (THPPs) by the reaction of aryl aldehyde, ethyl acetoacetate, hydrazine hydrate and urea in water at 80 °C (Scheme 1).



Scheme 1: The preparation of tetrahydro-pyrazolopyridines

Materials and Methods

Procedure for the synthesis of Zn-[2-bromophenyl-salicylaldehyde-methylpyranopyrazole]Cl₂ ([Zn-2BSMP]Cl₂)

A mixture of 6-amino-3-methyl-4-(4-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile, prepared according to previous literature [37], as an amine (1 mmol, 0.297 g) and ZnCl₂ (1 mmol, 0.136 g) was pulverized in a mortar and then added to a 25 mL round-bottomed flask containing 2-hydroxybenzaldehyde (1.5 mmol, 0.183 g) connected to a reflux condenser and stirred at 100 °C for appropriate time. The resulting mixture was then washed several times with ethyl acetate and hexane (9/1) to separate excess salicylaldehyde from the synthesized complex. The accuracy of the preparation of this complex was confirmed by IR analysis and comparison with the previous sample reported in the previous literature [35].

General procedure for the synthesis of tetrahydropyrazolopyridines

A mixture of hydrazine hydrate (2 mmol, 0.064 g), ethyl acetoacetate (2 mmol, 0.26 g), aryl aldehyde (1 mmol), urea (3 mmol, 0.18 g) and a few drops of water were added to 25 mL round-bottomed flask connected to a reflux condenser and heated at 80 °C for appropriate times. After completion of the reaction based on TLC test, in order to separate the reaction mixture from the Schiff base complex, the reaction mixture was extracted with warm ethanol (10 mL) and separated from the catalyst by filtration. Lastly, the product was purified by recrystallization from ethanol (90 %).

Selected spectral data of compounds

4-(2-chlorophenyl)-3,5-dimethyl-1,4,7,8-tetrahydropyrazolo[3,4-b:4',3'-e]pyridine (8)

White solid; m.p.=230-233 °C; ¹H-NMR (250 MHz, DMSO-*d*₆): δ (ppm) 1.90 (s, 6H, 2CH₃), 5.09 (s, 1H, CH), 7.17 (t, *J* = 7.50 Hz, 2H, ArH), 7.30 (d, *J* = 5.0 Hz, 1H, ArH), 7.50 (d, *J* = 5.0 Hz, 1H, ArH), 10.70 (s, 3H, 3NH); ¹³C-NMR (62.5 MHz, DMSO-*d*₆): δ

(ppm) 10.8, 31.8, 102.7, 126.8, 127.9, 129.4, 131.0, 132.7, 139.0, 141.1, 161.1.

3,5-dimethyl-4-p-tolyl-1,4,7,8-tetrahydropyrazolo[3,4-b:4',3'-e]pyridine (10)

White solid; m.p.=244-245 °C; IR (KBr, cm⁻¹): 3558, 3308, 2968, 1613, 1509, 1048, 750, 522; ¹H-NMR (250 MHz, DMSO-*d*₆): δ (ppm) 2.04 (s, 6H, 2CH₃), 2.20 (s, 3H, CH₃), 4.75 (s, 1H, CH), 6.98 (s, 4H, ArH), 11.03 (s, 3H, 3NH); ¹³C-NMR (62.5 MHz, DMSO-*d*₆): δ (ppm) 10.8, 20.9, 32.7, 104.8, 127.8, 128.7, 134.6, 140.1, 140.7, 161.5.

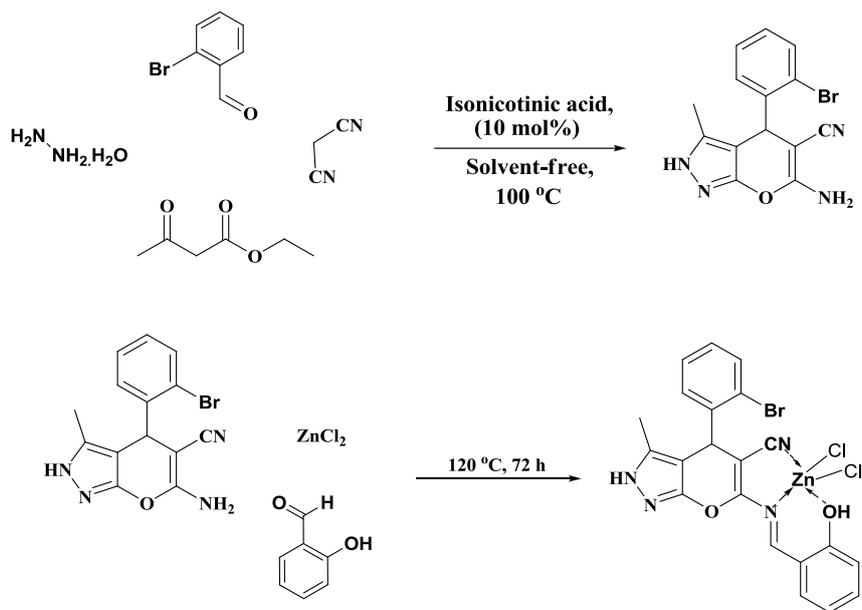
Results and Discussion

The related amine was prepared according to previous literature by the reaction of 2-bromobenzaldehyde with ethyl acetoacetate, malononitrile and hydrazine hydrate in acidic media [37]. Then, the prepared amine, namely 6-amino-4-(2-bromophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile, reacted with 2-hydroxybenzaldehyde and ZnCl₂ to give [Zn-2BSMP]Cl₂ as a nano-Schiff base complex and catalyst [35]. The steps for the synthesis of catalyst are shown in [Scheme 2](#).

The preparation of [Zn-2BSMP]Cl₂ was confirmed by FT-IR spectrum, based on which the broad peak at 3000-3600 cm⁻¹ is related to O-H stretching of hydroxyl group and a peak at 1654 cm⁻¹ is corresponded to stretching mode of C=N bond in the structure of catalyst. The important functional groups in the structure of catalyst were identified by FT-IR analysis.

Also, the morphology of [Zn-2BSMP]Cl₂ as a Schiff base complex and catalyst was investigated by scanning electron microscopy (SEM). SEM analysis of [Zn-2BSMP]Cl₂ is depicted in [Figure 1](#). Examination of [Scheme 1](#) proves the presence of nanoscale particles in the synthesized catalyst.

To further investigate the catalyst particle size, the prepared particles of [Zn-2BSMP]Cl₂ were studied by transmission electron microscopy (TEM). By checking the image obtained from the TAM analysis in [Figure 2](#), the presence of nano-sized particles in the synthesized catalyst is confirmed.



Scheme 2: The preparation of [Zn-2BSMP]Cl₂

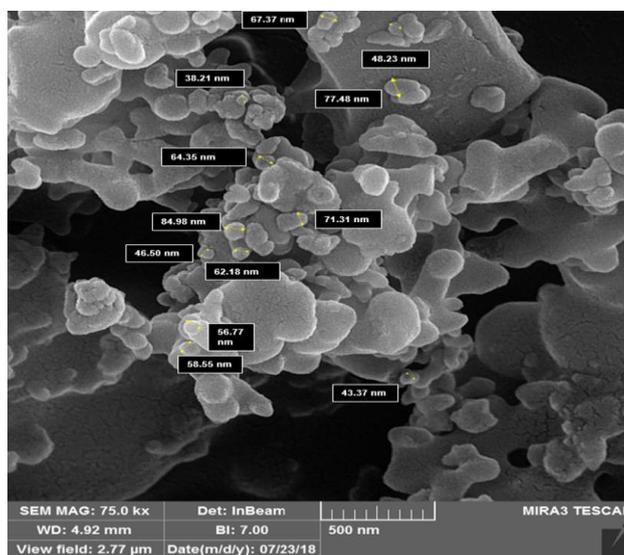


Figure 1: The SEM micrograph of [Zn-2BSMP]Cl₂

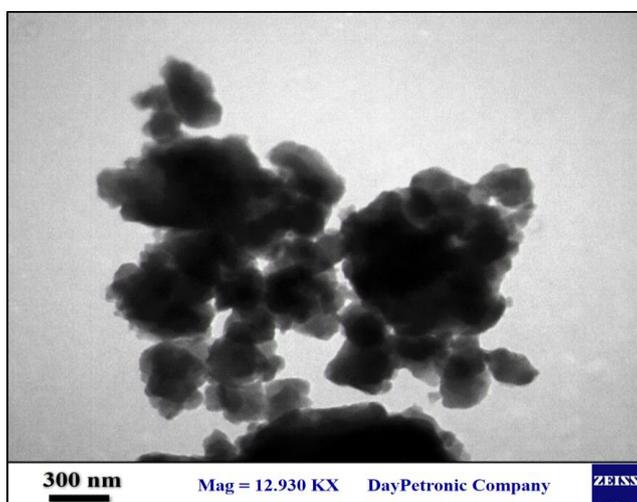


Figure 2: Transmission electron micrographs (TEM) of [Zn-2BSMP]Cl₂

In the next step, for the optimization of the reaction condition, the reaction of 4-chlorobenzaldehyde, hydrazine hydrate, ethyl acetoacetate and urea was considered as model reaction and different amounts of catalyst, temperature and different solvents, both polar and non-polar were examined on this reaction (Table 1). Different solvents such as ethanol, ethyl acetate, dichloromethane, water and chloroform were examined in this reaction, in which the best result was obtained using 5 mol% of [Zn-2BSMP]Cl₂ as a catalyst at 80 °C under solvent-free condition. The model reaction was also tested in the presence of ZnCl₂ in comparison with [Zn-2BSMP]Cl₂, which did not show the

efficiency of [Zn-2BSMP]Cl₂ to give the related product (Table 1).

After the optimization of the reaction condition, the optimal conditions were tested on the reaction of different aromatic aldehydes, containing electron donor and electron acceptor groups and halogens on different positions of the aromatic ring, with hydrazine hydrate, ethyl acetoacetate and urea to give 3,5-dimethyl-4-aryl-1,4,7,8-tetrahydrodipyrzolo[3,4-b:4',3'-e]pyridines (THPPs) with high yields and short reaction times (Table 2). The time and obtained yield from the synthesized products are shown in Table 2.

Table 1: The optimization of the reaction condition

Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (min)	Yield ^a (%)
1	[Zn-2BSMP]Cl ₂ (5 mol%)	-	80	60	95
2	[Zn-2BSMP]Cl ₂ (3 mol%)	-	80	60	75
3	[Zn-2BSMP]Cl ₂ (8 mol%)	-	80	60	95
4	[Zn-2BSMP]Cl ₂ (5 mol%)	-	60	60	65
5	[Zn-2BSMP]Cl ₂ (5 mol%)	-	100	60	95
6	[Zn-2BSMP]Cl ₂ (5 mol%)	Chloroform	Reflux	60	40
7	[Zn-2BSMP]Cl ₂ (5 mol%)	Ethyl acetate	Reflux	60	85
8	[Zn-2BSMP]Cl ₂ (5 mol%)	Ethanol	Reflux	60	90
9	[Zn-2BSMP]Cl ₂ (5 mol%)	Water	80	60	38
10	[Zn-2BSMP]Cl ₂ (5 mol%)	Dichloromethane	Reflux	60	45
11	-	-	80	60	15
12	ZnCl ₂ (5 mol%)	-	80	60	61

Table 2: The preparation of tetrahydro-pyrazolopyridines

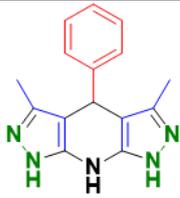
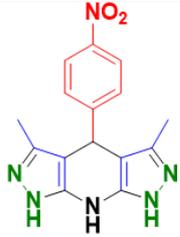
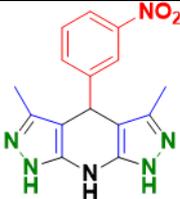
Entry	Product	Time (min)	Yield (%) ^a	M.p. °C (Lit.) [ref]
1		65	90	237 (240-242) [2]
2		60	92	291-293 (295-297) [2]
3		65	87	283 (286-288) [40]

Table 2: Continued

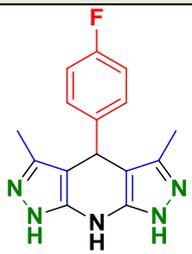
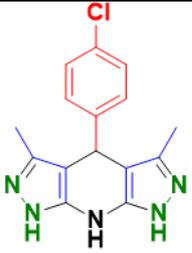
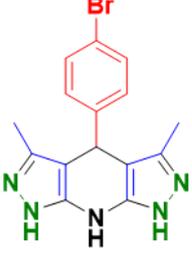
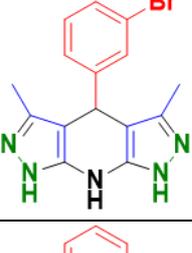
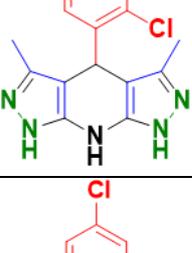
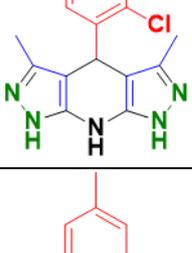
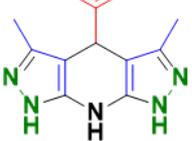
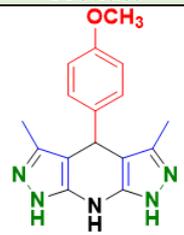
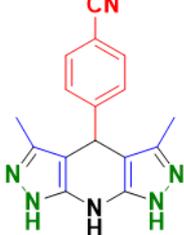
Entry	Product	Time (min)	Yield (%) ^a	M.p. °C (Lit.) [ref]
4		65	85	260 (258-260) [23]
5		55	95	254-256 (255-257) [2]
6		55	92	230 (221-224) [13]
7		60	88	240-242 (245-247) [41]
8		55	90	230-233 (220-222) [38]
9		65	82	290-291 (>300) [40]
10		70	85	244-245 (245-247) [23]

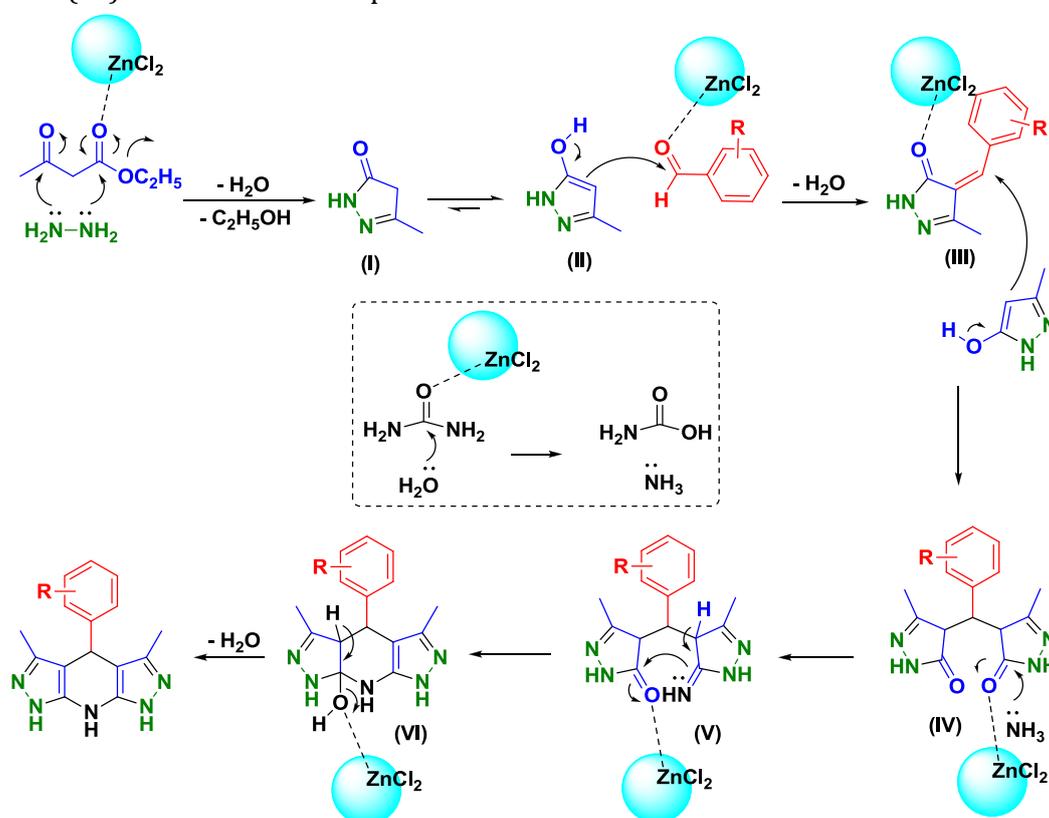
Table 2: Continued

Entry	Product	Time (min)	Yield (%) ^a	M.p. °C (Lit.) [ref]
11		75	70	205-207 (206-209) [13]
12		65	72	291-293 (286-288) [40]

^aIsolated yield

In the mechanism taken from previously reported literature [38-41], by the nucleophilic attack of hydrazine to the carbonyl groups of ethyl acetoacetate which is activated by the catalyst, 3-methyl-1*H*-pyrazol-5(4*H*)-one (**I**) is prepared after removing of one molecule of water and ethanol. Then, intermediate (**II**), which is prepared by the tautomerization of (**I**), reacts with activated aldehyde to give (**III**). Intermediate (**III**) as a Michael acceptor reacts

with another pyrazolone ring to furnish (**IV**). Catalytic hydrolysis of urea with water in the reaction mixture generates carbamic acid and ammonia [42, 43]. Nucleophilic attack of ammonia with (**IV**) prepares (**V**) converted to (**VI**) after intra molecular nucleophilic attack and cyclization. Finally, by removing of one molecule of water from (**VI**), the expected product is prepared (Scheme 3).



Scheme 3: The proposed mechanism for the preparation of tetrahydro-pyrazolopyridines

To study the ability of the catalyst to recover and reuse it for other reactions, the reaction mixture was extracted with warm ethanol and separated from the catalyst by filtration. The recovered catalyst was reused twice in the model reaction,

i.e. the reaction of 4-chlorobenzaldehyde, hydrazine hydrate, ethyl acetoacetate and urea, where the reaction times and obtained yields were acceptable. The results of this study are presented in Figure 3.

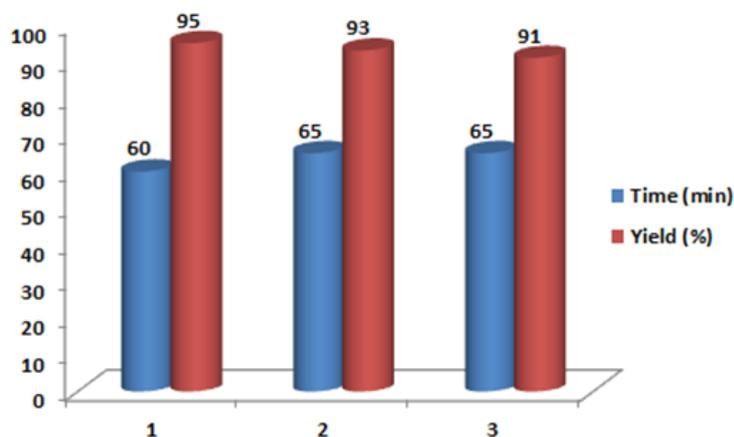


Figure 3: The reusability of the catalyst

Conclusion

As a result, [Zn-2BSMP]Cl₂ was directly used as a Schiff base complex and catalyst without using of any co-catalyst for the pseudo-six-component synthesis of tetrahydro-dipyrzolo-pyridines by the reaction of aryl aldehyde, hydrazine hydrate, ethyl acetoacetate and urea in the presence of a little amounts of water at 80 °C.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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