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Original Article

Selective Transformation of Isoeugenol to Licarin A using HKUST-1 Catalyst

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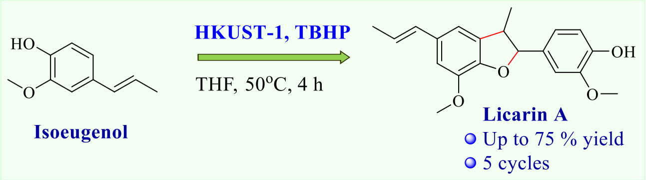
Abstract: The research delineated the utilization of Cu-MOF (HKUST-1) as a proficient heterogeneous catalyst for the selective transformation of isoeugenol to licarin A. The HKUST-1 was synthesized through a straightforward methodology, and its structure was confirmed by various characterization employing a range of techniques, including X-ray diffraction (XRD), scanning electron microscopy (SEM) with Energy Dispersive X-ray analysis (EDX), and N_2 adsorption/desorption. The catalyst exhibited outstanding catalytic efficacy in the selective oxidation of isoeugenol, resulting in a 75% yield of licarin A under mild conditions in the presence of TBHP. Furthermore, the catalyst demonstrated stability, retaining its activity after being reused at least four times without deterioration.



Keywords: Licarin A, isoeugenol, HKUST-1, Cu-MOF.

1. Introduction

Licarin A, a natural neolignan found in various plant species, has been the subject of numerous studies due to its medicinal properties, which include antioxidant, anti-inflammatory, and neuroprotective activities [1-5]. Licarin A has also exhibited various biological activities such as anti-viral, anti-oxidation, anti-inflammatory, antiparasitic, anti-mycobacterial, neuroprotective, and hypoglycemic properties [6-9]. Despite its medicinal importance, the traditional method of obtaining Licarin A through isolation from plants has limitations such as low yield and long time [2, 5]. As a result, chemical synthesis has become a more attractive alternative for producing Licarin A. There has been a significant interest in

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improving the selective oxidation of isoeugenol, which is the most efficient method for producing licarin A. Various attempts have been made to use alternative catalysts such as peroxidase enzymes, Pseudomonas putida bacteria, and cerium ammonium nitrate (CAN) [10-13]. However, these methods often involve the use of homogeneous catalysts or enzymes that are expensive and require the use of hazardous solvents. Furthermore, these methods are not environmentally friendly and usually have a prolonged reaction time with limited recycling. Therefore, there is a need for the development of new, recyclable heterogeneous catalysts to overcome these limitations and make the synthesis of licarin A more efficient and environmentally friendly.

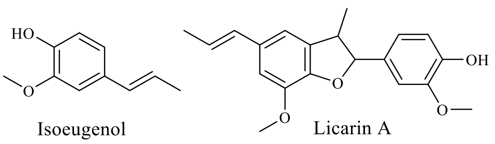


Figure 1. Structure of isoeugenol and licarin A.

Heterogeneous catalysts offer advantages over homogeneous catalysts in synthesizing licarin A, as they are easy to separate from the reaction mixture and can be recycled. To date, only Ag_2O is an efficient heterogeneous catalyst to synthesize licarin A from isoeugenol [13]. However, this catalyst has several limitations, such as a long reaction time or not being reused. Most recently, our group reported that $CuFe_2O_4$ nanoparticles are an efficient catalyst for the production of licarin A in high yield from isoeugenol [14]. The $CuFe_2O_4$ nanoparticle catalyst was robust and could be used at least several times without experiencing a decline in catalytic efficiency. Since the $CuFe_2O_4$ catalyst has a low surface area, it only played excellent catalytic activity in using nanoparticles. To overcome this problem, using porous materials has received much attention in the area of catalysts so far.

MOF-199 (HKUST-1), also known as Cu-BTC is a highly ordered mesoporous metal-organic framework (MOF) material with excellent physical and chemical stability has received attention as a catalyst in various chemical reactions. HKUST-1 has shown promising performance as a catalyst in C-C, C-N coupling, oxidation, and reduction reactions [15-20]. Additionally, HKUST-1 has shown great potential in green chemistry, as it allows for the use of mild reaction conditions and low amounts of metal catalysts and can be easily recovered and reused. These features make HKUST-1 a promising candidate for developing eco-friendly and efficient catalytic processes. In the last little while, our research reported that HKUST-1 is a highly active catalyst in synthesizing indole derivative-fluorescent active small compounds [17].

It is worldly that the use of HKUST-1 as a catalyst for producing licarin A from isoeugenol has not been reported in the available literature. Further research would be necessary to determine its effectiveness and efficiency in this specific reaction. Herein, this research discloses the HKUST-1 as a catalyst for synthesizing licarin A from isoeugenol.

2. Experimental Section

2.1. Chemicals

Copper nitrate hemi (pentahydrate) ($Cu(NO_3)_2·2.5H_2O$), Trimesic acid (H_3BTC, $C_6H_3(COOH)_3$), Isoeugenol (98%), ethanol, methanol, tetrahydrofuran, cyclohexane, toluene, ethyl acetate, n-hexane, hydroperoxide(H_2O_2), tert-butyl hydroperoxide (TBHP), and CuO were obtained from Sigma Aldrich. All compounds were used directly without further purification.

2.2. Preparation of HKUST-1

HKUST-1 catalyst was prepared by hydrothermal method following the previous report published [17]. Briefly, 1.8 mmol $Cu(NO_3)_2$. $3H_2O$ and 1.0 mmol of H_3BTC are dissolved in de-ionized water and ethanol, respectively. The two solutions are then combined and transferred to an autoclave, where the reaction mixture is heated to 120 °C for 12 hours. The resulting solid is filtered and washed several times with water and ethanol to remove unreacted chemicals, resulting in a blue powder, the HKUST-1 material.

2.3. Characterizations

The SEM images of HKUST-1 were taken by SEM 18701906 TM 4000 Plus instrument. SEM-EDX was measured by an Oxford instrument with detector X-stream 2 (EDX pulse processor). X-ray diffraction (XRD) patterns were collected using an XRD 202302 Miniflex 600. N_2 adsorption-desorption measurements were carried out at -196 °C using TriStar II Plus. The samples were degassed at 120 °C for 12 h before data collection. The specific surface areas were calculated from the N_2 adsorption isotherm using the BET (Brunauer-Emmett-Teller) equilibrium equation.

2.4. Synthesis of Licarin A

50 mg of the HKUST-1 catalyst was added to two neck flasks, then isoeugenol (2.0 mmol) and tert-butyl hydroperoxide (TBHP) were added to the flasks. The reactions were carried out at the desired temperature for 4 hours. The reaction mixture was analyzed using gas chromatography-mass spectroscopy (GC-MS) to determine the conversion and selectivity of the products. The product was further separated using column chromatography and identified using NMR spectra in the given solvent, which was performed using a Bruker Advance 500 spectrometer with a cryoprobe.

3. Results and Discussion

3.1. Characterization of Materials

XRD pattern of HKUST-1 displayed diffraction peaks at $2\theta = 6.6^\circ$, 9.5°, 11.4°, 13.4°, 17.5°, and 19.1o which can be attributed to different Miller indices (200), (220), (222), (400), (333), and (440) reflections of the crystalline structure (Figure 2), respectively (JCPDS card no: 00-062-1183). The absence of diffraction peaks of Cu_2O, CuO, and other copper compounds in the XRD pattern of HKUST-1 indicates that the HKUST-1 material is composed of a single phase, suggesting a pure and well-defined structure. In addition, the high sharp peak intensity in the XRD pattern of HKUST-1 indicates that the material has a high degree of crystallinity, meaning that the particles are well-ordered and have a consistent arrangement of atoms. Interestingly, the (222) peak having the highest intensity in the XRD pattern of HKUST-1 suggests that the material has an oriented growth in the (222) direction. This means that the particles have a preferential alignment along the (222) direction, which can affect the behavior and performance of the catalyst.

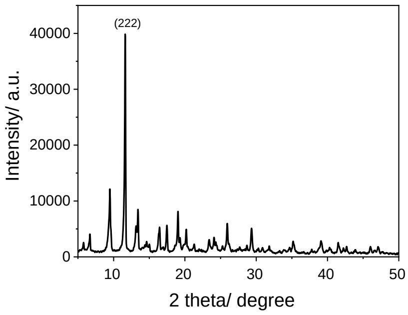


Figure 2. Powder XRD patterns of HKUST-1.

The N_2 adsorption/desorption isotherms were conducted to verify the preserved porous structure of the synthesized material. The isotherm revealed a type I isotherm and typical adsorption behavior of a highly microporous system, as depicted in Figure 3. The BET surface area of HKUST-1 was 1210 m^2/g. These results further indicate the formation of successful HKUST-1 synthesizing.

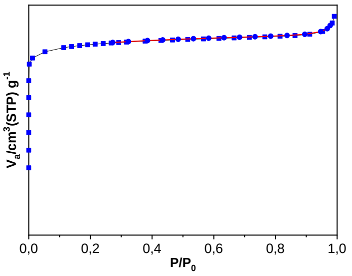


Figure 3. N_2 adsorption/desorption of HKUST-1.

The morphology of synthesized HKUST-1 was characterized via SEM and displayed in Figure 4. The morphologies of HKUST-1 exhibit layers with smooth surfaces, and are relatively uniform, suggesting the successful synthesis of HKUST-1. This result is consistent with the information obtained from XRD and N_2 adsorption/ desorption results.

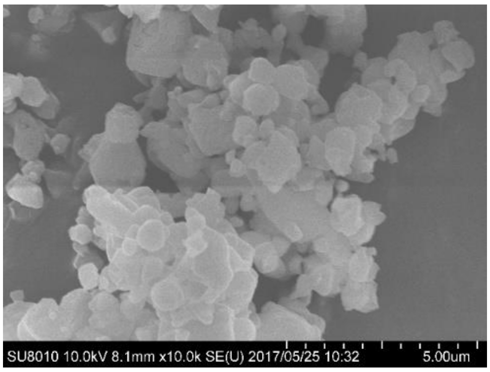
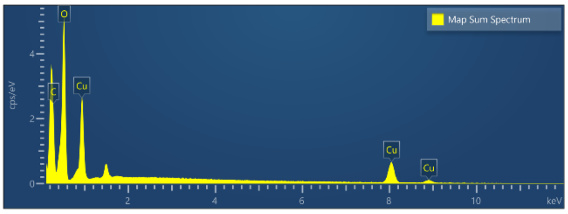


Figure 4. SEM image of HKUST-1.

To further confirm the successful synthesizing of HKUST-1, the SEM-EDX was measured to identify its component, and the results are shown in Figure 5.



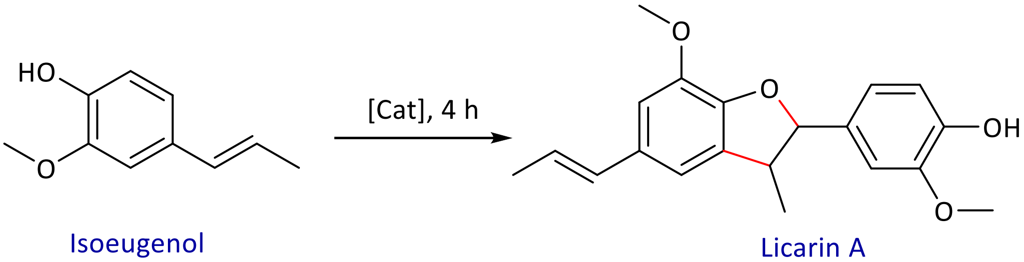
Element	Line Type	Weight %	Atomic %
O	K series	42.48	47.35
Cu	L series	27.21	7.64
C	K series	30.31	45.01
Total		100.00	100.00

Figure 5. SEM-EDX of HKUST-1.

3.2. Synthesis of Licarin A from Isoeugenol

Various conditions were optimized to develop a practical procedure for producing licarin A from isoeugenol, and the results are described in Table 1. Consequently, nearly all solvents demonstrated efficient conversion. Polar solvents exhibited superior conversion and higher selectivity for licarin A than nonpolar solvents, possibly owing to their capacity to stabilize the intermediate state (entries 1-6) [14]. Tetrahydrofuran (THF) emerged as the optimal solvent for producing licarin A (entry 1). In addition, other oxidizing agents underwent testing under identical reaction conditions. The oxidation of isoeugenol yielded excellent conversion and high selectivity for Licarin A in the presence of tert-butyl hydroperoxide (TBHP) at 50 °C with THF as the solvent. At the same time, the reaction progressed slowly in the presence of air (entry 8). In the case of hydrogen peroxide (H_2O_2), a moderate conversion of isoeugenol was achieved, but the yield of licarin A remained low (entry 7). This outcome may be attributed to the increased quantity of water in the reaction mixture. Interestingly, when copper oxide (CuO) was employed as a catalyst for the selective oxidation of isoeugenol (entry 9), the reaction exhibited lower yields than HKUST-1. Moreover, the reaction hardly proceeded without a catalyst (entry 10). These results indicate that achieving a high production of licarin A necessitated the presence of HKUST-1, TBHP, and THF as crucial components.

Table 1. Optimization condition for selective oxidation of isoeugenol to licarin A



No	**Catalyst**	**solvents**	**Oxidizing agents**	**Temperature**	**Conversion[a] (%)**	**Yield[b] (%)**
1	HKUST-1	THF	TBHP	50 °C	98.1	**75**
2	HKUST-1	MeOH	TBHP	50 °C	98.6	**65**
3	HKUST-1	Cyclohexane	TBHP	50 °C	85.8	**55**
4	HKUST-1	Toluene	TBHP	50 °C	87.4	**57**
5	HKUST-1	n-Hexane	TBHP	50 °C	86.8	**57**
6	HKUST-1	EtOH	TBHP	50 °C	98.1	**67**
7	HKUST-1	THF	H_2O_2	50 °C	56,4	**14[a]**
8	HKUST-1	THF	Air	50 °C	29.4	**11[a]**
9	CuO	THF	TBHP	50 °C	60.2	**39**
10	-	THF	TBHP	50 °C	35.6	**13[a]**
11	HKUST-1	THF	TBHP	40 °C	50.8	**30[a]**
12	HKUST-1	THF	TBHP	60 °C	98.2	48

Reaction conditions: isoeugenol (0.5 ml, 3.3 mmol), catalyst (50 mg), solvent (3 ml), 4 hour;
[a]Conversion of isoeugenol was determined by GC-MS;
[b]Product yield was separated by column chromatography.

Moreover, the findings also suggest that a substantial increase in temperature significantly improves the transformation of isoeugenol (entry 11). Nevertheless, the production yield of licarin A diminishes with the temperature increase from 50 to 60 °C, primarily attributed to the generation of byproducts at elevated temperatures (entry 12).

To confirm the role of the HKUST-1 catalyst, the solid catalyst was removed from the reaction after one hour, and the filtered solution was subsequently processed for an additional three hours under the same conditions. Nonetheless, the product yield remained constant, even when extending the reaction time to 12 hours (as shown in Figure 6). This outcome strongly implies that no active species leached from the HKUST-1 catalyst during the filtration test. In addition, in order to provide further evidence of the catalyst's stability, the filtrate was collected and subjected to ICP-MS analysis to detect the presence of any metal. The results revealed no traces of metal species in the solution, further affirming the catalyst's stability.

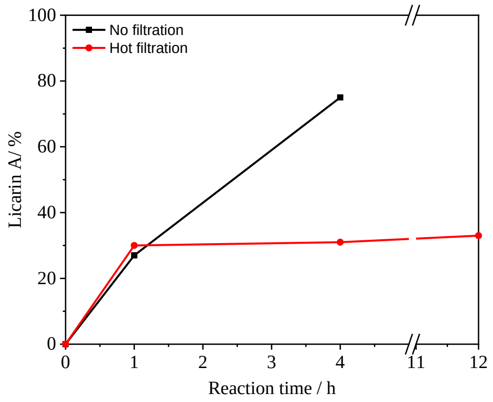


Figure 6. Hot filtration test for HKUST-1 catalyst.

Afterward, a sequence of experiments was undertaken to evaluate the HKUST-1 catalyst's potential for recycling in this reaction, and to assess its stability and durability. Remarkably, the catalyst demonstrated the capacity for reuse for up to four cycles, with only a slight reduction in its catalytic activity, as indicated in Figure 7.

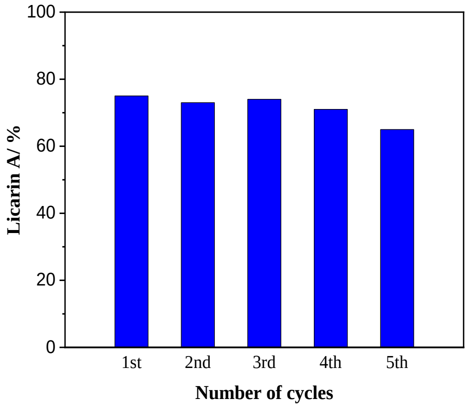


Figure 7. The recycling ability of HKUST-1 catalyst.

To provide additional verification of the structural stability of the HKUST-1 catalyst, we conducted an XRD analysis on the spent HKUST-1 catalyst and compared it to the XRD pattern of the fresh catalyst (as shown in Figure 8). The results revealed that nearly all the characteristic peaks of the reused HKUST-1 remained intact after the reaction, with a slight decrease in intensity. This finding underscores the robustness and stability of the HKUST-1 structure.

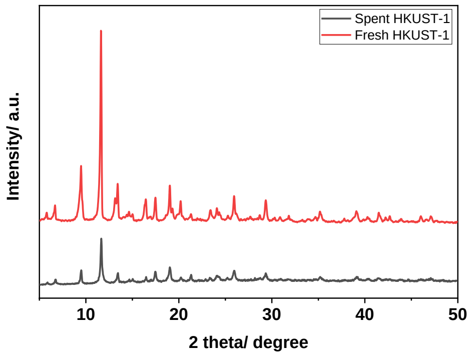


Figure 8. XRD parttern of spent HKUST-1.

4. Conclusion

This study explores novel potential applications for HKUST-1 heterogeneous catalyst for producing licarin A from isoeugenol. The catalyst is prepared and confirmed by various characterizations like XRD, SEM, SEM-EDX, and N_2 adsorption/desorption. The results of the isoeugenol oxidation demonstrate remarkable performance, achieving a conversion exceeding 98% and generating a substantial yield of licarin A when HKUST-1 is used in THF with TBHP under mild conditions. Additionally, the HKUST-1 catalyst exhibits stability and resilience, allowing it to be reused at least four times without any decrease in its catalytic efficacy.

Acknowledgements

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