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ORIGINAL PAPER

$ZnAl_2O_4/SiO_2$ nanocatalyst: a new efficient catalyst for Biginelli reaction with a specific product under safe, green, and solvent-free conditions

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Abstract

Lewis acid heterogeneous catalyst, $ZnAl_2O_4/SiO_2$ nanocomposite, was determined as a strong catalyst for the green and safe three-component reactions by the one-pot procedure. The effect of factors, such as the amount of catalyst, the molar ratio of reactants, reflux time and temperature on the three-component reactions were investigated. Also, the parameters of green chemistry were studied. These reactions under solvent-free conditions in the presence of $ZnAl_2O_4/SiO_2$ dramatically increased the yield of the formation of dihydropyrimidinones derivatives in a very short time. The results showed that $ZnAl_2O_4/SiO_2$ under solvent-free conditions greatly accelerate the three-component reactions with the advance of imine pathway and preventing the formation of unwanted side-products. Also, aromatic aldehydes with low electron density had the best outcomes. Lower reaction yield was produced by β-ketoesters with more steric hindrance. Without noticeably altering reaction time or yield, this catalyst employed six times. The technique is environmentally friendly, as shown by its low E-factor of 0.218–0.570 and high atom economy of 90.025–87.237.

Keywords Multi-component · Dihydropyrimidinones · Nanocatalyst · Lewis acid · Biginelli reaction · $ZnAl_2O_4/SiO_2$ nanocomposite

Introduction

Multi-component reactions are among the attractive and favorite fields of many researchers, so they have a special place in organic and medicinal chemistry [1–3]. Multi-component reactions, in general, are reactions that include more than two reactants and occur in a single step, producing a final product that contains a little amount of each reactant [4, 5]. A three-component reaction known as the Biginelli reaction creates 3,4-dihydropyrimidinone, also known as DHPM, by combining an aldehyde, β-ketoester, and urea [6, 7].

The Biginelli reaction has garnered a lot of interest once again due to the many medical uses of natural and synthesized dihydropyrimidinones as antiviral, antibacterial, anti-tumor agents, anti-inflammatory, anti-hypertensive, anti-epileptic, and calcium channel blockers [1, 8–16].

Regarding the crucial properties of dihydropyrimidinones and their applications in pharmaceutical industries, providing efficient and cost-effective methods to synthesize these compounds has been a concern for many researchers. In general, the main synthesis methods presented for this kind of compound are in a one-pot and one-step form and according to the old classical method of Biginelli reaction, during which the starting materials are mixed in the vicinity of an acid catalyst and the reaction takes place under special conditions. One of the important shortcomings of old Biginelli method is the low yield, especially in the case of highly-substituted starting materials, and the formation of acyliminium active intermediate in the slow reaction step [17–22]. It was attempted to accelerate reaching this stage by providing new and efficient methods and increasing the yield quickly. To achieve this goal, many acidic reagents and Lewis acids, such as H_3BO_3 [23], ascorbic acid [24], heteropoly acid [25], IRMOF-3 [26], silica-bonded S-sulfonic acid [27], silica sulfuric acid [28], metal–organic framework [29], Zn(II) MOF [30], carbon nanotubes supported by titanium dioxide

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nanoparticles [31], Hf(OTf)$_4$ [20], and acidic ionic liquid [32], were used in various conditions in recent years, and the yield has increased greatly. Regarding the importance of multi-component reactions, introducing more balanced conditions using new catalysts was considered.

Green chemistry encourages chemists to develop processes and products without pollution and hazards. A safe method and a suitable strategy regarding production costs, consumption, and health are needed for the synthesis of a chemical product. Anastas and Warner developed the twelve principles of green chemistry. They clearly express the purposes of green chemistry. The utilization of catalysts is one of the primary principles of green chemistry since they can achieve some green chemistry purposes, including reducing the use of materials, increasing atom economy, and reducing energy consumption.

$ZnAl_2O_4/SiO_2$ nanocomposite was used as a heterogeneous Lewis acid catalyst to synthesize the dihydropyrimidinones derivatives in a green and safe method under solvent-free conditions. The results indicate that we achieved the green chemistry purpose in the synthesis of dihydropyrimidinones derivatives using this catalyst. Also, factors such as short reaction time, solvent-free reaction, easy catalyst recovery and reuse, and high-temperature resistance of the catalyst made our process more beneficial.

Results and discussion

Optimizing reaction conditions for dihydropyrimidinones synthesis

Benzaldehyde, methyl acetoacetate, and urea were utilized as the base reaction to improve the reaction conditions (Scheme 1). In this experiment, the impact of reflux duration, temperature, the molar ratio of reactants, and the quantity of catalyst on reaction yield was investigated. The experiments follow a similar basic procedure as described in section optimizing reaction time. The physical and spectral data of all products are reported in complementary file (S1–S7).

Optimizing reaction time

In this part, all tests used the same starting materials. In addition, all other reaction conditions remained same; only the time of the reflux reaction was altered. Table 1 displays the outcomes of these tests. A round-bottom flask was used to combine 0.01 mol of benzaldehyde, 0.01 mol of methyl acetoacetate, 0.01 mol of urea, and 0.030 g of catalyst for this purpose. The reaction vessel was put in a 70 °C oil bath, and the reaction's progress was monitored using thin-layer chromatography (TLC). To ensure that the components in the reaction vessel were well mixed throughout the reflux phase, 1–2 ml of ethanol were added. After the reaction was finished, hot ethanol was added to the resultant mixture, and the catalyst was filtered out of the mixture. To get rid of all the products that had been adsorbed on the surface, the recovered catalyst was washed numerous times with hot ethanol. A rotary evaporator was used to remove the solvent from the reaction product, after which the product was identified.

Optimizing reaction temperature

In this section, the reaction temperature is variable, and the reflux time for all experiments is the optimal time of

Scheme 1 The three-component base reaction

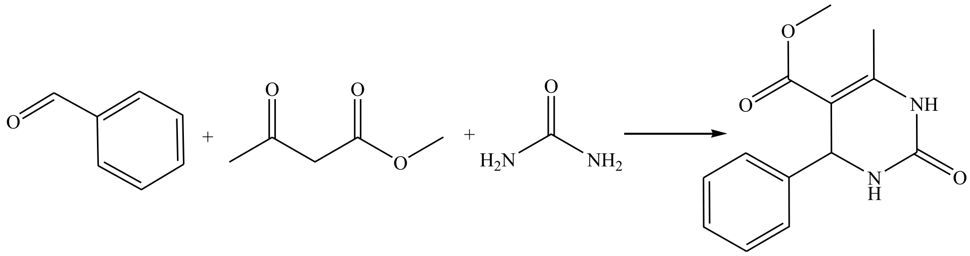


Table 1 The results of optimizing the duration of the three-component base reaction

Entry	Benzaldehyde: ethyl acetoac: urea (molar ratio)	Amount of catalyst (g)	Temperature (°C)	Time (min)	Yield (%)
1	1:1:1	0.030	70	5	32.4
2	1:1:1	0.030	70	10	48.6
3	1:1:1	0.030	70	15	63.8
4	1:1:1	0.030	70	20	63.9

15 min (Table 1, Entry 3). Table 2 shows the results of these experiments.

Optimizing the amount of catalyst

In these experiments, the amount of catalyst is variable. Reflux time and temperature are optimized values (Table 3).

Optimizing the molar ratio of reactants

In this section, the molar ratios of urea, methyl acetoacetate, and benzaldehyde used in the reaction are variable. Reflux time and temperature, and catalyst amount are optimized values (Table 4).

A series of aldehydes and β-ketoester were studied under optimal conditions to expand the effect of $ZnAl_2O_4/SiO_2$ nanocatalyst for the simple synthesis of dihydropyrimidinones with high yield under safe and green conditions (Table 5).

The results of changing the reaction time (Table 1) indicate that the yield increased by increasing the reflux duration, so by increasing the reflux time from 5 to 15 min, the yield increased from 32.4 to 63.8%. However, with a time longer than 15 min, no significant change was observed in the yield, and it remained almost constant.

As shown in Tables 2 and 3, increasing the temperature from 50 °C and the amount of catalyst from 0.020 g caused no significant change in the yield and remained almost constant. The results of changes in the molar ratio of benzaldehyde:methylacetoacetate:urea (Table 4) shows that the yield increased by increasing the amount of urea. However, there was no significant change in the yield by changing the amounts of methyl acetoacetate and benzaldehyde. The best result is in the molar ratio of 1:1:1.3 (benzaldehyde:methyl acetoacetate:urea) in the presence of 0.020 g of catalyst at a temperature of 50 °C, a period of 15 min of reflux.

Considering three possible mechanisms of this multi-component reaction, as shown in Scheme 2 [3, 20], the reason to increase the yield with the increase of urea can be explained by the possible mechanism a (imine pathway). As seen in this mechanism, first, benzaldehyde and urea react with a stoichiometric ratio of 1:2, and an imine intermediate is produced. The primary product is produced when this intermediate interacts with methyl acetoacetate. Therefore, the imine pathway is advanced by the current nanocatalyst. In multi-component reactions, a suitable catalyst is essential

Table 2 The results of the effect of reaction temperature on yield

Entry	Benzaldehyde: ethyl acetoac: urea (Molar ratio)	Amount of catalyst (g)	Temperature (°C)	Time (min)	Yield (%)
1	1:1:1	0.030	30	15	33.2
2	1:1:1	0.030	40	15	45.8
3	1:1:1	0.030	50	15	63.6
4	1:1:1	0.030	60	15	63.8

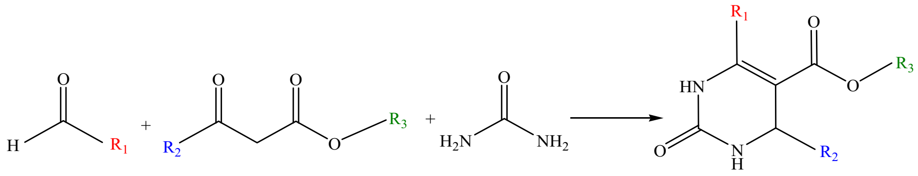
Table 3 The results of the effect of catalyst amount on yield

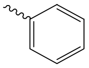
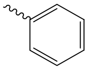
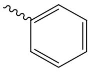
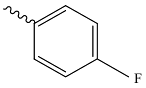
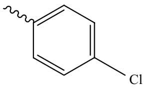
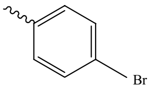
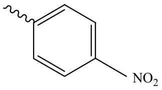
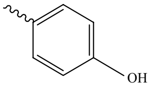
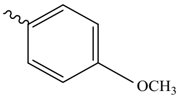
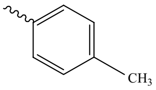
Entry	Benzaldehyde: ethyl acetoac: urea (Molar ratio)	Amount of catalyst (g)	Temperature (°C)	Time (min)	Yield (%)
1	1:1:1	0.000	50	15	12.2
2	1:1:1	0.010	50	15	36.5
3	1:1:1	0.015	50	15	50.8
4	1:1:1	0.020	50	15	63.3
5	1:1:1	0.025	50	15	63.5

Table 4 The results of the changes in the molar ratio of reactants on yield

Entry	Benzaldehyde: ethyl acetoac: urea (Molar ratio)	Amount of catalyst (g)	Temperature (°C)	Time (min)	Yield (%)
1	1.2:1:1	0.020	50	15	63.6
2	1:1.2:1	0.020	50	15	63.5
3	1:1:1.2	0.020	50	15	75. 2
4	1:1:1.1	0.020	50	15	63.3
5	1:1:1.3	0.020	50	15	83.4

Table 5 Yield and reaction time for the three-component reaction involving urea and various aldehydes and β-ketoester



Product	R_1	R_2	R_3	Time of reaction (min)	Yield (%)
P_1		$-CH_3$	$-CH_3$	15	83.4
P_2		$-CH_3$	$-C_2H_5$	15	85.2
P_3		$-CH_3$	$-CH_2CH(CH_3)_2$	20	43.5
P_4	 	$-CH_3$	$-CH_3$	15	98.9
P_5	 	$-CH_3$	$-CH_3$	20	91.8
P_6	 	$-CH_3$	$-CH_3$	15	87.4
P_7	 	$-CH_3$	$-CH_3$	20	90.7
P_8	 	$-CH_3$	$-CH_3$	20	76.8
P_9	 	$-CH_3$	$-CH_3$	20	79.3
P_{10}	 	$-CH_3$	$-CH_3$	20	81.6

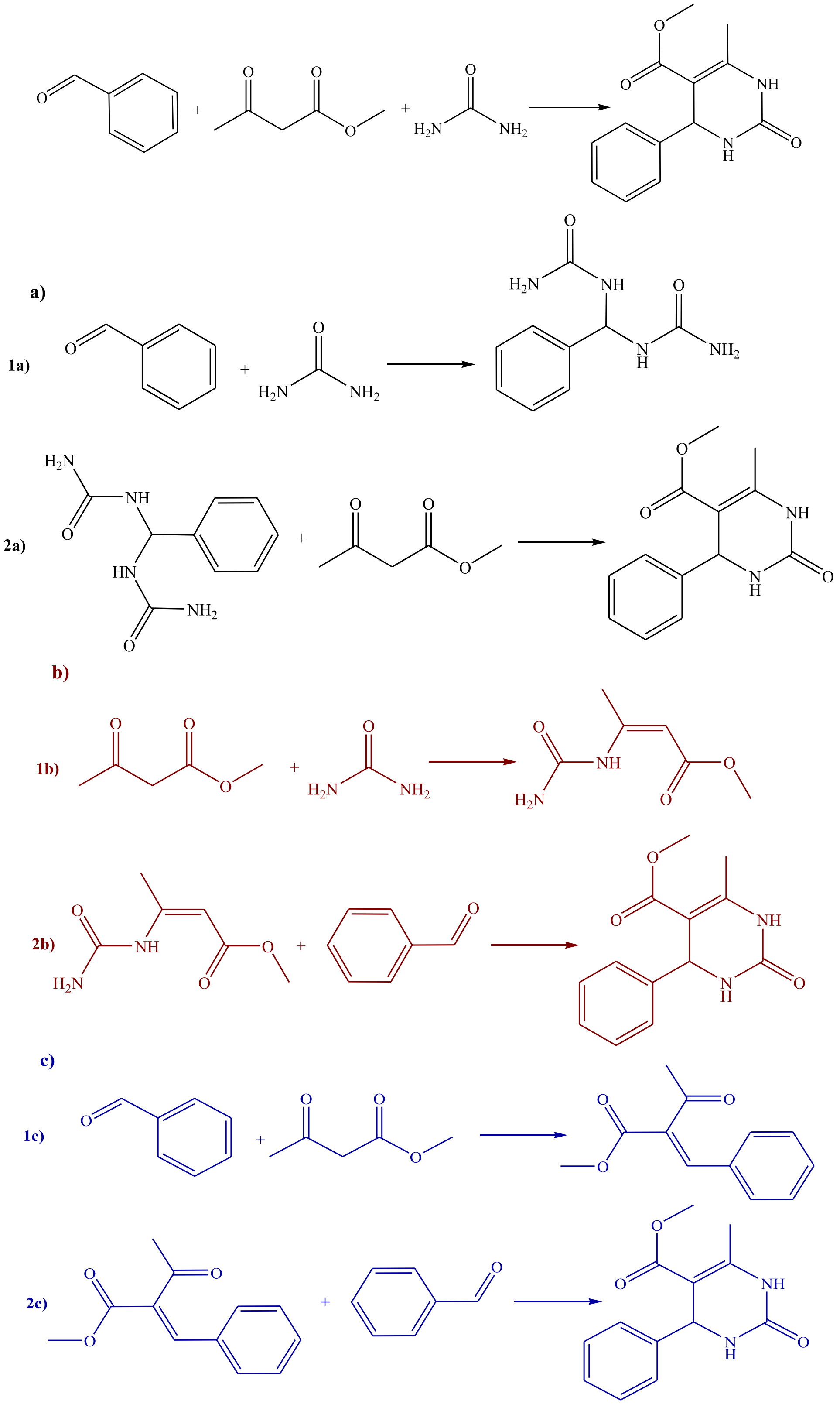
for enhancing selectivity toward one reaction pathway in addition to yield and reaction time improvements [3, 21].

Based on the results in Tables 1, 2, 3, and 4, the time, temperature, amount of catalyst, and molar ratio of the optimal reactants for the base reaction are 15 min, 50 °C, 0.020 g, and 1:1:1.3, respectively.

Various aldehydes and β-ketoester were used under safe and green conditions to expand the effect of the present nanocatalyst for the simple synthesis of dihydropyrimidinones with high yield. Additionally, the basic experiment's response time and yield were compared to those of these trials in order to better understand them. Changing the type of β-ketoester had no discernible impact on the reaction time or yield, as shown in Table 5, but changing the aldehyde had a significant impact. Aldehyde, β-ketoester, and urea were used in each experiment in a ratio of 1:1:1.3, on a scale of 0.01 mol, with 0.02 g of catalyst, and at a temperature of 50 °C.

The first nucleophilic attack of urea on the electron-deficient aldehyde carbon is the most widely recognized mechanism and the rate-determining step, according to the imine route mechanism [3, 33]. As a result, the aldehyde carbon is more vulnerable to attack the more electrophilic it is. Negative mesomeric effects and negative induction effects point to an increase in the electrophilicity of the aldehyde functional group's carbon and the removal of electrons from the

Scheme 2 The possible mechanism of one-step three-component reaction: **a** imine pathway, **b** enamine pathway, and **c** Knovenagel pathway



remainder of the ring, respectively. Additionally, the electron donation to the ring caused by the positive mesomeric and induction effects suggests a reduction in the electrophilicity of the carbon in the aldehyde functional group and prevents the urea's nucleophilic assault. When contrasting the reaction times and yield of those compounds produced using

4-fluorobenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, and 4-nitrobenzaldehyde, the negative induction effects may be noticed. Meanwhile, based on their reaction durations and yields (20 min, 76.8 and 79.3%, respectively), 4-hydroxybenzaldehyde and 4-methoxybenzaldehyde are in the center of the range. Their more favorable positive mesomeric effects are consistent with this. According to the data, choosing a β-ketoester has less of an impact on reaction yield than choosing an aldehyde. The addition of β-ketoester does not significantly alter the reaction rate, since it is not a rate-determining step. Both methyl and ethyl acetoacetate produced yields that were appreciable, while the second one produced yields that were greater. Very significant yields were obtained with benzyl acetoacetate, while β-ketoester with more steric hindrance, such as isobutyl acetoacetate, led to lower reaction yields.

Catalyst recovery method

Under ideal circumstances, the base reaction involving benzaldehyde, methyl acetoacetate, and urea was chosen for this purpose. After the reaction was finished, hot ethanol was added to the mixture, and the catalyst was filtered out of the reaction mixture. To get rid of all the products that had been adsorbed on the surface, the recovered catalyst was washed numerous times with hot ethanol. A 110 °C oven was used to dry the recovered catalyst for 2 h. New starting materials were introduced to the reaction vessel along with the dried catalyst. The catalyst's effectiveness was assessed after this procedure was done multiple times. The findings, which are shown in Table 6, demonstrate that this catalyst recycled at least six times without noticeably affecting the reaction time or yield.

Table 6 Results of reusability of the $ZnAl_2O_4/SiO_2$ nanocatalyst

Run	Reaction time (min)	Yield (%)
1	15	83.4
2	15	82.8
3	15	80.2
4	15	78.3
5	15	76.7
6	20	75.2

Green chemistry criteria

Green chemistry involves the efficient use of materials used in the reaction and the elimination of production waste. Green criteria include determining the environmental coefficient (E) and calculating the atom economy [4, 33, and 34].

The E-factor is defined as the weight of the product divided by the total weight of trash generated. The difference between the mass of reactants and products is the created waste. The E-factor is thus perfect for calculating the volume of waste generated and determining the strength of the reaction source. The product may be regarded sustainable having less of an effect on the environment the closer the E-factor value is to zero, since less trash is created. Equation 1 yields the E-factor; the results are shown in Table 7:

$$\mathrm{E-Factor} = \frac{\text{Mass of waste}}{\text{Mass of product}} \tag{1}$$

Most of the tested reactions have an E-factor value close to zero, resulting from the performance of the recoverable catalyst present in this project and the test solvent-free conditions. It means that the multi-component reactions performed under these conditions produce little waste. Thus, they are considered green and sustainable.

Another crucial factor to take into account, while developing green chemistry criteria is atom economy. It shows what proportions of the materials employed in the multi-component reaction are present in the finished product. It is computed by multiplying this ratio by 100 and dividing the product's relative molecular mass by the sum of all the other chemicals utilized in the reaction (Eq. 2).

$$\text{Atom economy} = \frac{\text{Molecular mass of product}}{\text{Sum of molecular mass of reactants}} \times 100 \tag{2}$$

All experimental reactions yielded high values for atom economy (Table 8), indicating that the end product effectively incorporated all of the reactants employed in the process.

Experimental section

Previous research has reported on the $ZnAl_2O_4/SiO_2$ nanocomposite synthesis and identification process [35, 36]. To further understand the role of the $ZnAl_2O_4/SiO_2$ nanocatalyst

Table 7 The results shown from Eq. 1

Entry	Mass of reactants (g)	Mass of product (g)	E-factor
1	3.003	2.054	0.462
2	3.143	2.218	0.417
3	3.424	1.254	1.730
4	3.183	2.613	0.218
5	3.347	2.577	0.299
6	3.792	2.842	0.334
7	3.453	2.642	0.307
8	3.163	2.014	0.570
9	3.303	2.191	0.507
10	3.143	2.124	0.479

Table 8 The results obtained from Eq. 2

Entry	Sum of molecular mass of reactants (g/mol)	Molecular mass of product (g/mol)	Atom economy (%)
1	282.296	246.266	87.237
2	296.323	260.293	87.841
3	324.377	288.347	88.892
4	300.286	264.256	88.001
5	316.738	280.708	88.625
6	361.192	325.162	90.025
7	327.293	291.263	88.991
8	298.295	262.265	87.921
9	312.322	276.292	88.464
10	296.323	260.293	87.841

in the straightforward, high yield, safe, and environmentally friendly synthesis of dihydropyrimidinones, we adjust the reaction conditions for their synthesis and carry out the reaction on a range of aldehydes and β-ketoesters.

Materials and apparatuses used

The Merck, Folica, and Aldrich businesses provided all used compounds, which were then utilized without additional purification. At room temperature, DMSO and $CDCl_3$ solvents were used to record nuclear magnetic resonance spectra using a Bruker Ultrasheird NMR system. Thin-layer chromatography plates containing UV 254 detector were used to check the reaction progress and determine the reaction completion time. Ethyl acetate and normal hexane were used for TLC solvent tank. Melting points were determined with a Hanon-Mp470 melting point apparatus. GC/MS (SHIMADZU—2010) was used to examine the mass spectra of all products.

Conclusion

A reliable catalyst for secure and environmentally friendly multi-component reactions has been found to be the $ZnAl_2O_4/SiO_2$ nanocomposite. With the advancement of the imine pathway, this reaction under solvent-free conditions significantly boosts the yield of the creation of dihydropyrimidinones. The findings showed that the reaction is faster and produces the highest yield the more electrophilic the carbon aldehyde is, the more vulnerable it is to attack. Lower reaction yields were observed for β-ketoesters with more steric hindrance. It was simple to separate the product from the reaction mixture and recover the catalyst because the reaction was carried out under heterogeneous catalysis. Without significantly affecting reaction time and yield, this catalyst used at least six more times. The multi-component reaction using a $ZnAl_2O_4/SiO_2$ nanocatalyst was found to meet the criteria for green chemistry and to be sustainable.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13738-024-03020-y.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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