

# Synthesis of 3-substituted Indoles through Yonemitsu Reaction with Copper Benzene-1,3,5-tricarboxylate Acid Catalyst

Fariba Heidarizadeh\* & Ehsan Rahimi

Department of Chemistry, Shahid Chamran University of Ahvaz, Ahvaz, 6135743169, Iran

Corresponding author: [heidarizadeh@scu.ac.ir](mailto:heidarizadeh@scu.ac.ir) ( F. Heidarizadeh )



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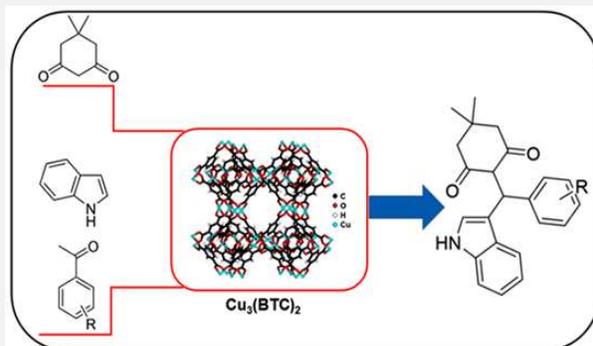


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## ABSTRACT

3-substituted indole derivatives as a key intermediate for the synthesis of complex indole alkaloids have been synthesized by Yonemitsu condensation reaction between indole, dimedone, and benzaldehyde. This reaction was carried out using a copper benzene-1,3,5-tricarboxylate acid catalyst for the first time. In addition to its acidic properties, the aforementioned catalyst has a 3D network, and the existence of these holes can help to advance the reaction. This reaction proceeds smoothly and has achieved good yields (80-90%) by using water as a green solvent at 60°C. The investigations show that the electron-withdrawing groups on the aldehyde compound perform the reaction at a higher speed, which is completely consistent with the presented mechanism and the presence of the carbocation. This modified reaction has numerous advantages, including high efficiency, short reaction time, low reaction temperature, and the use of water as a green solvent.



**Keywords:** One-pot reactions, metal-organic frameworks, 3-substituted indoles, Yonemitsu condensation reaction

## 1. Introduction

Indoles are widely found in nature, many of which exhibit significant biological activities. Furthermore, many natural and synthetic indoles are used as medicinal products and agricultural chemicals. Indole derivatives exist in the structure of numerous natural molecules so more than 1000 types of alkaloids with indole structures have been known so far. Many of these natural compounds exhibit strong physiological properties. The 3-substituted indoles are the most significant part of biologically active indole compounds and natural products.

The amino acid tryptophan and its metabolites like tryptamine, serotonin, and indole-3-acetaldoxime all have an indole structure and participate in biological processes. Some examples are sumatriptan, zolmitriptan, indomethacin and tadalafil [1].

Metal-organic frames are complex coordinating polymers composed of metal as a center and organic ligands as links. These chemicals are crystalline and porous [2]. In addition to being designable, these compounds have shown good catalytic properties and were used in oxidation-reduction reactions, coupling, and acid-base reactions. The acid catalyst of benzene-1,3,5-copper tricarboxylate (**Figure 1**) is also a metal-organic compound that has the necessary potential to be used in the synthesis of indole derivatives due to its acidic properties and the presence of holes [3-6]. Sulfonated-polystyrene-Cu (II)@ Cu<sub>3</sub>(BTC)<sub>2</sub> core-shell microsphere catalysts [7], and porous Cu-BTC@polymer composite [8] are other kinds of this catalyst.

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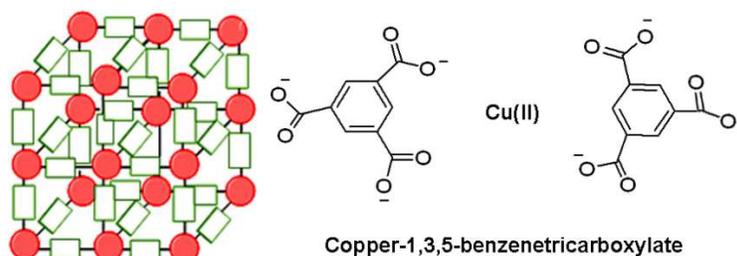


Figure 1. Structure of the copper-1,3,5-benzenetricarboxylate

Indole and its derivatives are very important in heterocycle chemistry and drug discovery [9]. In 1978, Unemitsu and his colleagues used a one-pot three-component reaction including indole, aldehydes, and Meldrum acid for the synthesis of 3-substituted indoles [10]. The reaction attracted the attention of scientists and several research groups used it to produce biologically active molecules. The catalysts used in this research included 2-Chloroethylene on graphene oxide modified with imidazole [11], titanium(IV)/trimethylamine [12], L-proline [13], etc.

The aforementioned catalysts may prepare the product with good to excellent efficiency. But in some of them, the use of organic solvents, expensive catalysts, the use of a stoichiometric amount of catalysis, long reaction time, high reaction temperature, and side products cause problems. Over the past few years, the use of copper catalysts has received much attention because of their abundance, cost, and appropriate efficiency in multi-component reactions [14]. Considering the importance of 3-substituted indole, the synthesis of this compound was investigated by Yonemitsu reaction using the 1,3,5-benzenetricarboxylate copper acid catalyst.

## 2. Materials and methods

### 2.1. Materials

All chemicals were obtained from Merck and Aldrich. All solutions were prepared with double distilled water. Infrared spectrum (FTIR) was recorded by Fourier transform infrared spectrophotometer BOMEM model MB-Series 1998 by KBr tablet in the range of 400-4000  $\text{cm}^{-1}$ .  $^1\text{H}$ NMR spectra in DMSO solvent were recorded by DPX Advanced MHz Bruker 500 MHz spectrometer. Stability The thermal properties of the stabilized catalysts were investigated using a TGA Q50 Build V6.3 with a heating rate of 15  $^{\circ}\text{C}/\text{min}$  in the temperature range of 0 to 100  $^{\circ}\text{C}$ . Scanning electron microscope analyzes were performed using a FESEM device. Thin-layer chromatography was used to check the progress of the reactions.

### 2.2. Experimental

#### 2.2.1 Synthesis of copper benzene-1,3,5-tricarboxylate catalyst

$[\text{Cu}_3(\text{BTC})_2]$  was prepared according to the procedure described in ref. [15].

#### 2.2.2 Synthesis of 2-((2-chlorophenyl)(1H-indol-3-yl)methyl)-3-hydroxy-5,5-dimethylcyclohex-2-enone

In a flask (25 ml) a mixture of indole (117 mg, 1 mmol), 2-chlorobenzaldehyde (0.1 ml, 1 mmol), dimedone (140 mg, 1 mmol), catalyst (7 mg), and water (1.5 ml) was poured and heated to 60  $^{\circ}\text{C}$ . The completion of the reaction was checked by TLC. At the end of the reaction, water was decanted and warm ethanol (5 ml) was added to the reaction mixture. The catalyst was separated and the obtained precipitate was purified by recrystallization in ethanol.

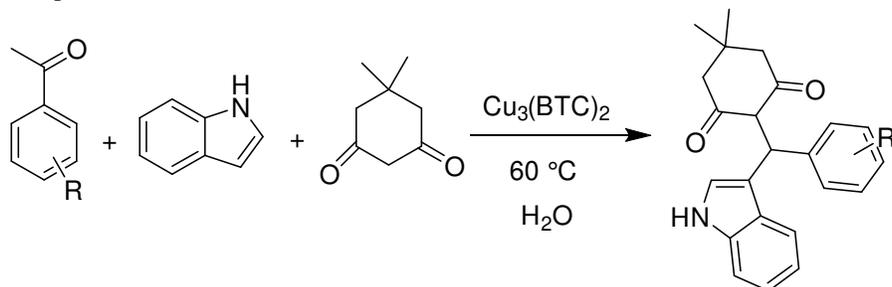
White solid, FTIR ( $\nu_{\text{max}}/\text{cm}^{-1}$ , KBr): 3334, 3161, 2958, 2922, 1635, 1564, 1463, 1377, 1246, 1151, 1074, 885, 794  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  10.73 (s, 1H), 10.22 (s, 1H), 7.29 (t, 2H), 6.10-7.96 (m, 5H), 6.79-6.84 (m, 2H), 5.87 (s, 1H), 2.10-2.37 (m, 4H), 0.98 ppm (s, 6H).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ): 142.22, 136.91, 133.18, 132.76, 129.00, 127.30, 125.99, 124.83, 121.19, 118.98, 129.62, 118, 115.43, 115.11, 111.90, 34.36, 32.00, 31.24 ppm.

## 3. Results and discussion

Multicomponent reactions are an invaluable tool for the synthesis of heterocyclic compounds. These reactions offer the opportunity to synthesize molecules in new ways which may be difficult or impossible with conventional

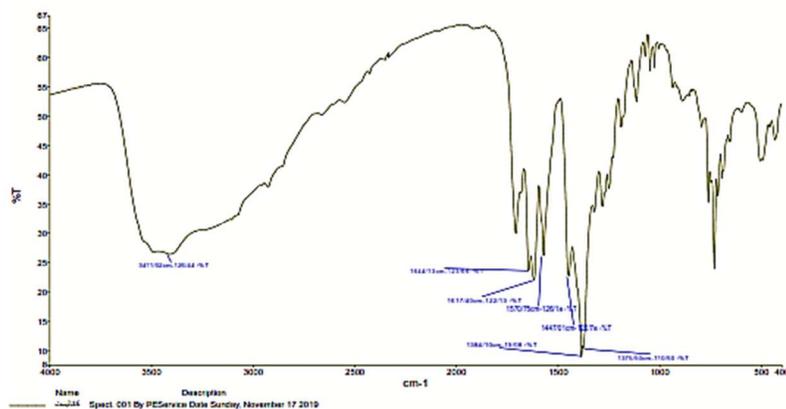
methods. It also enables the quick synthesis of medicinal compounds easily. In addition, it offers the opportunity to make environmentally friendly reactions to minimize waste, cost, and time. The development of these techniques facilitates the synthesis of complex molecules.

In this research work, using  $[\text{Cu}_3(\text{BTC})_2]$  as an efficient catalyst, we synthesized 3-substituted indoles through one-pot multicomponent processes (**Scheme 1**).



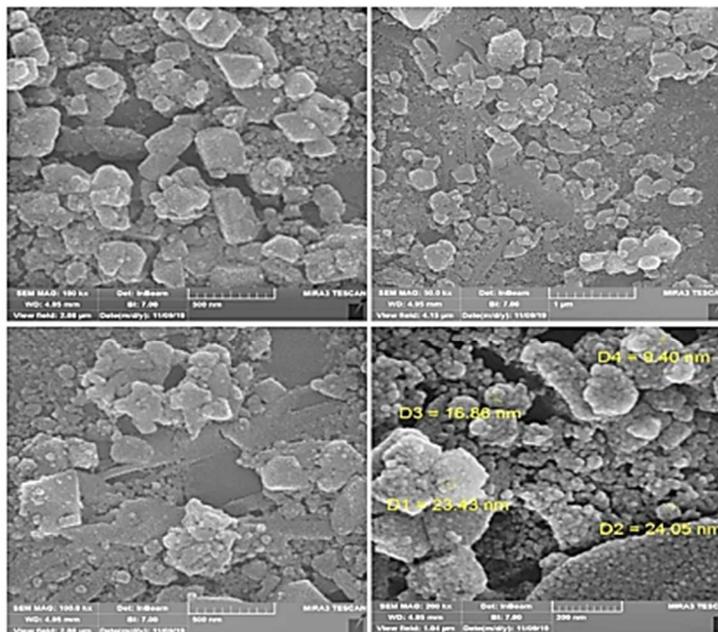
**Scheme 1.** Yonemitsu condensation reaction using metal-organic catalyst  $[\text{Cu}_3(\text{BTC})_2]$

The catalyst  $[\text{Cu}_3(\text{BTC})_2]$  used was analyzed by FTIR spectroscopy, followed by SEM, and finally TGA thermal analysis. Spectral data were used to verify the resulting structure. The broad peak in the range of  $3411\text{--}3520\text{ cm}^{-1}$  is related to the symmetric vibration of the hydroxyl group. The peaks seen in the range of  $1570\text{--}1644\text{ cm}^{-1}$  and  $1384\text{--}1447\text{ cm}^{-1}$  respectively indicate the asymmetric and symmetric vibration of the carboxylate group attached to the metal (**Figure 2**) [16].



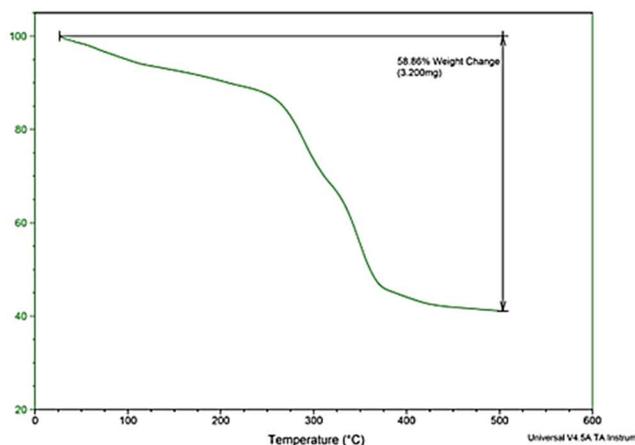
**Figure 2.** FTIR spectrum of catalyst  $[\text{Cu}_3(\text{BTC})_2]$

The morphology and size of catalyst particles were determined by the SEM technique, and are depicted in **Figure 3**. The maximum particle size is 24 nm (**Figure 3**).



**Figure 3.** SEM images of  $[\text{Cu}_3(\text{BTC})_2]$  catalyst

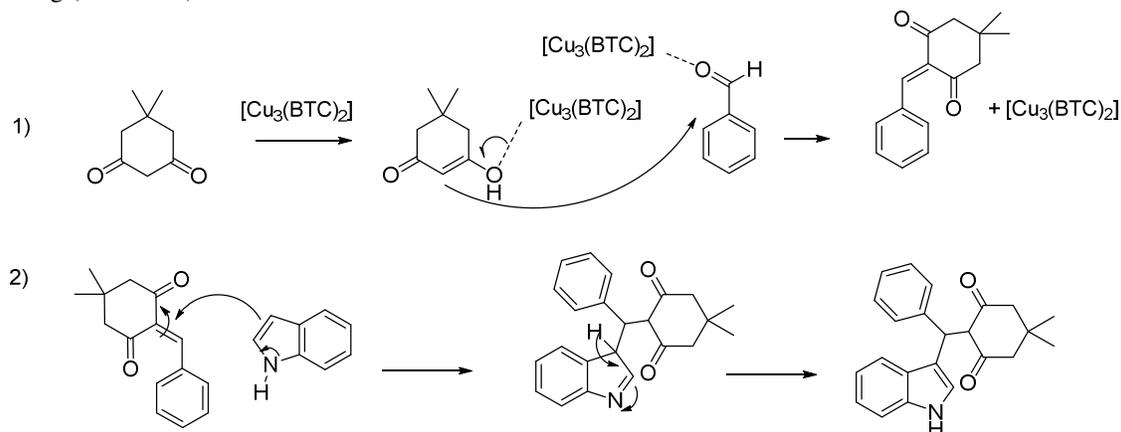
In the TGA analysis, the downward trend of the graph shows that the mass of the sample is decreasing with increasing temperature. Three stages of weight loss can be seen, in the first stage in the temperature range before 240 °C, is related to the loss of water absorption molecules in the catalyst framework, and the next weight loss in the temperature between 240-450 °C is related to the decomposition of the catalyst structure. The results demonstrate the success of catalyst synthesis and it can be used well at high temperatures (**Figure 4**).



**Figure 4.** TGA spectrum of  $[\text{Cu}_3(\text{BTC})_2]$  catalyst.

First, the catalyst is added to dimedone, which is a compound containing active methylene, and a pseudo-enolic form is created, and then the two-step mechanism is performed. 1) In the first step, Knoevenagel condensation reaction occurs and the dimedone compound with active methylene is added to the carbonyl group of the aldehyde compound and an  $\alpha, \beta$ -unsaturated compound is obtained. its carbonyl group and the reaction will be improved. 2) In the second step, the addition of Michael from the indole ring to the composition of  $\alpha, \beta$ -unsaturated compound takes place. Finally,

the final product is obtained from the compound formed in this reaction after losing hydrogen and aromatizing the indole ring (**Scheme 2**).



**Scheme 2.** Proposed reaction mechanism.

To confirm the resulting structure, spectral information was used. In the FTIR spectrum, the wide peak in  $3413\text{ cm}^{-1}$  is linked to the hydroxyl group and the absorption of  $3302\text{ cm}^{-1}$  is related to the absorption of NH indole. The phenyl peaks are found in  $1583\text{ cm}^{-1}$  and  $1455\text{ cm}^{-1}$  and the peak in  $1613\text{ cm}^{-1}$  is linked to the double bond. The carbonyl group will also be absorbed in the region of  $1698\text{ cm}^{-1}$ .

In order to determine precisely the structure obtained, data from the  $^1\text{H NMR}$  spectrum were used. In this spectrum, the peak in the region of  $1.045\text{ ppm}$  is due to the hydrogen of two methyl groups that appear as single branches. The peak shown at  $1.2$  to  $2.5\text{ ppm}$  is related to two methylene groups that appear as multi-branches. The peak at  $5.48\text{ ppm}$  is due to CH hydrogen, which is mono-branched. At  $6.48\text{ ppm}$ , peaks of double-bond hydrogens can be seen.

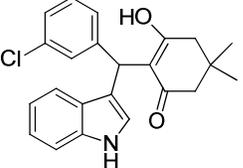
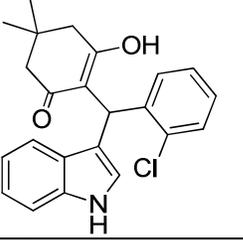
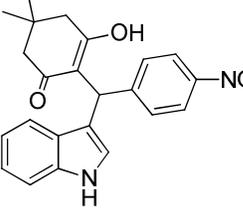
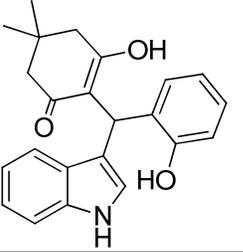
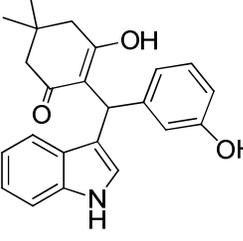
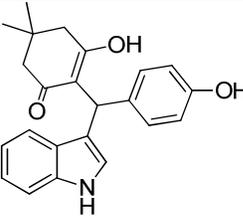
The peaks corresponding to the hydrogens of phenyl rings are visible from  $6.98$  to  $7.9\text{ ppm}$ . The hydrogen peak of NH appears in the region of  $10.24\text{ ppm}$  and the hydrogen peak of the hydroxyl group appears at  $10.76\text{ ppm}$ .

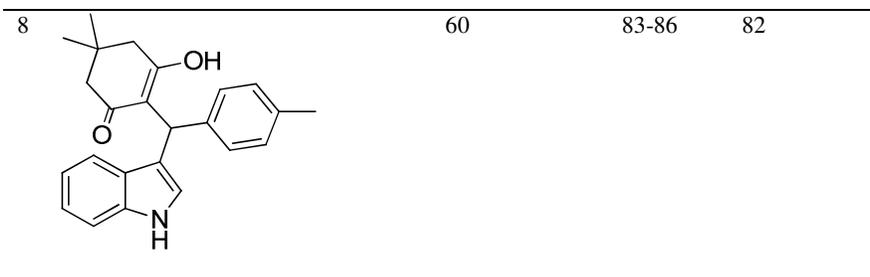
The results of the  $^{13}\text{C NMR}$  spectrum are also consistent with the confirmation of the product structure. The carbonyl carbon in the  $195\text{ ppm}$  area and the carbon in the  $170\text{ ppm}$  area are related to the carbon in the hydroxyl group. Peak  $140$  is related to the NH functional group and the peaks at  $118$ - $136\text{ ppm}$  are related to benzene ring carbons and  $111\text{ ppm}$  and  $115\text{ ppm}$  are related to double-bond carbons. CH carbon peaks at  $50.7\text{ ppm}$  and methylene carbon at  $43.8$  and  $37.8\text{ ppm}$ . And finally, the peaks of the two methyl groups are  $31.9\text{ ppm}$  and  $28.4\text{ ppm}$ .

Under optimized conditions for Yonemitsu condensation (catalyst, solvent, and optimal temperature), a series of reactions were carried out to investigate this method using a variety of aldehydes with electron donor and acceptor groups. Based on the information obtained, it can be concluded that the electron withdrawal groups perform the reaction at a higher speed, which is fully compatible with the mechanism presented. In particular, 4-methoxy benzaldehyde produces a product with medium efficiency due to its high electron-donating power. In addition to this, the reaction was also investigated in terms of spatial crowding, which was seen to have no significant effect on the reaction efficiency (**Table 1**).

**Table 1.** The results of Yonemitsu's multicomponent condensation reaction <sup>a</sup>

	Product	Time (Min.)	M.p. (°C)	Yields (%)
1		85	158-162	80

2		45	207-210	87
3		40	209-211	88
4		35	210-212	90
5		50	192-195	85
6		55	191-193	83
7		50	197-199	86



<sup>a</sup> Reaction conditions: benzaldehyde (1 mmol), indole (1 mmol), dimedone (1 mmol),  $[\text{Cu}_3(\text{BTC})_2]$  (7 mg), and water (as solvent) in 60 °C.

The modified reaction in this project is based on the twelve principles of green chemistry and presents the following benefits:

- 1) One-pot reaction
- 2) The use of small quantities of catalysts and their easy separation.
- 3) Use of a green solvent.
- 4) Perform Low Temperature (60 °C) Reaction

In summary, the method used can be said to be highly effective and the use of the catalyst  $[\text{Cu}_3(\text{BTC})_2]$  was presented for the first time in the Yonemitsu reaction.

To show the superiority of the reaction carried out in this project, the results of the Yonemitsu reaction in the presence of the acidic catalyst  $[\text{Cu}_3(\text{BTC})_2]$  were compared with other results reported in the articles and it was observed that the present method is very effective (**Table 2**).

**Table 2.** Comparison of the current method in the Yonemitsu reaction with other catalysts referred to in the articles.

	Catalyst	Solvent	Yield (%)	References
1	$[\text{Cu}_3(\text{BTC})_2]$	Water	85	Present work
2	RS-HM*	Water	87	[17]
3	MgO	Water	77	[17]
4	GO-IL-NH <sub>2</sub> **	Water	98	[11]

\* Rectangular thin sheet of hydromagnesite

\*\* Graphene oxide-ionic liquid-NH<sub>2</sub>

Finally, the recovery and reuse of the catalyst were investigated. For this purpose, the Yonemitsu reaction was performed in the presence of an acid catalyst  $[\text{Cu}_3(\text{BTC})_2]$  for aldehyde with no substitution. In this study, the recycled catalyst was used four times and no notable changes were observed in the efficiency of the reaction (**Table 3**).

**Table 3.** Effect of recycling on the catalytic performance of  $\text{Cu}_3(\text{BTC})_2$  in the Yonemitsu reaction

Reaction cycle	Yield (%)
1	85
2	84
3	84
4	83
5	82

## 4. Conclusions

In this study, it was established that  $[\text{Cu}_3(\text{BTC})_2]$  is a powerful catalyst for the one-pot multicomponent synthesis of 3-substituted indole derivatives. This reaction has the benefits of high efficiency, quick reaction time, low temperature, and the use of water as a green solvent. This catalytic activity makes it a promising candidate for other Lewis acid-catalyzed condensations leading to biologically active compounds. However, the catalytic activity of the metal-organic frameworks is highly sensitive to reaction conditions, and there is a limitation mainly due to the low thermal stability of the organic linker. As a result, additional activity improvement is required for each reaction.

## Authors' contributions

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

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## Declaration of competing interest

The authors declare no competing interest.

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## Data availability

Data will be made available on request.

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