

## Enhanced Methods for Synthesizing Hydroxyxanthone Using Eaton and $ZnCl_2$ Catalyst with Microwave Irradiation

Emmy Yuanita<sup>1\*</sup>, Farica Eryani<sup>1</sup>, Maulida Septiyana<sup>1</sup>, Ima Arum Lestardini<sup>2</sup>, Ni Komang Tri Dharmayani<sup>1</sup>, Taufan Hari Sugara<sup>3,4</sup>

<sup>1</sup>Department of Chemistry, University of Mataram, Mataram, 83236, Indonesia

<sup>2</sup>Department of Medicine, University of Mataram, Mataram, 83236, Indonesia

<sup>3</sup>University of Muhammadiyah Mataram, Mataram, 83115, Indonesia

<sup>4</sup>Research Center for Marine and Land Bioindustry, BRIN, Jakarta, 12710, Indonesia

\*Corresponding author: emmy\_yuanita@unram.ac.id

### Abstract

The methods for synthesizing hydroxyxanthone compounds are continually advancing. Among these, microwave-assisted organic synthesis (MAOS) has emerged as a particularly advantageous technique due to its reduced reaction times, improved yields, and enhanced selectivity. This study reports the efficient synthesis of 3,7-dihydroxyxanthone through the reaction of 2,5-dihydroxybenzoate and resorcinol, using Eaton's reagent and zinc chloride ( $ZnCl_2$ ) as catalyst under MAOS conditions. The structures of the resulting compounds were analyzed using Fourier-transform infrared spectroscopy (FTIR) and proton nuclear magnetic resonance ( $^1H$ -NMR). The efficiency of the catalytic systems was evaluated based on the product yields. The Eaton reagent catalysis resulted in a 9.38% yield of a red solid, while the  $ZnCl_2$ -catalyzed reaction produced a significantly higher yield of 23.07%, with the product appearing as an orange solid. These results demonstrate that  $ZnCl_2$  is a more effective catalyst under the applied MAOS conditions, delivering superior yields and a distinct product color profile.

### Keywords

3,7-dihydroxyxanthone, MAOS, Eaton's Reagent,  $ZnCl_2$

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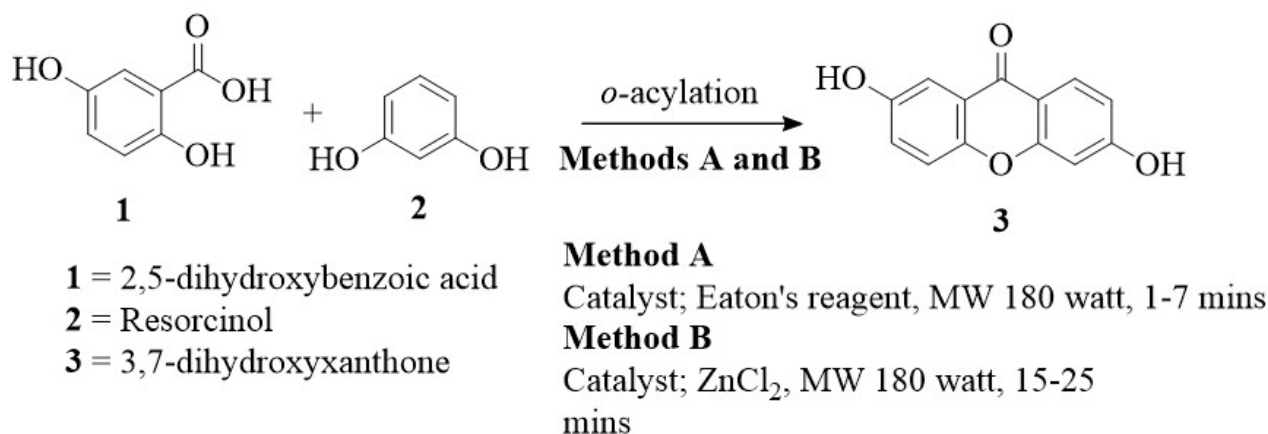
## 1. INTRODUCTION

Xanthenes are a structurally diverse group of compounds belonging to a significant class of oxygenated three-membered heterocyclic compounds characterized by their dibenzo- $\gamma$ -pyrone scaffold. As a privileged structure, xanthenes exhibit a broad spectrum of pharmacological activities, including anti-inflammatory (Feng et al., 2020), anti-allergic (Aye et al., 2020), and anti-fungal (Resende et al., 2018), making them promising candidates for drug development (Liu et al., 2017; Liu et al., 2019; Rovani et al., 2018). The biological activity of xanthone compounds can be enhanced by modifying the xanthone backbone through the substitution of functional groups that influence their efficacy as drug candidates (Huang et al., 2021). Commonly substituted functional groups include hydroxyl, halogen, sulphate, and nitrate, in which the hydroxyl group in xanthone compounds plays a crucial role in antibacterial activity due to its ability to depolarize the membrane potential, leading to protein leakage in bacteria (Lu et al., 2023).

Substitution of the hydroxyl group in xanthone compounds can be achieved through synthetic methods, which allow varia-

tion in the type and position of substituents (Fatmasari et al., 2022). Developing synthetic methods for xanthenes is considered promising for achieving higher yields and a greater diversity of derivatives (Pinto et al., 2021). The synthesis of xanthone compounds is typically carried out using the Grover, Shah, and Shah (GSS) method, which involves the reaction of salicylic acid with phenolic derivatives, heated together with zinc chloride in phosphoryl chloride ( $ZnCl_2/POCl_3$ ) as a solvent (Ramakrishnan et al., 2023). However, the GSS method often forms a benzophenone intermediate, which can reduce the yield of the xanthone product. Another reagent that can be used to reduce the formation of benzophenone intermediates is Eaton's reagent (Bosson, 2023). Thus, Yuanita et al. (2018) obtained 81-85% yield using Eaton's reagent as a catalyst with a reflux method for 3 hours. Furthermore, recent research reports that synthesis using Eaton's reagents as catalysts in 30-minute reactions acquired yields up to 65% (Ramakrishnan et al., 2023).

Besides conventional heating methods, synthesis xanthone can be efficiently carried out using Microwave-Assisted Organic Synthesis (MAOS) (Aamate et al., 2019; Castanheiro



**Figure 1.** Scheme of Synthesis 3,7-Dihydroxyxanthone (DHX)

et al., 2009). This technique has been widely utilized in organic and inorganic synthesis, nanomaterial, and cocrystal formation, moreover it has numerous advantages regarding reaction rate and improving yield (Gawande et al., 2014; Martina et al., 2021; Sulistyowaty et al., 2024). Microwave irradiation has been successfully employed in the synthesis of various organic compounds, and numerous other reactions also have been reported to proceed with high efficiency, delivering excellent yields within remarkably short reaction times. For example, synthesis of ferrocenyl chalcone derivatives (Yadav et al., 2019), synthesis of pyrazoline and triazoles derivatives (Dharavath et al., 2020; Praceka et al., 2021), reaction on heterocyclic molecules that contain oxygen and nitrogen (Tiwari et al., 2023), and oxidation of secondary alcohols and benzyl alcohols using phase transfer catalysts (Maurya et al., 2015).

The MAOS method also has been used in synthesis xanthone derivatives, Genovese et al. (2015) successfully synthesized several xanthone compounds using the MAOS method for 5 minutes with Yb (OTf)<sub>3</sub> as a catalyst, achieving an 83% yield for 1,3,7-trihydroxyxanthone and a 78% yield for 3,7-dihydroxyxanthone. Additionally, 1,3,7-trihydroxyxanthone was synthesized using ZnCl<sub>2</sub> as a catalyst via MAOS and achieving a yield of 77.2% within 30 minutes of reaction (Liu et al., 2017). Therefore, with the combination of the microwave method that increased reaction efficiency and product and using prepared catalysts for xanthone synthesis, this study aims to synthesize 3,7-dihydroxyxanthone using the MAOS method and Eaton's and ZnCl<sub>2</sub> as catalysts. The product compounds were characterized using FTIR and <sup>1</sup>H-NMR and compared with the predicted results of <sup>1</sup>H-NMR using Density Functional Theory (DFT).

## 2. EXPERIMENTAL SECTION

### 2.1 Materials

The materials used in this study include 2,5-dihydroxybenzoic acid (C<sub>7</sub>H<sub>6</sub>O<sub>4</sub>), resorcinol (C<sub>6</sub>H<sub>6</sub>O<sub>2</sub>), Eaton's reagent (P<sub>2</sub>O<sub>5</sub>/CH<sub>3</sub>SO<sub>3</sub>H), zinc chloride (ZnCl<sub>2</sub>), distilled water (H<sub>2</sub>O), ethan-

ol (C<sub>2</sub>H<sub>5</sub>OH), n-hexane (C<sub>6</sub>H<sub>14</sub>), ethyl acetate (C<sub>4</sub>H<sub>8</sub>O). These reagents were purchased from Sigma-Aldrich in pro-analytical grade and used without further purification.

### 2.2 Instruments

The initial identification and reaction monitoring of synthesis was determined by thin layer chromatography (TLC). Structure elucidation of the synthesized products was performed using FTIR spectrometer (Shimadzu Prestige 21) and proton NMR spectrometer (<sup>1</sup>H-NMR, JEOL JNMECA 500 MHz). The DFT computation was conducted using a PC with Intel® Core™ i5 and Gaussian® 6.0.16 for running.

### 2.3 Methods

#### 2.3.1 The Synthesis of 3,7-Dihydroxyxanthone (DHX) Using Eaton's Catalyst and ZnCl<sub>2</sub> via the MAOS Method

The synthesis of 3,7-dihydroxyxanthone was carried by two methods, using Eaton's Catalyst (method A) and using ZnCl<sub>2</sub> (method B) as catalyst. The synthesis involved reacting 2,5-dihydroxybenzoic acid (5 mmol) and resorcinol (5 mmol), along with Eaton's catalyst (5 mmol). The mixture was then irradiated using microwaves at a power of 180 watts. Reaction times were varied at 1, 2, 3, 5, and 7 minutes. The mixture was poured into ice-cold distilled water to precipitate the product. The resulting precipitate was stirred for 30 minutes, filtered using a Buchner funnel, and washed with distilled water. The final product was dried in a desiccator for 24 hours to obtain solid 3,7-dihydroxyxanthone. The scheme of synthesis is shown in Figure 1. The product of method A obtained as a red solid with a yield of 9.38%. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3420 (O-H), 1613 (C=O), 1480 (C=C), and 1248 (C-O-C). The product of method B obtained as an orange solid with a yield of 23.07%. IR (KBr)  $\nu$  (cm<sup>-1</sup>): 3248 (O-H), 1620 (C=O), 1458 (C=C), and 1242 (C-O-C). <sup>1</sup>H-NMR  $\delta$ /ppm (500 MHz): 8.10 (1H, d, J = 2.44 Hz); 6.86 (1H, dd, J = 8.96; 1.84 Hz); 7.00 (1H, d, J = 8.96 Hz); 7.25 (1H, d, J = 3.04 Hz); 6.95 (1H, dd, J = 9.0; 3.2 Hz); and 7.69 (1H, d, J = 2.88 Hz).

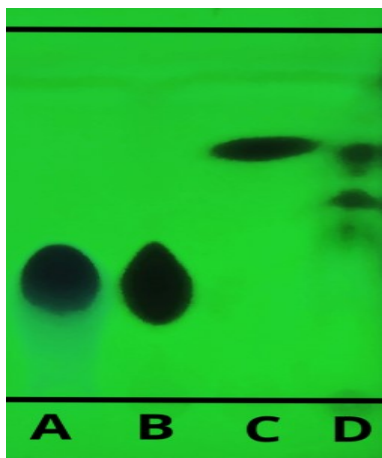
### 2.3.2 <sup>1</sup>H-NMR Calculation Prediction Using the Hartree-Fock and DFT Method

The <sup>1</sup>H-NMR prediction calculation was done by GaussView 6.0.16. This calculation was carried out by optimizing the predicted compound structure using the HF (3-21G), HF (6-31G), DFT (3-21G), and DFT (6-31G) methods, then saved in the form of a log file. The next stage was to calculate the energy of the predicted compound and then calculate its chemical shift using the Gauge-Including Atomic Orbital (GIAO) ground state, DFT method (B3LYP/6-31G). The predicted <sup>1</sup>H-NMR calculation data were compared with the <sup>1</sup>H-NMR of the 3,7-dihydroxyxanthone compound from the experiment.

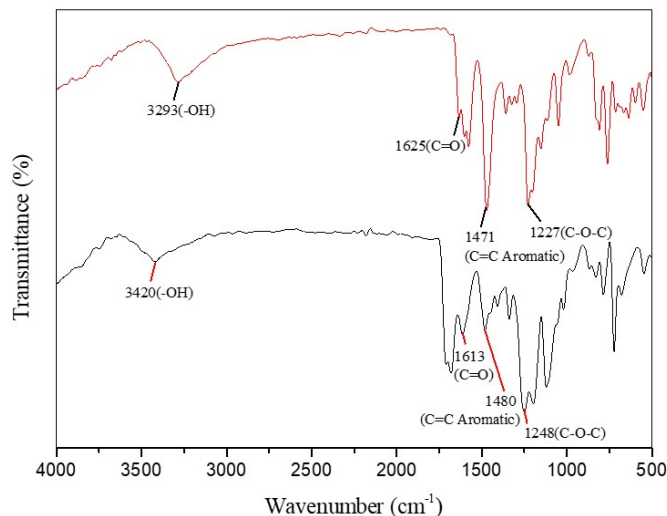
## 3. RESULTS AND DISCUSSION

### 3.1 Synthesis and Characterization of 3,7-dihydroxyxanthone

The compound was synthesized through a cyclization reaction between 2,5-dihydroxybenzoic acid and resorcinol with a microwave method using two catalyst approaches, including Eaton's catalyst and ZnCl<sub>2</sub>. The microwave-assisted Organic Synthesis (MAOS) method offers significant advantages, particularly in shorter reaction times (Xochicale-Santana et al., 2021). Therefore, in this study, the synthesis processes were carried out using several variations in the reaction time. The Eaton's reagent synthesis was performed with reaction times of 1, 2, 3, 5, and 7 minutes, while the ZnCl<sub>2</sub>-catalyzed reaction used 15, 17, 22, and 25 minutes. The yields for 1, 2, 3, 5, and 7 minutes were 7.19% (0.082 g), 9.38% (0.107 g), 4.73% (0.054 g), 6.23% (0.071 g), and 2% (0.023 g), respectively. Based on these provided data, if the reaction time exceeds 7 minutes for Eaton's catalyst or 25 minutes for ZnCl<sub>2</sub>, the trend suggests that longer reaction times may lead to decomposition, side reactions, or polymerization, reducing the product yield. The highest results using Eaton's were obtained at 9.38%, while ZnCl<sub>2</sub> as a catalyst yielded 23.07%.



**Figure 2.** Chromatogram of 2,5-Dihydroxybenzoic acid (A), Resorcinol (B), and 3,7-Dihydroxyxanthone with Eaton's Catalyst (C), with ZnCl<sub>2</sub> Catalyst (D)



**Figure 3.** The FTIR Spectra of 3,7-Dihydroxyxanthone (DHX) Using Eaton Catalyst (A) and ZnCl<sub>2</sub> Catalyst (B)

The reaction progress was monitored using thin-layer chromatography (TLC) with a non-polar eluent of n-hexane and ethyl acetate (7:3) shown in Figure 2. The TLC results revealed higher stain patterns (C) and (D) when compared to the starting materials (A) and (B), indicating that the product has been formed. The presence of lower stain patterns (D) suggested the possible formation of benzophenone intermediates.

**Table 1.** Comparison of the FTIR Data for 3,7-Dihydroxyxanthone and 3,6-Dihydroxyxanthone

Functional Group	Wavenumber ( $\nu$ ) (cm <sup>-1</sup> )		Ref (Yuanita et al., 2018)
	3,7-Dihydroxy-xanthone (Eaton)	3,7-Dihydroxy-xanthone (ZnCl <sub>2</sub> )	
O-H	3293	3420	3248
C=O	1625	1613	1620
C=C	1471	1480	1458
Aromatic	1471	1480	1458
C-O-C	1227	1248	1242

Characterization of the synthesis results was conducted qualitatively using FTIR and <sup>1</sup>H-NMR spectrophotometer. In the FTIR spectra, shown in Figure 3, the formation of 3,7-dihydroxyxanthone was indicated by the presence of a strong absorption of the ether group (C-O-C) at 1227 cm<sup>-1</sup> (A) and at 1248 cm<sup>-1</sup> (B). Additionally, the presence of a carbonyl (C=O) at 1625 cm<sup>-1</sup> (A) and at 1613 cm<sup>-1</sup> (B), typically an absorption carbonyl group in xanthone, strengthened the evidence of forming 3,7-dihydroxyxanthone (Kurniawan et al., 2024). The carbonyl interaction in the xanthone compound is marked by absorption at a lower  $\nu$  than the carbonyl range

reported at 1650–1700  $\text{cm}^{-1}$  (Yuanita et al., 2018). The reduction is influenced by the interaction of two conjugated aromatic carbons, which restricts their vibrational freedom and lowers the peak position by approximately 30  $\text{cm}^{-1}$  on average (Kurniawan et al., 2024). In addition, there is an absorption at 1471  $\text{cm}^{-1}$  (A) and at 1480  $\text{cm}^{-1}$  (B) indicating aromatic C=C vibration, moreover at 3293  $\text{cm}^{-1}$  (A) and 3420  $\text{cm}^{-1}$  (B) indicating the vibration of the hydroxyl group (–OH) with broad and strong intensity.

**Table 2.** Energy Calculations

Basis Set	Energy (kJ/mol)
HF	-791.975683
DFT	-796.685439
3-21G	-796.087843
6-31G	-800.873682

Comparing the FTIR spectra of 3,7-dihydroxyxanthone synthesized with Eaton and  $\text{ZnCl}_2$  catalysts, notable similarities and differences emerge: the Eaton spectrum shows a strong absorption at  $\nu$  1227  $\text{cm}^{-1}$  for the ether (C–O–C) interaction and a peak at  $\nu$  1625  $\text{cm}^{-1}$  for the carbonyl (C=O) interaction, characteristic of xanthone, while the  $\text{ZnCl}_2$  spectrum indicates an absorption at  $\nu$  1248  $\text{cm}^{-1}$  for the ether group, also suggesting ring formation. Despite slight variations in peak positions, both spectra consistently reflect the presence of functional groups, indicating the effectiveness of both catalysts in synthesizing 3,7-dihydroxyxanthone, with minor differences likely arising from the unique electronic environments each catalyst creates. The comparison of the FTIR data results shown at Table 1.

In the  $^1\text{H-NMR}$  spectrum, the first peak appears at a chemical shift ( $\delta$ ) of 8.10 ppm (1H, d,  $J = 2.44$  Hz) (H-1), representing the most deshielded peak, as it is influenced by the carbonyl group rather than the –OH group on the ring. The second peak occurs at  $\delta\text{H}$ -8 7.96 ppm (1H, d,  $J = 2.88$  Hz), indicating that the proton is in the meta position relative to H-6. The third peak at  $\delta\text{H}$ -5 7.25 ppm (1H, d,  $J = 3.04$  Hz) shows that the proton is ortho to H-6. The fourth peak at  $\delta\text{H}$ -4 7.00 ppm (1H, d,  $J = 8.96$  Hz) indicates that the proton is in the meta position relative to H-2. Subsequent peaks appear at chemical shifts of  $\delta\text{H}$ -6 6.95 ppm (1H, dd,  $J = 9.0; 3.2$  Hz) and  $\delta\text{H}$ -2 6.86 ppm (1H, dd,  $J = 8.96; 1.8$  Hz). The coupling constants ( $J$ ) for these peaks correspond to protons in ortho and meta positions relative to one another. The differences in chemical shifts are attributed to the hydroxyl group being attached to neighbouring positions of the protons. This peak is the most shielded, influenced by the –OH group (an electron-donating group). The shifting pattern is consistent with previous studies by Yuanita et al. (2018), Yuanita et al. (2023), and Yuanita et al. (2024).

Validation and confirmation of the  $^1\text{H-NMR}$  measurement results were performed by comparing experimental measure-

ments with predictions obtained through computational calculations. The calculations were conducted using Hartree-Fock (HF) and Density Functional Theory (DFT), based on the energy calculations for the most stable conformation in its lowest or ground state. The energy calculation results from both methods indicated that the DFT method with the 6-31G basis set yields a lower energy value (more stable), and the energy calculation data can be found in Table 2.

The analysis results of the prediction of  $^1\text{H-NMR}$  spectrum compared to the experimental data showed a correlation value ( $R^2$ ) close to 1, precisely 0.965 (shown in Table 3). This correlation value indicated that the chemical shifts in the prediction and experimental  $^1\text{H-NMR}$  spectra do not differ significantly. Based on the comparison of the experimental  $^1\text{H-NMR}$  spectrum with the predicted one, it can be confirmed that the synthesized compound is 3,7-dihydroxyxanthone.

**Table 3.** Comparison of the  $^1\text{H-NMR}$  Spectrum from Computational Calculations with Experimental Results

Proton	Prediction $\delta\text{H}$ (ppm)	Experiment $\delta\text{H}$ (ppm)
1	8.24	8.10 (1H, d, $J = 2.44$ Hz)
2	6.12	6.86 (1H, dd, $J = 8.96; 1.84$ Hz)
4	6.68	7.00 (1H, d, $J = 8.96$ Hz)
5	7.00	7.25 (1H, d, $J = 3.04$ Hz)
6	6.28	6.95 (1H, dd, $J = 9.0; 3.2$ Hz)
8	7.86	7.69 (1H, d, $J = 2.88$ Hz)
$R^2 = 0.965$		

Table 4 shows several results of synthesizing hydroxyxanthones derivatives with various methods. Based on the yield results, the best method for synthesizing hydroxyxanthone is by microwave with  $\text{Yb}(\text{OTf})_3$  or  $\text{ZnCl}_2/\text{POCl}_3$  reagents (Genovese et al., 2015). The low yield obtained by microwave using Eaton's reagents assumed that the hydroxy group on the starting material of gentisic acid diminished protonation by Eaton's reagent. That is supported by the results of other studies, which are lower when using hydroxy-substituted gentisic acid as the starting material. Even though the synthesis results using the microwave method with Eaton's and  $\text{ZnCl}_2$  catalysts were lower, research on the use of the microwave method with Eaton and  $\text{ZnCl}_2$  catalysts has enhanced the development of synthesis methods for hydroxy xanthone derivatives in the future.

The mechanism for synthesizing 3,7-dihydroxyxanthone using  $\text{ZnCl}_2$  begins with activating the acyl group in 2,5-dihydroxybenzoic acid.  $\text{ZnCl}_2$  interacts with the carbonyl oxygen, forming a more reactive lewis acid complex susceptible to nucleophilic attack. Resorcinol, acting as the nucleophile, targets the activated acid's electrophilic carbon, forming a benzophenone intermediate. This intermediate then undergoes intramolecular cyclization, where one hydroxyl group attacks the carbonyl group, ultimately creating the xanthone ring.  $\text{ZnCl}_2$  also facili-

**Table 4.** Comparison of Yield of the Reported Synthesizing Hydroxyxanthone Derivatives

Compounds	Reagents	Methods	Yield (%)	References
3,7-dihydroxyxanthenes	P <sub>2</sub> O <sub>5</sub> /MeSO <sub>3</sub> H	MW (180 W), 2 h	9.38	-
	ZnCl <sub>2</sub>	MW (180 W), 22 min	23.07	
	Yb(OTf) <sub>3</sub>	MW, 5 min	79	(Genovese et al., 2015)
1,3-dihydroxyxanthenes	P <sub>2</sub> O <sub>5</sub> /MeSO <sub>3</sub> H	Refluxes 80°C, 3 h	85.5	(Yuanita et al., 2018)
		Refluxes 85°C, 2.5 h	61	(Wu et al., 2019)
1,6-dihydroxyxanthenes	P <sub>2</sub> O <sub>5</sub> /MeSO <sub>3</sub> H	Refluxes 80°C, 3 h	33.42	(Fatmasari et al., 2022)
		Yb(OTf) <sub>3</sub>	MW (200 W), 5 min	80
	AlCl <sub>3</sub>	MW, 50 s	63	(Verbanac et al., 2012)
	ZnCl <sub>2</sub>	MW, 50 s	71	
	TiCl <sub>4</sub>	MW, 50 s	76	
1,3,7-trihydroxyxanthenes	P <sub>2</sub> O <sub>5</sub> /MeSO <sub>3</sub> H	Refluxes 80°C, 3 h	70	(Ramakrishnan et al., 2023)
	ZnCl <sub>2</sub> /POCl <sub>3</sub>	MW, 30 min	97	(Liu et al., 2017)

tates the removal of water produced in the reaction, potentially resulting in a hydrate (Kurniawan et al., 2024).

In contrast, the synthesis of 3,7-dihydroxyxanthone with Eaton's catalyst begins with the protonation of the carbonyl group, creating a reactive electrophile. In this step, methanesulfonic acid (CH<sub>3</sub>SO<sub>3</sub>H) is crucial for forming a carbocation. Resorcinol then conducts a nucleophilic attack on the protonated carbocation, followed by cyclization via a dehydration reaction (Yuanita et al., 2018). Phosphorus pentoxide (P<sub>2</sub>O<sub>5</sub>) in Eaton's catalyst helps to bind the water produced during the reaction, resulting in phosphoric acid. Overall, both methods effectively synthesize 3,7-dihydroxyxanthone, but they employ different activation mechanisms and intermediates, underscoring the importance of water management in the reactions.

#### 4. CONCLUSIONS

The synthesis of 3,7-dihydroxyxanthone was successfully carried out using the MAOS method with Eaton and ZnCl<sub>2</sub> catalysts, resulting in yields of 9.38% and 23.07%, respectively. FTIR characterization confirmed the formation of 3,7-dihydroxyxanthone, with absorption peaks at 1227 cm<sup>-1</sup> and 1248 cm<sup>-1</sup>, indicating the presence of ether groups typical of xanthone formation. Additionally, <sup>1</sup>H-NMR analysis revealed proton signals at a chemical shift of 7.69 ppm (d, J = 2.88 Hz, H-8), indicating the proton's meta position relative to H-6. The signal at 7.86 ppm (dd, J = 8.96; 1.8 Hz, H-2) suggests this proton is ortho to H-1 and meta to H-4. These proton signals provide confirm the structural characteristics of 3,7-dihydroxyxanthone.

#### 5. ACKNOWLEDGEMENT

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