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Efficient and Mild method for Synthesis of quinazoline derivatives using 2-aminobenzoamide and different aldehydes

Mohammad Anwar Erfan
anwarerfan94@gmail.com
Ghor Higher Education Institute, Afghanistan
Abdulrahim Rahimi
Panjshir Higher Education Institute, Afghanistan
Sayed Ali Aqa Sadat
Alberoni University, Afghanistan
Sayed Abdul Aziz Ahmady Falah
Parwan University, Afghanistan

Abstract: Heterocyclic chemistry as the subject of half of organic chemistry research is an important branch in chemistry. In particular, heterocycles containing nitrogen atom have attracted a lot of attention due to their use in many biological processes. Among them, 2,3-dihydroquinazoline-4 (H1) derivatives, as key skeletons in agricultural chemistry, medicinal chemistry and organic chemistry, are widely used in nature, especially in biologically active molecules and are found medicinally. Recent studies show the important biological and medicinal activities of these compounds, including anticancer, antitumor, antibiotic and antihypertensive properties. There are various methods for the synthesis of 3,2-dihydroquinazoline-4(H1)-one derivatives in the literature. Condensation of anthranilate amide with aldehyde or ketone is one of the simplest methods for preparing 3,2-dihydroquinazolin-4(H1)-one derivatives using homogeneous and heterogeneous catalysts. In the present study, the quick, efficient, easy and environmentally friendly synthesis of 3,2-dihydroquinazolin-4(H1)-one derivatives using GPTMS-TSC-CuI16-SBA is reported. The mentioned meso structure catalyst, with its unique cage-like structure and narrow distribution of particles with size (3-7 nm) has excellent catalytic activity in the synthesis of 3,2-dihydroquinazolin-4(H1)-one from the condensation of 2-aminobenzamide and aldehyde. It shows high efficiency in solvent-free conditions. In addition, GPTMS-TSC-CuI16-SBA as a heterogeneous catalyst is stable under reaction conditions and can be recycled at least 5 times without loss of catalytic activity.

Keyword: green, efficient, synthesis, solvent-free

INTRODUCTION

Heterocyclic chemistry as the subject of half of organic chemistry research is an important branch in chemistry. In particular, heterocycles containing nitrogen atom

have attracted a lot of attention due to their use in many biological processes [1]. Derivatives, 3,2-dihydroquinazoline-4(H1)-one are known pharmaceutical skeletons. These compounds are part of the family of nitrogen-containing heterocyclic compounds and form a main structural part in various biologically active compounds in organic chemistry and medicinal chemistry [2]. 3,2-Dihydroquinazoline-4(H1)-ones consist of a phenyl ring welded to a six-membered ring with two nitrogen atoms in positions 1 and 3 and a carbonyl group in position 4 of carbon figure. 1

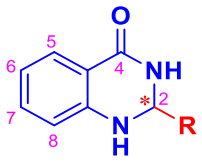


Figure.1 of 2,3-dihydroquinazolin-4(H1)-ones

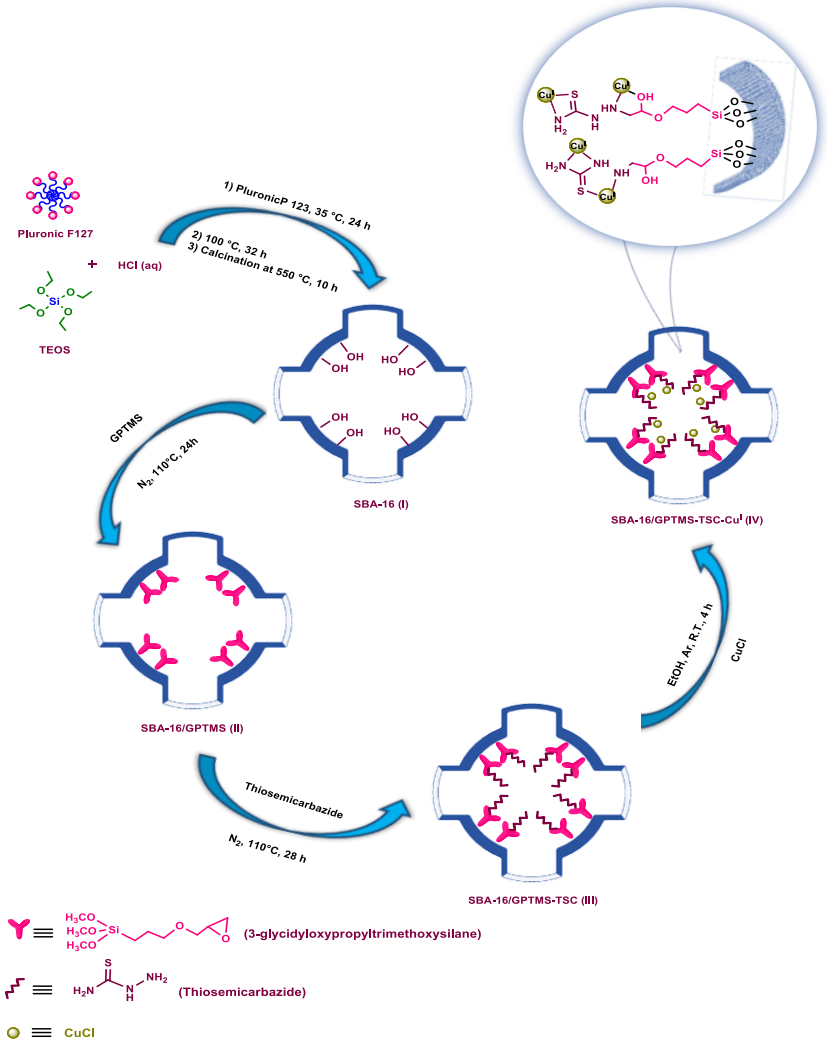
Most of the derivatives of 2,3-dihydroquinazolin-4(H1)-ones have substitution at carbon 2 as a chiral center. These compounds, due to their interesting properties, have been of interest to organic chemists as an important synthetic intermediate, and various methods for their preparation as racemic mixtures have been reported [3].

Recent studies show important biological and medicinal activities of 2, 3-dihydroquinazolin-4(H1)-ones, including anticancer [4], antitumor [5], antibiotic [6] and antihypertensive properties. [7] is This structure is used in the construction of antihypertensive drugs, diuretics, congestive heart failure and nutritional supplements. The purpose of the research

Most of the synthesis methods of 3,2-dihydroquinazoline 4(H1)-ones from 2-aminobenzoamide and aldehydes require the use of acidic environment and homogeneous catalysts. Separating the catalyst from 3,2-dihydroquinazoline 4(H1)-ones obtained in these methods is tedious and difficult. The use of multiple metal catalysts in the synthesis of 3,2-dihydroquinazoline 4(H1)-ones can partially overcome this problem. But these methods also have defects such as expensive metal, use of toxic solvents and long reaction time. Therefore, achieving catalysts with high efficiency and recovery capability is one of the most important goals of development and improvement of catalytic systems. Economic factors and environmental effects play a fundamental role in the design and manufacture of catalysts. In order to achieve this goal, in the present study, the performance of heterogeneous catalytic system of copper supported on mesoporous 16SBA in the synthesis of 3,2-dihydroquinazoline 4(H1)-one derivatives in solvent-free and low temperature conditions, in line with the principles of chemistry Green has been paid. High efficiency, ease of catalyst separation, increases the purity of products and brings high economic and environmental benefits.

Materials and methods**:** The materials used in this research were obtained from Merck. All materials were used after preparation without further purification. Determining the purity of the products and the progress of the reaction were checked

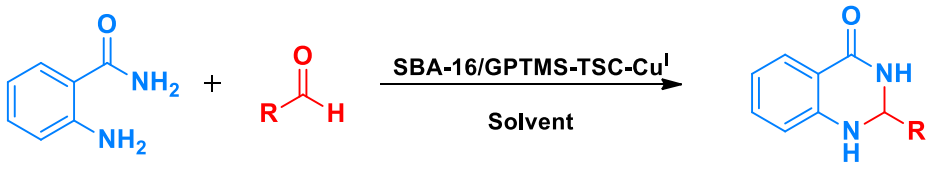
by thin layer chromatography on a TLC plate made of silica gel and type 254 STL G/UV. The separated products were purified using recrystallization in ethanol or column chromatography and the yield of the reactions was determined based on the weight of the pure products. The products were identified by comparing the FT-IR, HNMR 1, CNMR 13 spectra and their physical properties with the data reported in the sources. The melting points of the products were determined by an electro thermal device 9100IA in an open capillary tube. Mass spectra were recorded using AVarianmat Bremem 7CH device at 70eV. Infrared spectra (FT-IR) were recorded by FTIR Thermo Nicolet 370 AVATAR spectrophotometer. Nuclear magnetic resonance spectra were recorded and studied by AVANCE spectrometer model 300 Bruker DRX- with a power of 300 MHz in dimethyl sulfoxide (DMSO-d6) solvent. Inductively coupled plasma spectrometer (ICP-OES) model Across spectra was used to measure the amount of elements and metals in the catalyst. The catalyst used for the synthesis of 3,2-dihydroquinazoline 4 (H1)-ones was prepared and used by the previously reported method [8].



Results: Recently, the successful synthesis of GPTMS-TSC-CuI16-SBA (copper supported on mesoporous 16-SBA functionalized by 3-glycidyloxypropyltrimethoxysilane aminated with thiosemic carbazide) as a new

heterogeneous mesostructure catalyst for the preparation of diaryl sulfides The symmetry of the reaction of aryl halides with thiourea or S8 was reported (figure 2) [9]. In line with the research done in green chemistry, in the current research, another catalytic activity of the heterogeneous catalyst /GPTMS-TSC-CuI16-SBA in the synthesis of various derivatives of 3,2-dihydroquinazoline-4(H1)-ones in a short period of time and mild conditions are provided.

The synthesis of a number of 3,2-dihydroquinazolin-4(H1)-one derivatives from the condensation reaction of different aldehydes and 2-aminobenzamide in the presence of different solvents and using GPTMS-TSC-CuI16-SBA catalyst was investigated. In Figure 3, the schematic of the reaction is shown



R= Ph, 4-FPh, 4-ClPh, 2-ClPh, 3-BrPh, 4-O_2NPh, 4-CH_3Ph, 3-CH_3Ph, 4-CH_3OPh, 4-HOPh, 2-HOPh, 3,4-$(HO)_2$Ph, 3-HOPh, 4-$(CH_3)_2$NPh, 4-C_5H_4N, 2-C_4H_3S, 2-C_4H_3O, PhCH=CH, C_2H_5, $(CH_3)_2CH$, $CH_3(CH_2)_7CH_2$

Figure (3) Schematic of the reaction of 3,2-dihydroquinazolin-4(H1)-one

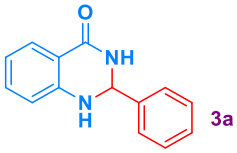
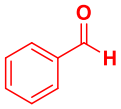
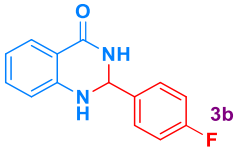
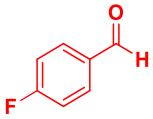
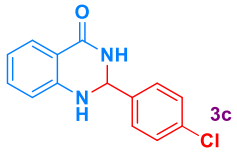
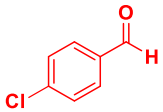
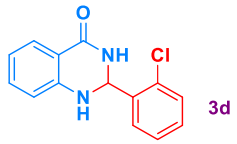
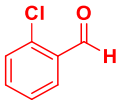
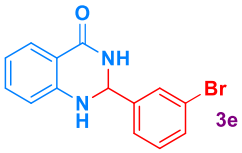
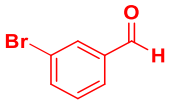
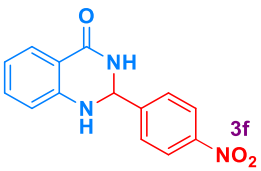
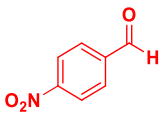
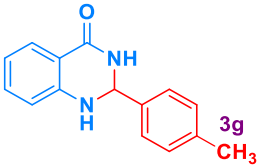
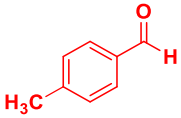
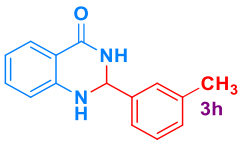
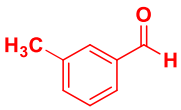
The effect of various factors such as solvent, temperature and amount of catalyst in the condensation reaction of 2-aminobenzamide and benzaldehyde was investigated as a model reaction to achieve the highest reaction efficiency in the shortest possible time and at the minimum required temperature. The obtained results are presented in Table 1

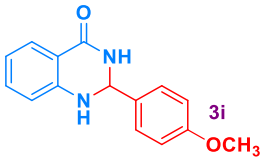
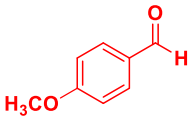
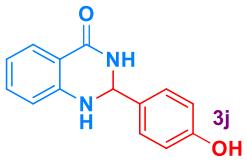
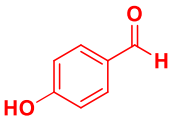
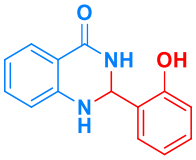
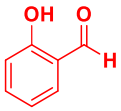
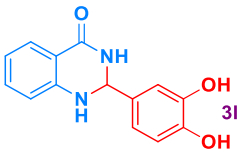
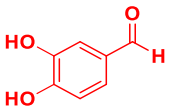
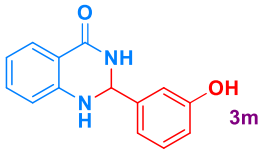
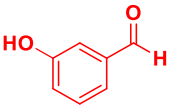
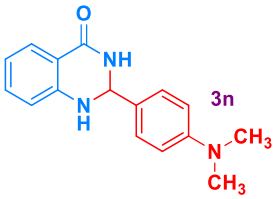
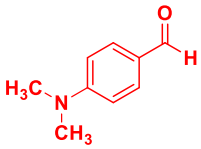
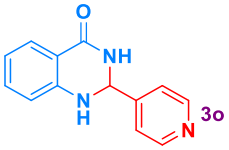
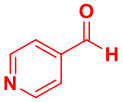
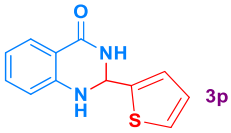
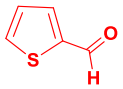
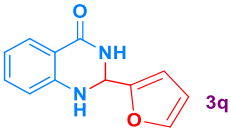
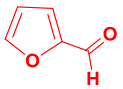
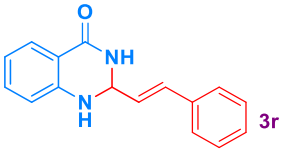
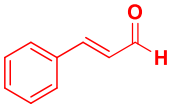
Number	Time series (minutes),	temperature (°C)	solvent	molar percentage, catalyst	yield percentage
1	10	reflux	water	-	insignificant
2	20	reflux	water	3/9	98
3	20	reflux	Ethanol	3/9	25
4	20	reflux	Acetonitrile	3/9	64
5	20	reflux	Toluene	3/9	55
6	20	reflux	4,1-dioxane	3/9	23
7	20	reflux	Dichloromethane	3/9	0
8	20	100	-	3/9	98
9	20	room temperature	water	3/9	10
10	20	room temperature	-	3/9	10
11	20	60	water	3/9	45
12	20	60	-	3/9	98
13	20	70	-	3/9	98
14	20	50	-	3/9	78
15	20	40	-	3/9	60
16	20	60	-	1/11	98
17	20	60	-	4/7	98
18	20	60	-	6/5	24

19	20	60	-	0.04	45
20	20	60	-	0.04	45
21	20	60	-	0.04	45
22	20	60	-	4/7	24

In order to check the generality of the method used in the synthesis of different dihydroquinazolines in the presence of the catalyst /GPTMS-TSC-CuI16-SBA, the optimal conditions (7.4 mol % of the catalyst and temperature of 60 °C in solvent-free conditions) in the preparation of other 2,3- Substituted dihydroquinazolin-4(H1)-ones were applied using the condensation reaction of aldehydes and 2-aminobenzamide.

Table 2: Synthesis of 3,2-dihydroquinazoline-4 (H1) of different ones in the presence of catalyst

Percentage return	product	Aldehyde	time (minutes)	row
98	 3a		20	1
90	 3b F		30	2
95	 3c Cl		35	3
85	 3d		50	4
93	 3e		30	5
90	 3f NO_2		35	6
93	 3g CH_3		25	7
87	 3h CH_3		40	8

92	 3i		25	9
92	 3j		25	10
82	 3k		60	11
85	 3l		60	12
88	 3m		30	13
80	 3n		35	14
85	 3o		40	15
88	 3p		35	16
85	 3q		30	17
95	 3r		50	18

Based on ICP-OES analysis, the exact amount of Cu in the recycled catalyst after five consecutive runs was 1.80 mmol/g, while the freshly prepared catalyst contained 1.86 mmol Cu/g/GPTMS- It is TSC-CuI16-SBA. Therefore, the obtained results confirm the strong coordination of copper ions with the surface of the mesostructured catalyst. This means that the catalyst has high stability and reusability, and in the synthesis reaction of 2-phenyl-2,3-dihydroquinazolin-4(H1)-

one, copper ion is not separated from the catalyst surface under optimal reaction conditions. Also, infrared spectroscopy (FT-IR) of the catalyst that was recycled for the fifth time compared to the fresh catalyst showed no significant changes in the intensity, frequency and shape of the absorption peaks. Figure (4)

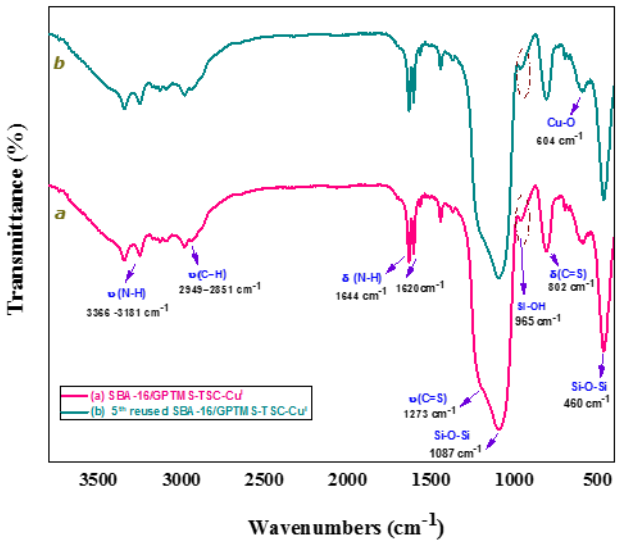


Figure 4: FT-IR spectrum of (a) newly prepared catalyst/GPTMS-TSC-CuI16-SBA (IV) and (b) catalyst

Discussion

In the method presented in this research, the completion of the reaction was confirmed by the disappearance of (aldehyde and 2-aminobenzamide) on the TLC plate. All synthesized derivatives of 3,2-dihydroquinazolin-4(H1)-ones were identified after separation and purification. At first, the melting point of the obtained compounds were compared with the previously reported authentic samples and the results confirmed the successful synthesis of the desired compound. The mass spectra of these compounds showed molecular ion peaks at appropriate m/Z values.

To determine the structure of the products, the structures of some selected compounds (a 3, c3, f 3, g 3, i 3, j 3, k 3, l 3, m3, n3, p3, q3, r3, u3) using spectroscopy FT-IR, HNMR1 and CNMR13 were identified. The absorption band in the 1648-11670 cm region corresponding to the carbonyl group of the dihydroquinazoline ring in the FT-IR spectrum confirms the formation of the product. Also, the stretching vibrations of two N-H bonds appeared around 3182-3337 cm-1 and 3133-3199 cm-1. In the 1HNMR and 13CNMR spectra, all signals were consistent with the synthesized structure. In the HNMR spectrum of these compounds, two broad single peaks in the range of 7.5-30.98 ppm and 8.91-8.24 ppm related to NH indicate the successful synthesis of 2,3-dihydroquinazolin-4(H1)-ones. It is through the ring closing reaction and the single peak in the range of 71.71-6.5 ppm indicates the proton of dihydroquinazoline. Peaks related to phenyl ring protons appeared as multiples in the range of 7.6-66.35 ppm. In the 13CNMR spectrum, the

peak appearing in the range of 149-166 ppm confirms the presence of carbonyl carbon and the peak appearing in the range of 113-159 ppm is related to the resonance of aromatic carbons, which is consistent with the desired structure.

Based on the proposed mechanism in scheme (3-3), the acidic nature of the catalyst /GPTMS-TSC-CuI16-SBA facilitates the synthesis of 2,3-dihydroquinazolin-4(H1)-ones from the condensation reaction of aromatic and aliphatic aldehydes with 2-aminobenzamide. It can be at first, the electrophilic character of carbonyl aldehyde group is strengthened by metal (CuI) and it is more easily attacked by the nucleophilicity of 2-aminobenzamide (NH2 group). Then, by removing the water molecule from intermediate I, imine intermediate II is formed. Next, the imine part of intermediate II is activated by the metal present in the catalyst and intermediate III is formed. Finally, the 2,3-dihydroquinazoline-4(H1)-one compound IV is formed by the intramolecular nucleophilic attack of the nitrogen atom of the amide group on the activated imine group. In the shown mechanism, the catalyst is used while being recovered in the next cycle.

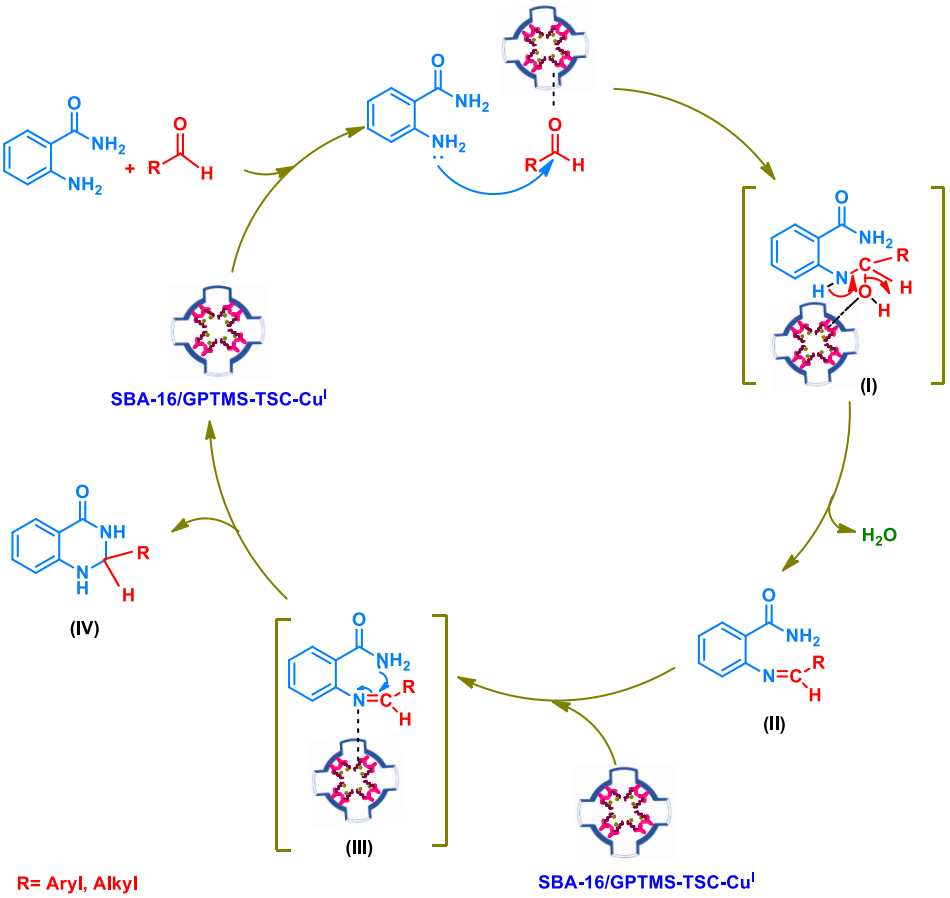


Figure 5: The proposed mechanism for the synthesis of 2,3-dihydroquinazolin-4(H1)-ones in the presence of a catalyst

CONCLUSION

In this study, GPTMS-TSC-CuI16-SBA with a unique cage-like structure and a narrow distribution of particles with size (3-7 nm) as an efficient, environmentally friendly, safe, chemically stable and with the nature of heterogeneous meso structure,

it was used in the condensation reaction of 2-aminobenzamide with substituted aromatic and aliphatic aldehydes for the synthesis of 2,3-dihydroquinazolin-4(H1)-ones in solvent-free conditions. This method generally had the advantages of compatibility with the environment, high yield, short reaction time, simple operation method and the use of reagents with different substitution groups. In addition, the results clearly show the excellent recovery capability of the catalyst (up to 5 times with the lowest loss of activity) and all these indicators are the reason for the advantage of the present method over the existing methods.

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