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Synthesis of hexahydroquinoline (HHQ) derivatives using $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ as a potential green catalyst and optimization of reaction condition using design of experiment (DOE)

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In this investigation, hexahydroquinoline (HHQ) derivatives were synthesized by one-pot reaction using dimedone, b-ketoester, ammonium acetate, and with different aryl aldehyde. $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ was used as the potential green catalysts, commercially available solid material, with low toxicity, low cost, ease of handling, and high activity. The reaction condition was optimized using response surface method (Central Composite Design (CCD)) with three replicates at a central point. Optimization showed that optimum temperature and catalyst amount are 83.75 °C and 0.15 mol%, respectively. Loss of reaction yield after 83.75 °C is related to the formation of a new crystalline phase of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$. The fitted quadratic polynomial model to the experimental yield could well predict the experimental reaction yield. Ecofriendly reaction condition, easy workup procedure, the reusability of the catalyst, short reaction times with high yields are some advantages of this work.

Introduction

Multicomponent reactions (MCRs) are one-pot reactions which more than two starting material reacts together, where most of the starting materials atoms present in the target molecule.¹ MCRs are atom economic, effective, convergent, and show a high bond-forming-index (BFI) (several non-hydrogen atom bonds are formed in one-pot reaction).² So, MCRs are often more useful than conventional sequential multistep synthesis.

One of the most important and conventional MCR is the dihydropyridine (DHP) synthesis which is attributed to Arthur Hantzsch which discovered in 1881.³ Due to the versatility and the general stability of the products, Hantzsch method has remained the most common method for the synthesis of 1,4-dihydropyridines. First, Dihydropyridines were discovered to be active part of nicotinamide adenine dinucleotide (NADH), the essential reducing coenzyme in animals. Finally, nifedipine (a DHP derivative) came to market as a calcium channel modulating agent.⁴ Although DHPs were primarily developed as cardiovascular agents, but they are vasodilator, antihypertensive, bronchodilator, antiatherosclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective, and antidiabetic agents.⁵ Their widespread pharmacological properties have interested the researchers to find new derivatives which are more effective, selective, stable, and perhaps with different modes of action.⁶ Modification of DHP ring and its substitutes is a combinatorial chemistry that makes it possible to prepare a large number of compounds which can be analyzed by structure activity relationship to design better DHPs.^{7, 8} One of possible structural scaffold modifications of DHP is incorporating fused ring to DHPs, that leads to hexahydroquinoline (HHQ) derivatives, which are successfully explored by the Safak's group.⁹

HHQs clearly show the remarkable potential of novel dihydropyridine derivatives as sources of valuable drug candidates. HHQs derivatives possess a variety of biological activities, such as vasodilatory, bronchodilatory, antiatherosclerotic, antitumor, geroprotective, hepatoprotective, and antidiabetic property.^{10, 11}

Without using any catalyst, transformation of starting material to HHQs derivatives has long reaction times, harsh reaction conditions, and large quantities of organic solvents and commonly gives low yields. So, various catalysts such as Lewis acids,^{12, 13} bases,^{14, 15} salts,¹⁶ and ionic liquids^{17, 18} have been used to solve mentioned problems. Although some of these are successful, but most of them are expensive, toxic, and are difficult to be separated from the reaction medium. Therefore, it is important to apply an effective catalyst that does not have the above mentioned problems. So, we have reported a clean, ecofriendly, facile, and rapid solvent-free reaction for the synthesis of HHQs derivatives in the presence of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$. This is a commercially available solid material, with low toxicities (LD50 $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ oral rate = 2950 mg/kg), low costs, ease of handling, high activity. The zirconium (IV) compounds are ecofriendly and potential green catalysts or reagents which are used in many organic reactions under mild condition with excellent yield.^{18, 19} It should be noted that, many of the chemists optimize their reactions using one variable at a one time (OVAT). Optimization by OVAT method is valid only when the variables have not cross interaction.²⁰ In this study optimization of the reaction condition was done by design of experiments.

Experimental

Materials

All chemicals were purchased from Merck and Fluka Chemical Companies. The products were identified by ^1H , ^{13}C NMR, mass analysis and melting points as well as IR spectra. The corresponding spectral data have been reported in the Experimental section. The ^1H , ^{13}C NMR (500 MHz) was recorded on a Bruker Avance DPX-400 FT-NMR spectrometer (δ in ppm). Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX 85 apparatus. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. Infrared spectrum of products was recorded by Perkin Elmer PE-1600-FTIR. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates.

General procedure for Preparation of HHQs

ZrOCl₂.8H₂O (0.0451 g, 14 mol%) as a catalyst, was added to a mixture of dimedone (0.28 g, 2mmol), aryl aldehyde (2 mmol), beta-ketoester (2 mmol) and ammonium acetate (0.185 g, 2.4 mmol) in a test tube, then the resulting mixture was firstly stirred magnetically, and after solidification of the reaction mixture with a small rod, at 90°C. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature. Then, ethyl acetate (25 mL) was added, stirred and refluxed for 3 min. The solid catalyst was collected by filter paper and separated from the solution of product and remaining starting materials. The crude product was purified by recrystallization from ethyl acetate as a less toxic Class III solvent.²¹ The reaction is shown in the Fig. 1.

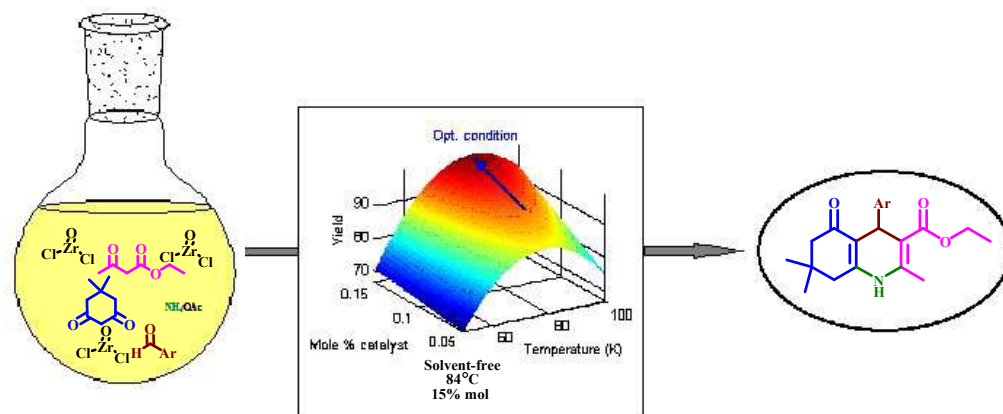


Fig. 1 Preparation of hexahydroquinoline at optimum condition using $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ as the clean and ecofriendly catalyst.

Results and discussion

First, to find reaction condition for the synthesis of HHQs derivatives, reaction of aryl aldehydes, dimedone (5,5-dimethylcyclohexane-1,3-dione), ethyl acetoacetate and ammonium acetate was selected as a representative reaction. The reaction was carried out in various solvents with $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ as a catalyst to investigate the effect of solvent on the reaction time. In addition, the reaction was carried out with catalyst in the solvent-free condition. From time and yield point of view, the reaction in solvent-free condition is more efficient than in the presence of solvents. The results are given in the Table 1.

Table 1 Time and yield of the model reaction with and without solvent in the presence of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ as a catalyst.

Entry	Solvent	Time (min)	Yield ^a (%)
			<u>50 °C</u>
1	---	5	96
2	EtOAc	25	93
3	CH_2Cl_2	60	95
4	H_2O	60	50
5	<i>n</i> -Hexane	60	80
6	Acetonitrile	15	95
7	EtOH	60	86

^aIsolated yield.

Therefore, the solvent-free method is more efficient (entry 1) and can be selected for the representative reaction. In other hand, Lewis acids catalyst such as $ZrOCl_2 \cdot 8H_2O$, ZrO_2 , and $FeCl_3$ were applied to investigate the effect of various catalyst on the reaction (Table 2). As it given in Table 2, $ZrOCl_2 \cdot 8H_2O$ (10 mole %) as a catalyst, leads to higher yield and shorter reaction time.

Table 2 Effect of different catalysts on the time and yield of the reaction.

Entry	Catalyst	Amount of catalyst (mol %)	Time (min)	Yield ^a (%)
1	$ZrOCl_2 \cdot 8H_2O$	10	5	96
2	ZrO_2	10	15	90
3	$FeCl_3$	10	20	85

^aIsolated yield.

Statistical analysis and the model fitting

The Central Composite Design (CCD) as a response surface method, with three replicates at central point was employed to fitting the experimental data to a polynomial model. Two main factors that can affect the yield of the reaction are temperature (X_1) and amount of catalyst (X_2). These variables were coded to three levels of +1, 0, and -1. The levels of the variables and the corresponding response values (reaction yield) are shown in Table 3.

Table 3 Levels of the experimental variables and the corresponding response values of the CCD.

Runs	Independent variables				Dependent variable
	X_1 (temperature)		X_2 (amount of catalyst)		
	Coded levels	Actual levels	Coded levels	Actual levels	Yield
1	0	75.00	0	0.10	92.00
2	+1	100.00	0	0.10	85.00
3	-1	50.00	-1	0.05	67.00
4	0	75.00	0	0.10	91.00
5	0	75.00	-1	0.05	88.00
6	-1	50.00	+1	0.15	73.00
7	-1	50.00	0	0.10	67.00
8	+1	100.00	+1	0.15	93.00
9	+1	100.00	-1	0.05	73.00

10	0	75.00	0	0.10	93.00
11	0	75.00	+1	0.15	95.00

Table 4 Analysis of variance for the response surface quadratic model for yield

Source	p-val. prob.>F
Model (yield)	0.0003
X ₁	0.0004
X ₂	0.0015
X ₁ X ₂	0.0223
X ₁ ²	<0.0001
X ₂ ²	0.9852

Reaction yield was used as the dependent variables and to investigate the effect of variables on the reaction yield, all of the runs (reactions) of Table 3 were stopped after 2 minutes. Analysis of variance (ANOVA) shows that quadratic can well predict the experimental data (Table 4). The p-values show that the model is significant from a statistical point of view. The smaller the p-value, the more significant the term. The coefficient of determination (R²) for yield is 0.9813 with the derived model, which demonstrates that theoretical values are in good agreement with the experimental data. Polynomial response surface models for time and yield based on significant levels and actual values are resulted from experimental design:

$$Y(\text{Yield}) = -59.37 + 3.73X_1 - 102.10X_2 + 2.8X_1X_2 - 0.025X_1^2 + 10.53X_2^2 \quad (1)$$

It can be seen from coefficient of equation (1) that X₂ (amount of catalyst) has a greater impact on the reaction yield than X₁ (temperature) and there is a considerable interaction between X₁ and X₂. Generally, the terms that have minus and plus sign have negative and positive effect on yield, respectively. The magnitude of the effect of X is related to the value of coefficients in Y. Fig. 2 represents the contour and three dimensional of reaction yield versus temperature and

amount of catalyst. As it is shown in Fig. 2, by increasing the amount of catalyst, the reaction yield increases, but as temperature increase, a maximum point can be seen in the reaction yield.


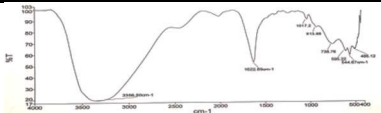

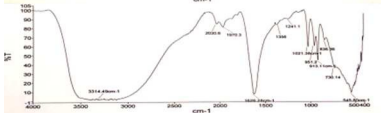

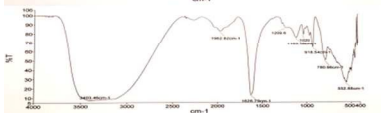

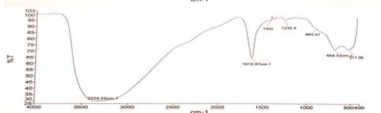

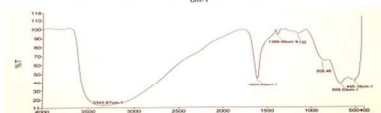

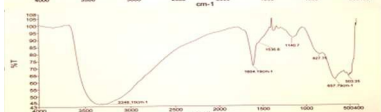

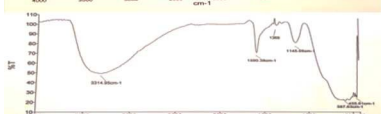
This behavior can be related to the dehydration/decomposition of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ at temperature above 85°C . Using differential thermal analysis (DTA) and thermogravimetric analysis (TGA),²²⁻²⁴ a broad endothermic feature is evident in the DSC curve for zirconyl chloride octahydrate up to about 55°C , which reflects the removal of weakly held water molecules (lattice waters) from the crystal between 25 and 55°C . The integrity of the tetranuclear zirconyl cations appears to be unaffected within this temperature range.²⁵ Above 55°C , a prominent exothermic peak centered about 73°C and a minor exothermic maximum about 85°C has been observed, which indicate an increase in the degree of structural ordering (crystallization). TG data has been revealed the removal of the third lattice and one of the four coordinatively bound water molecules, respectively, by 73 and 90°C . Thus, the removal of these two water molecules results in the formation of a new crystalline phase. For the formation of the tetrahydrate a reduction of the Zr coordination number from eight to seven has been proposed.²⁶ Two well-separated endothermic peaks has been observed above 110°C (125 and 175°C), which indicate a significant reduction in crystallinity of the compound (melting). Melting might be initiated by the removal of chloride counterions above 100°C .²⁴

Based on above discussion, yield reduction at temperatures above 85°C can be related to the removal of the third lattice and one of the four coordinatively bound water molecules, new crystalline phase formation, and changes the Zr coordination number ion from eight to seven. It can be deduced that tetranuclear zirconyl cations are the actual catalytic species. In other hand, these finding is good agreement with our previous research that the maximum yield of the

reaction in the presence of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ as a catalyst was obtained at 60 watt of microwave power.²⁷

To investigate the connectivity between the decomposition/dehydration of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ and its catalytic activity, 0.075 gr of catalyst was heated for 30 minutes. The catalyst was weighed before and after heating. Then the reaction was carried out in room temperature with the decomposed/dehydrated catalyst. Infrared spectra, weight of the catalyst before and after the heating, and reaction yield are provided in the Table 5.

Table 5 The effect of temperature on the dehydration/decomposition of the $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$

Heating temperature (°C)	Weight (before)	Weight (after)	Yield (%)	Image	IR spectra
50	0.075	0.0616	70		
75	0.075	0.0556	96		
100	0.075	0.0495	90		
125	0.075	0.0407	76		
150	0.075	0.0347	65		
200	0.075	0.0341	51		
250	0.075	0.0338	32		

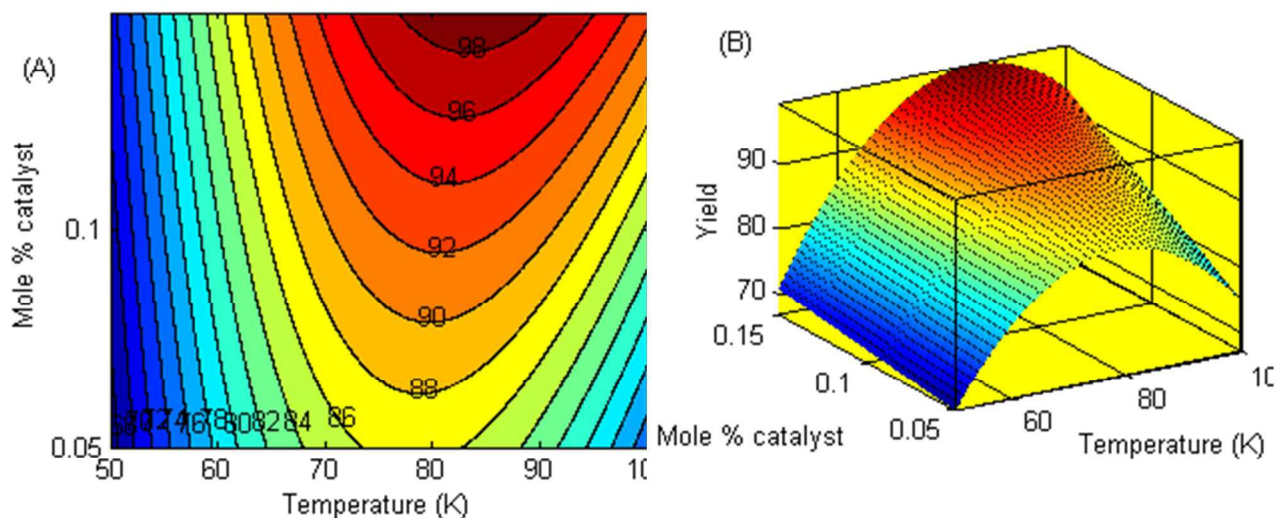


Fig. 2 The contour and three dimensional of reaction yield versus temperature and amount of the catalyst

Optimization of reaction condition and validation of the model

Optimization of the equation (1) as the constrained problem showed that optimum reaction conditions are $X_1=83.75$ and $X_2=0.15$. At these optimum conditions corresponding maximum yield is 99.21%. The validity of the model for predicting reaction yield was tested using the optimum condition. The predicted and experimental optimum responses are shown in Table 6.

Table 6. Predicted and experimental value of responses at the optimum condition

Optimum	Optimum variables		Optimum response	
	X_1	X_2	Time (min)	Yield (%)
Predicted	83.75	0.15	1	99.21
Experimental	85.00	0.15	1	97.00

A mean value of 97.00% (N=3) and with deviation of 2.27% for yield was obtained from experimental results deviation in that are in good agreement with predicted responses. This shows that one can using equation (1) predict the experimental yield with an acceptable

deviation. In order to investigate the effect of ZrOCl_2 as a catalyst on the reaction yield, the optimum condition was repeated without catalyst ($X_1=85.00$ and $X_2=0.15$). Result shows that the presence of ZrOCl_2 is a key factor to decrease reaction time to reach a specified yield (Table 7).

Table 7. Checking optimum condition without catalyst

	Variables		response	
	X1	X2	Time (min)	Yield (%)
With catalyst	85.00	0.14	<1	96
Without catalyst	85.00	0.14	>25	94

Using Optimal condition

After optimization of the reaction conditions, the efficiency and applicability of the method were studied by the reaction of dimedone, ethyl acetoacetate and ammonium acetate with different aryl aldehyde derivatives in the presence of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$. The results are given in Table 8. As Table 8 shows, hexahydroquinonine derivatives could be obtained in high to excellent yields (75.41-95.82%) within short reaction times (40-180 Sec.). Benzaldehyde derivatives, including electron-releasing, electron-withdrawing substituents or halogens on the 2', 3', 4', 5', and 6' position and aromatic rings with heteroatoms were successfully tested in this reaction condition (Table 8, compounds 1-15). Using optimum condition, less reaction time and almost equal reaction yield can be obtained to the amounts reported in the literatures.²⁸⁻³⁷

Table 8. Time, yield, and melting point of products using optimal condition. A=time (Sec.), B=yield (%),C=melting point (°C)

A	40	60	50	60
B	97	81	85	91
C	219-222 [35]	205-207 [28]	257-259 [33]	233-235 [29]
A	90	150	180	40
B	80	90	89	86
C	231-234 [36]	244-245 [33]	243-245 [35]	228-230 [32]
A	40	80	60	180
B	84	98	90	80
C	264-265 [35]	204-206 [34]	205-207 [31]	251-253 [37]
A	60	100	60	
B	87	79	86	
C	232-233 [28]	242-243 [30]	246-248 [33]	

^aYield refers to isolated product.

Molar ratio: dimedone, ethyl acetoacetate, aldehyde, ammonium acetate (1:1:1:1.2)

Reaction condition: temperature (85 °C), catalyst (0.14 mole)

Proposed mechanism

A possible mechanism (Scheme 2) is given in the Fig. 3 which is supported by the literature.³⁴

ZrOCl₂ is a Lewis acid catalyst that catalyzes Knoevenagel type coupling of aldehydes with active methylene compounds (direction 2 and 5) and Michael type addition reactions (direction 3

and 7). To investigate the possible mechanism and the proper role of $ZrOCl_2$, Infrared (IR) technique was used. After 20 seconds at the optimum reaction condition, two intermediate were detected and separated by the plate. The possible structure of these intermediate were identified and characterized by FT-IR. Details of collected data were summarized in supporting information.

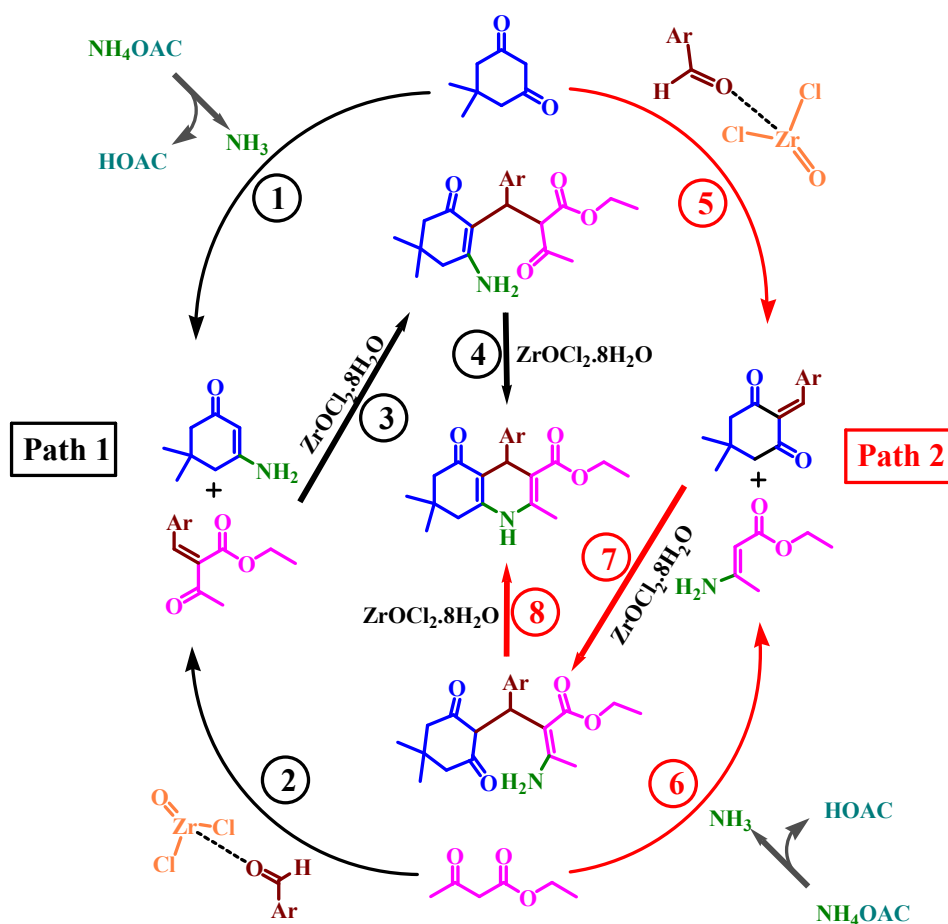


Fig. 3 The possible mechanism for the synthesis of hexahydroquinolines derivatives catalyzed by $ZrOCl_2$

Regeneration of the catalyst

$ZrOCl_2 \cdot 8H_2O$ catalyst is a yellowish solid. First, 0.15 mole of $ZrOCl_2 \cdot 8H_2O$ were added to the reaction mixture at optimum reaction temperature ($85^\circ C$), after the reaction was complete (40 seconds), 25 ml ethyl acetate was added to the reaction mixture at $50^\circ C$ and was mixed for 5

minutes. All of the unreacted reagents and product were extracted to ethyl acetate, but $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ remained unsolved. After the filtration and drying, the $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ was regenerated to use in the next reaction cycle. Decrease in the reaction yield to the number of reaction cycles is shown in Fig 4.

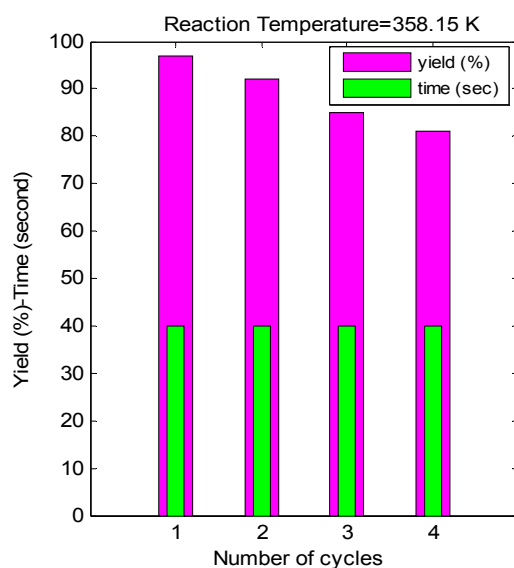


Fig. 4 Decrease in the reaction yield to the number of reaction cycles (at optimized reaction condition)

Conclusion

In conclusion, we have introduced $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ as an efficient, cheap and recyclable catalyst under solvent-free condition for the one-pot multi-component reaction to synthesis of hexahydroquinoline derivatives. Optimization of the reaction condition was studied by the central composite design (CCD). It was shown that by increasing the amount of catalyst, the reaction yield increases, but as temperature increase, a maximum point can be seen in the reaction yield. This behavior can be related to the dehydration/decomposition of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ at temperature above 85°C . The quadratic model was best fitted (coefficient of determination=0.90) to the experimental data. Predicting response values using the obtained

model were in a good agreement with the experimental results. The promising points for the presented protocol were efficiency, high yields, short reaction times, cleaner reaction profile and simplicity.

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Supporting Information

Supplementary data associated with this article can be found, in the online version, at
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