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Synthesis of 9-(4-hydroxyphenyl)-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione Using Lime and Lemon Juice as an Acidic Catalyst and its Antioxidant Activity

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Abstract. The 1,8-dioxo-octahydroxanthene has many derivatives. One of those is 9-(4-hydroxyphenyl)-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione. This compound has been successfully synthesized from 4-hydroxybenzaldehyde and 1,3-cyclohexanedione. This reaction has been catalyzed by lime and lemon juice under the free solvent condition. It is assumed that citric acid in both materials has a role in catalyzing this reaction. The advantages of using them as catalysts are biodegradable, environmentally safe, and cheap. Besides that, the synthesis of this compound only required one reaction stage, and the product was easily purified. The structure of the pure product was determined by FT-IR, H-NMR, and GC-MS. The antioxidant activity of this compound was investigated by the DPPH method. This compound had an antioxidant activity with inhibition percentage over 53.42%.

INTRODUCTION

The derivative of 1,8-dioxo-octahydroxanthene, 9-(4-hydroxyphenyl)-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (Compound 1), is a compound with –OH group substituted in para position ring of benzene and has a pyran located between two rings of cyclohexene-2-one [1]. Recently, the synthesis of 1,8-dioxo-octahydroxanthene and its derivatives have become intriguing to be investigated by organic chemists due to their bioactivity potencies, such as antioxidant [2], anticancer [3], antibacterial [4], anti-inflammation, and anti-tuberculosis [5]. These compounds can be synthesized from Knoevenagel condensation between cyclic diketone compound and an aldehyde using acid or basic catalyst [6]. Knoevenagel condensation reaction is a reaction involving aldehyde and α -Hydrogen compound toward two activation groups (i.e., C=O or C=N). This reaction could be explained as aldol reaction modification with nucleophilic addition of active hydrogen compound to a carbonyl group and followed by dehydration reaction [7], therefore, to synthesize Compound 1, derivatives of 1,8-dioxo-octahydroxanthene, can be carried out by a reaction of 1,3-cyclohexanedione compound with 4-hydroxybenzaldehyde using an acid catalyst.

The –OH group in 4-hydroxybenzaldehyde is an electron-donating group [8]. Its position in the benzene ring can affect the steric effect of the compound. The para position will give less steric effect than in its ortho or meta position. The carbonyl group reactivity will also be increasing with this para position since it enables a nucleophile, 1,3-cyclohexanedione, to easier attack the group to form Compound 1, so it makes the synthesis more profitable. While the roles of acid catalyst in this reaction are to protonate the carbonyl group on the 4-hydroxybenzaldehyde so that it can get a nucleophilic attack from 1,3-cyclohexanedione. Additionally, it also aids in the pyran cyclization. The proposed mechanism of Compound 1 formulation is illustrated in Figure 1.

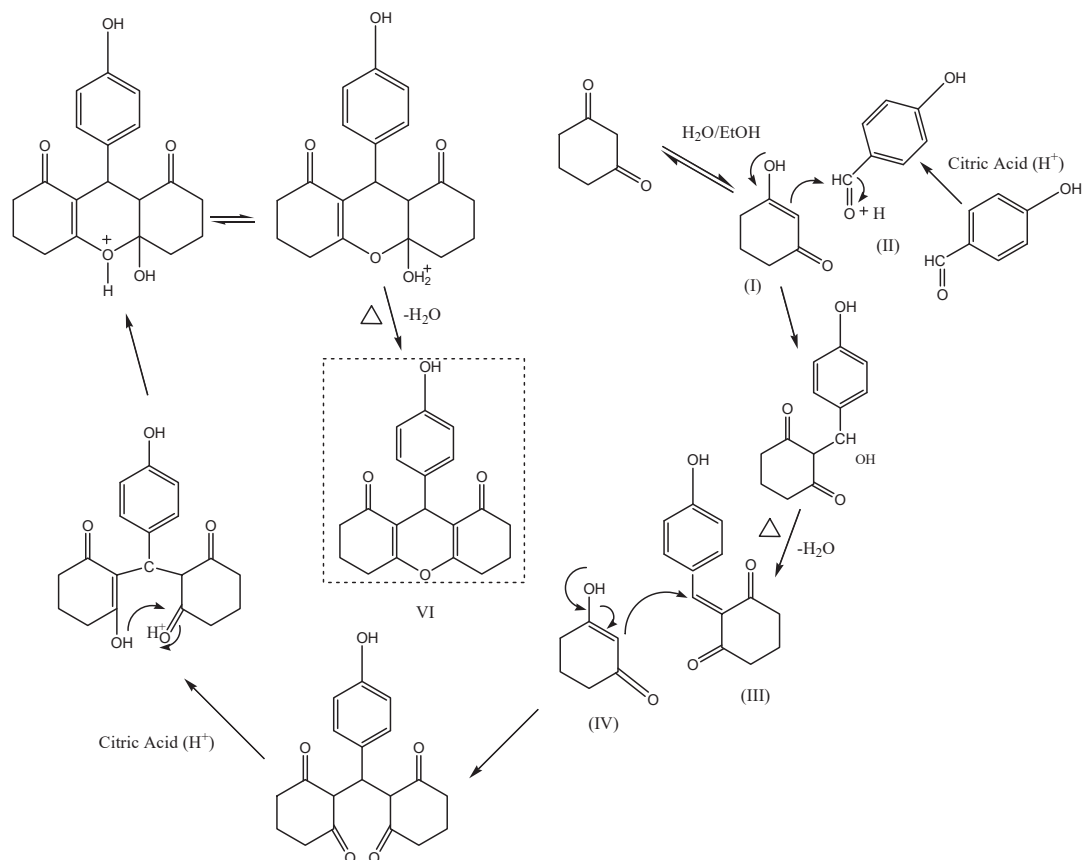


FIGURE 1. Proposed mechanism of compound 1 formulation [5]

Generally, the proposed mechanism of Compound 1 formation are involving some several steps, i.e. Knoevenagel condensation, Michael addition, and dehydration. Initially, 1,3-cyclohexanedione did nucleophilic attack to 4-hydroxybenzaldehyde which had been protonated firstly by acid, then followed by dehydration to provide Knoevenagel product **III**. Through Michael addition, **III** would be attacked secondly by 1,3-cyclohexanedione with nucleophilic attack and produced intermediate **V**. In the next step, this intermediate **V**, with the help of the catalyst, would be nucleophilic attacked by hydroxyl group in its C=C to get cyclisation and formed the desired compound (**VI**).

Various types of already developed catalysts can be used for this synthesis, such as *p*-dodecyl benzene sulfonate acid in the water [9], NaHSO₄.SiO₂ [10], alumina sulfuric acid in ethanol [11], iodine in isopropanol [3], and ZnO nanoparticle [12]. Most of those catalysts are effective; however, they have been identified to carry some weaknesses, such as relatively high-priced, require complicated preparations, and not environmentally friendly. Therefore, this research will use lime and lemon juice, a Green Catalyst, as one of the alternatives acid catalyst which is environmentally friendly in the preparation of Compound 1. Lime and lemon are used as potential catalyst since they contained 7 - 8 % of citric acid out of their pulp [13]. In addition to their reasonable price and their abundant availability in Indonesia, the usage of lime and lemon juice as catalyst supports “Green Chemistry” concept by its non-poisonous, non-volatile, and biodegradable characteristics [14].

Antioxidant is a property of compounds which has an important role in the body protection from free radicals and in the prevention of its further reactions [15]. It stabilizes or reduces free radicals by completing their electron deficiency and prohibits the chain reaction from free radicals formulation that can produce oxidative stress [16]. Therefore, substances containing sufficient antioxidant are very needed by human body intake. The antioxidant is classified into two, i.e natural and synthetic antioxidants [16]. The natural antioxidant can be isolated from natural products. The use of natural product gives more benefits since it is low priced and has abundant availability. However, it carries some drawbacks, such as limited compound, requires a long time, and complicated refining process. Therefore, the invention of synthetic metabolism is more thought-provoking and promising since the structure of the

targeted compound can be discovered evidently. This creates an opportunity to establish new antioxidant compounds with great antioxidant activity [17].

One of the synthesized compound that has potential as an antioxidant is the 1,8-dioxo-octahydroxanthene and its derivatives [18,19]. The antioxidant activity of some 1,8-dioxo-octahydroxanthene derivatives substituted by hydroxy group bounded to benzene ring had been reported. They have a different percentage of inhibition in each sample concentration used. The hydroxy group attached to those compound was able to prevent the continuity of free radical reaction through hydroxy homolytic reaction by donating hydrogen to it; thus new more stable as well as less reactive free radical would be formed. This condition would also be followed by the increasing of compound inhibition percentage [20].

The procedure used to test the antioxidant activity of a compound is conducted by measuring the interception of free radicals from DPPH (1,1-diphenyl-2-picrylhydrazyl). The method is relatively simple, easy, economical, and quick. Antioxidant activity is showed by decreasing of DPPH colour intensity and followed by the decreasing of its absorbance. The absorbance obtained can be used to calculate the preventing or inhibition percentage. The higher the inhibition percentage, the more DPPH free radical reduced formed non radical DPPH (DPPH₂). Thus, a compound can be classified having antioxidant activity.

Besides the discovery of pharmacology compound particularly as an antioxidant is very needed, and the antioxidant activity of Compound 1 has never been reported, so the antioxidant testing of this compound need to be done. This synthesis can be completed through two procedures, a reflux method in the temperature of 60 and 78 °C. The synthesis results can be obtained in two hours, as proven by previous studies that synthesize some derivatives of 1,8 dioxo-octa-hydro xanthene using 60 and 78 °C temperature for two hours [21-23]. This study investigates the effectiveness of lime and lemon juices as an acid catalyst. Besides, the work also identifies the structure of the synthesized product using FT-IR (Fourier Transform Infra-Red), GC-MS (Gas Chromatography-Mass Spectroscopy), and ¹H-NMR (H-Nuclear Magnetic Resonance) instruments. The results from each instrument are compared with the related literature.

EXPERIMENTAL DETAILS

Materials

The materials used in this study come from Sigma Aldrich, such as 1,3-cyclohexanedione (powder), 4-hydroxybenzaldehyde (powder), ethanol p.a, methanol, dimethyl sulfoxide (DMSO), 1,1-diphenyl-2-picrylhydrazyl (DPPH), aquades, aluminum foil, universal indicator, filter paper. Lime used in this research was obtained from a garden located in Dau Malang, while the lemon was purchased from Superindo convenience store Malang.

Synthesis of 9-(4-hydroxyphenyl)-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione Compound

A 0.2243 g (2 mmol) 1,3-cyclohexanedione and 0.1221 g (1 mmol) 4-hydroxybenzaldehyde was put in a 50 mL two neck round bottom flask. Then, 10 mL of the squeezed lime or lemon water that has been centrifugated to separate its water and pulp was added. It was refluxed for two hours at 60 °C temperature. After two hours, it was set aside for ± 10 min to let the residue went down. The residue was filtered, dried, and heated in an oven at 100 °C for 1-2 minutes to eliminate the water left. Later, it was purified using the recrystallization technique until the pure compound was obtained. The same procedure was conducted at 78 °C reflux temperature. The calculation of synthesized product attenuation was obtained by comparing the mass of the synthesized product and the theoretical mass (Equation 1).

$$\% \text{ Rendement} = \frac{\text{Mass of yield}}{\text{Theoretical mass}} \times 100\% \quad (1)$$

Characterization and Identification of Synthesized Product

The characterization of the synthesized product includes the shape, color, and melting point. Meanwhile, the identification of the pure synthesized compound was carried out using FT-IR, GC-MS, and ¹H-NMR instrument.

Antioxidant Activity Test of 9-(4-hydroxyphenyl)-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione Compound

First step in preparation of sample or testing solution, it required 0.001 gram of Compound 1, put in a 10 mL volumetric flask and then DMSO was also added to this flask until the volume reached the boundary mark. After that, this solution was diluted to several concentration variations such as 2, 4, 6, 8, and 10 ppm. 2 mL from each sample concentration was taken and added with 1 mL DPPH 20 ppm reagent. The control solution was 2 mL DMSO solvent mixed with 1 mL DPPH 20 ppm solution. The control and mixture solution was set aside for 30 min in a dark room and at room temperature. After 30 min, its absorbance was measured in duplo at a wavelength of $\lambda = 517$ nm using a UV-Vis spectrophotometer [24-26]. The estimation of the antioxidant compound inhibition percentage toward DPPH radical was completed using Equation 2.

$$\text{Inhibition Percentage} = \frac{A_c - A_s}{A_c} \times 100\% \quad (2)$$

Description : A_c = control absorbance; A_s = sample absorbance

RESULTS AND DISCUSSION

The synthesized product was in white-colored solids that dissolves in dimethyl sulfoxide (DMSO) solvent. The purity of a compound could be identified by determining its melting point. A sample was considered pure if the range of its initial and final melting temperature was equal to 1 – 2 °C. Additionally, pure compound generally had higher melting point compare to the impure one. The measurement showed that the melting point of the reaction product that catalyzed by lime and lemon juice at 60 and 78 °C reflux temperature were 227 – 229 °C. This result explained that the expected pure product had been formed, because it had different melting point from its reactant which was 106 °C for 1,3-cyclohexanedione and 117 °C for 4-hydroxybenzaldehyde. Table 1 showed that lime juice was better catalyst than lemon for the synthesis of Compound 1 at temperatures of 60 and 78 °C, even if both lime and lemon possess citric acid. The rendement of this synthesise was summarized in Table 1.

TABLE 1. Mass and percentage of rendement

No	Catalyst	Temperature 60 °C (2 h)		Temperature 78 °C (2 h)	
		Mass (g)	Rendement (%)	Mass (g)	Rendement (%)
1.	Lime juice	0.2728	88.00	0.2512	81.03
2.	Lemon juice	0.2379	76.74	0.2421	78.09

In the market, lime also has a lower price than lemon, so that the use of lime as a catalyst is more economical and beneficial. The initial pH for each lime and lemon before reaction was 2.43 and 2.36. The pH of both materials was relatively similar; therefore, the catalyst effectiveness difference was presumed to come from another component in the lime that accelerated this compound synthesis. Besides, previous research has reported that the citric acid in the lime is (8.4%) higher than the citric acid of lemon (3.49%) [27]. Both of lime juice and lemon juice also can be reused until two more of synthesis process.

Structure identification of the synthesized product was analyzed using FT-IR to reveal the functional groups of a sample or compound. FT-IR analysis of both reactants of 4-hydroxybenzaldehyde and 1,3-cyclohexanedione, along with the synthesized product with lime and lemon catalyst, have been carried out. Each compound has a typical IR spectrum. If the product's IR spectra are different from both reactants, the product formulation has been confirmed. The products have distinctive absorption bands from the reactant's absorption bands (Figure 2), which indicates that the product has been successfully synthesized using lime and lemon catalyst. Besides, the interpretation of the synthesized product's IR spectra is also supported by previous research, as shown in Table 2 [28].

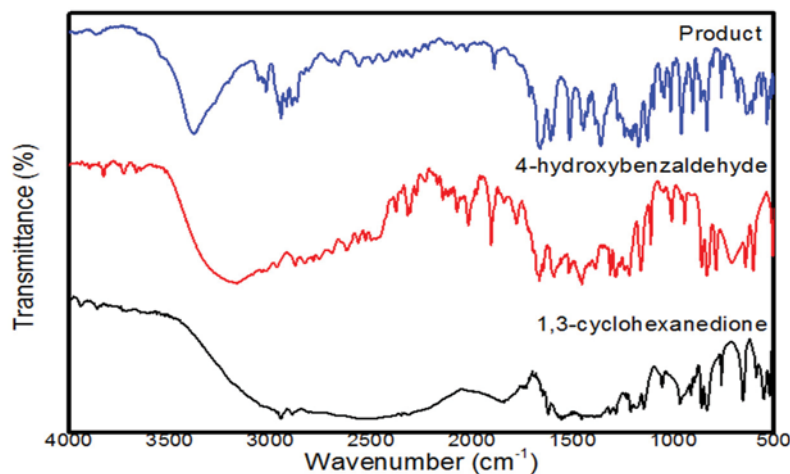


FIGURE 2. IR spectrum of reactants and products

TABLE 2. Interpretation of synthesized product IR spectra and previous research findings

Typical Vibration	Wave Number (cm ⁻¹)	Intensity	Research by Li-Bin, <i>et al.</i> [28] (cm ⁻¹)
Stretching O-H	3381.21	Strong, widen	3379
Stretching C-H aromatic	3022.45	Moderate, sharp	3021
Stretching C-H aliphatic	2949.16	Moderate, sharp	2949
Stretching C=O ketones	1651.07	Strong, sharp	1662
Stretching C=C aliphatic	1610.56	Strong, sharp	1612
Stretching C=C aromatic	1516.05	Strong, sharp	1515
Stretching C-O	1207.44	Strong, sharp	1207

The ¹H-NMR analysis results showed eight primary signals. The signal (2H, *s*) at 1.82 and 1.93 ppm indicated proton methylene on cyclohexene rings (H-20 and H-15). Meanwhile, the signal (4H, *t*) at 2.25 and 2.62 ppm represented H-19, H-21, H-14, and H-16. The main characteristic of ¹H-NMR spectrum of 1,8-dioxooctahydroxantene was signal at 4.46 ppm indicating proton methine in pyran ring (H-8). The phenolic protons (H-1, H-2, H-3, and H-5) was represented by signal (2H, *d*) at 6.59 and 6.93 ppm (H-1, H-2, H-3, and H-5). The proton of hydroxyl group was showed by signal (1H, *s*) at 9.16 ppm. The ¹H-NMR prediction can be shown in Figure 3.

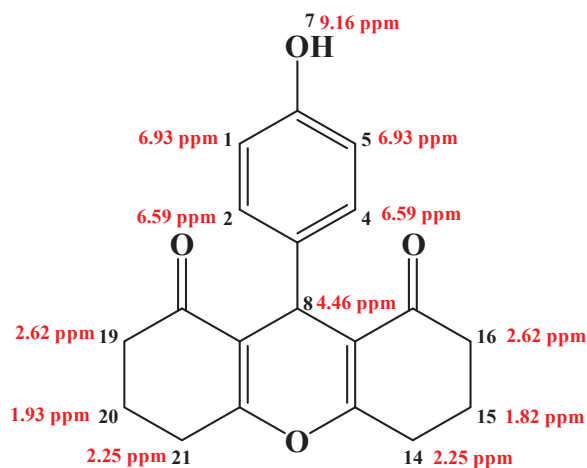


FIGURE 3. The chemical shift of each proton in compound 1

However, the singlet signal on δ 1.82 ppm and δ 1.93 ppm should have appeared as a triplet because it has two neighboring hydrogens. Similarly, the triplet signal on δ 2.25 ppm should have occurred as a quintet because it possesses four neighboring hydrogens. This is caused by the $^1\text{H-NMR}$ spectrophotometer uses low resolution so that the protons have no ability to perform splits. Contrarily, with an integrated $^1\text{H-NMR}$ technique, a hydrogen number ratio of 2 : 2 : 4 : 4 : 1 : 2 : 2 : 1, in line with the amount of H proton group on the targeted compound structure, was obtained. The interpretation of $^1\text{H-NMR}$ spectrum results for the synthesized product is supported by previous results findings, as presented in Table 3 [28].

TABLE 3. Interpretation of $^1\text{H-NMR}$ spectrum for synthesized product and results of the previous study

Protons	Chemical Shift (ppm)	A Study by Li-Bin, <i>et al.</i> [28] (ppm)
H-15	1.82	1.86
H-20	1.93	1.94
H-14 & H-21	2.25	2.27
H-16 & H-19	2.62	2.63
H-8	4.46	4.48
H-2 & H-4	6.56	6.59
H-1 & H-5	6.93	6.95
H-7	9.13	9.19

In order to assure $^1\text{H-NMR}$ interpretation, analysis using GC-MS was done to determine molecular mass of expected compound. GC analysis result of product which was catalyzed by lime juice at 60 and 78 °C reflux temperature gives a single peak at chromatogram and 100% surface area assumed to be pure compound. The MS spectrum showed a peak at m/z 310.0, estimated to be targeted molecular ion $[\text{M}^+]$ of Compound 1. These exact results were also obtained in the measurement of product which was produced using lemon catalyst. The product formulation was also confirmed by the fragmentation pattern of ion molecule, illustrated in Figure 4.

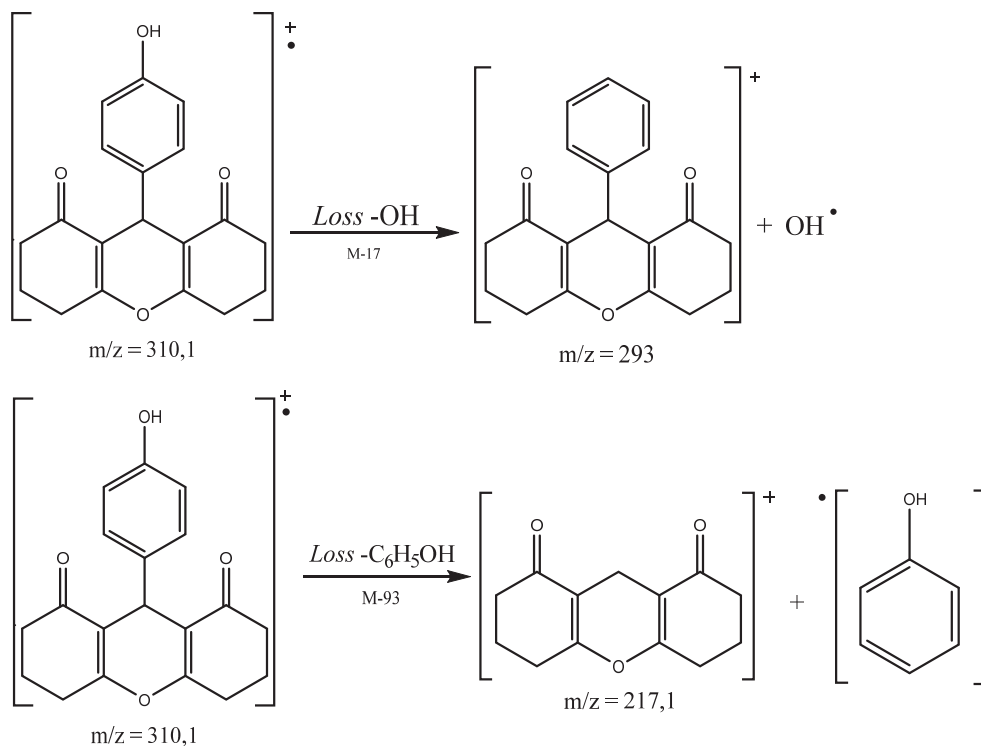


FIGURE 4. Fragmentation pattern of ion molecule

The interpretation of IR spectra, mass spectra, and ¹H-NMR spectrum results indicated that the characteristic of the targeted compound structure was 9-(4-hydroxyphenyl)-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (the 1,8-dioxo-octahydroxanthene derivative). Therefore, that compound has been successfully synthesized using lime and lemon juice. The reusability of the lime and lemon juice was also studied in this research. The mixture of the reaction product was separated by filtration. The filtrate contained recovered lime and lemon juice gave pH value same as their initial pH. These filtrates could be used again as catalyst in the second synthesis of Compound 1. The result showed that the isolated yield of Compound 1 was small decrease as shown in Figure 5.

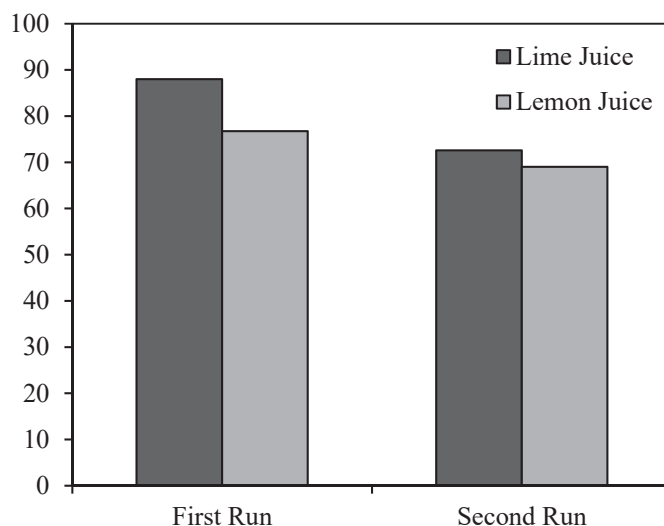


FIGURE 5. Graphs of the first and second synthesis results

Antioxidant activity was tested using DPPH inhibition method by UV-Vis spectrophotometer absorbance measurement. This method has many advantages such as simple, easy, fast, and need fewer samples. The antioxidant compound will react with free radical DPPH to form non-radical DPPH (DPPH₂) indicated by the change in purple color intensity become lighter and absorbance decreasing. The inhibition percentage of the antioxidant compound was calculated using Equation 2. The UV-Vis spectrometer analysis and inhibition percentage is shown in Table 4.

TABLE 4. Results of inhibition percentage calculation for compound 1

Sample Concentration (ppm)	Average Absorbance	Inhibition Percentage (%)
0	0.8899	0
2	0.4145	53.422
4	0.3955	55.557
6	0.3905	56.119
8	0.2855	67.918
10	0.278	68.761

A sample with 0 ppm was a blank or control solution used as comparative in determining antioxidant activity of the sample. Besides, it also reveals the DPPH radical absorbance that was not reduced by the sample. The data showed that the higher the sample concentration is, the inhibition percentage is greater. It is because higher concentration will give more atoms H used to stabilize free radical DPPH. The more radical DPPH stabilized is, the color intensity is weaker and so are the absorbance value. The decreasing in absorbance value will give an increase in inhibition percentage. Antioxidant potency of a compound is related to its inhibition percentage. Based on the inhibition percentage calculation, Compound 1 has IC₅₀ less than 2 ppm. This result was predicted from the value of inhibition percentage at concentration 2 ppm more than 50%. But, this conclusion needs to be proved in further research.

SUMMARY

Synthesize of 9-(4-hydroxyphenyl)-3,4,6,7-tetrahydro-2*H*-xanthene-1,8(5*H*,9*H*)-dione using one simple step and economics reaction has been successfully done. This process consists of Knoevenagel condensation between 1,3-cyclohexanedione and 4-hydroxybenzaldehyde in the presence of lime juice or lemon juice as Green Catalyst. Research proved that lime juice is more effective catalyst than lemon juice in the formation of Compound 1 with yield more than 80%. This compound has antioxidant activity with inhibition percentage over 53.42%.

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REFERENCES

1. Atta-ur-Rahman, "Different Concepts of Catalysis in the Synthesis of Xanthenediones : A Brief Overview," 2017.
2. G. S. Suresh Kumar, A. Antony Muthu Prabhu, P. G. Seethalashmi, N. Bhuvanesh, dan S. Kumaresan, "Self-catalyzed syntheses, structural characterization, DPPH radical scavenging-, cytotoxicity-, and DFT studies of phenoxyaliphatic acids of 1,8-dioxo-octahydroxanthene derivatives," *J. Mol. Struct.*, vol. 1059, hlm. 51–60, Feb 2014, doi: 10.1016/j.molstruc.2013.11.016.
3. N. Mulakayala dkk., "Catalysis by molecular iodine: A rapid synthesis of 1,8-dioxo-octahydroxanthenes and their evaluation as potential anticancer agents," *Bioorg. Med. Chem. Lett.*, vol. 22, no. 6, hlm. 2186–2191, Mar 2012, doi: 10.1016/j.bmcl.2012.01.126.
4. A. Khazaei, M. Rezaei, A. R. Moosavi-Zare, dan S. Saednia, "Solvent-free Synthesis of 1,8-Dioxo-octahydroxanthenes and Tetra-hydrobenzo[a]xanthene-11-ones over Poly(N,N ' -dibromo- N -ethylnaphtyl-2,7-sulfonamide): Solvent-free Synthesis of Xanthene Derivatives," *J. Chin. Chem. Soc.*, vol. 64, no. 9, hlm. 1088–1095, Sep 2017, doi: 10.1002/jccs.201700082.
5. A. A. Napoleon dan F.-R. Nawaz Khan, "Potential anti-tubercular and in vitro anti-inflammatory agents: 9-substituted 1,8-dioxo-octahydroxanthenes through cascade/domino reaction by citric fruit juices," *Med. Chem. Res.*, vol. 23, no. 11, hlm. 4749–4760, Nov 2014, doi: 10.1007/s00044-014-1033-x.
6. F. Rajabi dkk., "Solvent-Free Preparation of 1,8-Dioxo-Octahydroxanthenes Employing Iron Oxide Nanomaterials," *Materials*, vol. 12, no. 15, hlm. 2386, Jul 2019, doi: 10.3390/ma12152386.
7. J. Julianus dan E. Luckyvano, "Sintesis Asam Sinamat Dari Benzaldehida Dan Asam Malonat Dengan Katalis Dietilamina," hlm. 6, 2014.
8. Oktaviana, "Pengaruh gugus hidroksi pada senyawa 4-hidroksibenzaldehida dalam sintesis senyawa N-((2-hidroksinaftalen-1-il)4-hidroksi-benzil)etanamida melalui metode sintesis bebas pelarut dengan katalis asam borat," 2015.
9. T.-S. Jin, J.-S. Zhang, J.-C. Xiao, A.-Q. Wang, dan T.-S. Li, "Clean Synthesis of 1,8-Dioxo-octahydroxanthene Derivatives Catalyzed by p-Dodecylbenzenesulfonic Acid in Aqueous Media," *Synlett*, vol. 2004, no. 05, hlm. 0866–0870, Mar 2004, doi: 10.1055/s-2004-820022.
10. B. Das, P. Thirupathi, K. R. Reddy, B. Ravikanth, dan L. Nagarapu, "An efficient synthesis of 1,8-dioxo-octahydroxanthenes using heterogeneous catalysts," *Catal. Commun.*, vol. 8, no. 3, hlm. 535–538, Mar 2007, doi: 10.1016/j.catcom.2006.02.023.
11. A. Pramanik dan S. Bhar, "Alumina-sulfuric acid catalyzed eco-friendly synthesis of xanthenediones," *Catal. Commun.*, vol. 20, hlm. 17–24, Apr 2012, doi: 10.1016/j.catcom.2011.12.036.
12. Z. Lasemi dan E. Mehrasbi, "ZnO nanoparticles: an efficient and reusable catalyst for one-pot synthesis of 1,8-dioxo-octahydroxanthenes," *Res. Chem. Intermed.*, vol. 41, no. 5, hlm. 2855–2866, Mei 2015, doi: 10.1007/s11164-013-1394-7.
13. C. Navarro, C. Sierra, dan C. Puentes, "Aqueous citric acid as 'green' reaction media for the synthesis of octahydroxanthenes," 2013.
14. N. Ariyana, "Pengaruh Ekstrak Kulit Jeruk Lemon (Citrus Limon) Terhadap Peningkatan Kadar Hdl Dalam Darah Tikus Putih Jantan (Rattus Norvegicus) Yang Diinduksi Minyak Goreng Deep Frying," 2018.

15. A. Widyasanti, D. Rohdiana, dan N. Ekatama, "Aktivitas Antioksidan Ekstrak Teh Putih (*Camellia Sinensis*) Dengan Metode DPPH (2,2 Difenil -1- Pikrilhidrazil)," hlm. 9, 2016.
16. Fadlillah, "Isolasi, Karakterisasi, dan Uji Aktivitas Antioksidan dan Sunscreen Suatu Terpenoid dari Fraksi Kloroform Biji Pepaya (*Carica papaya* Linn)," 2015.
17. S. Y. Prabawati, "Synthesis Of 1,4-Bis [(1-Hydroxy-4-T-Butyl-Phenyl) Methyl]Piperazine As Antioxidants," *Molekul*, vol. 11, no. 2, hlm. 220, Nov 2016, doi: 10.20884/1.jm.2016.11.2.244.
18. A. Seca, S. Leal, D. Pinto, M. Barreto, dan A. Silva, "Xanthenedione Derivatives, New Promising Antioxidant and Acetylcholinesterase Inhibitor Agents," *Molecules*, vol. 19, no. 6, hlm. 8317–8333, Jun 2014, doi: 10.3390/molecules19068317.
19. S. Zukić dkk., "Antioxidant, Antimicrobial and Antiproliferative Activities of Synthesized 2,2,5,5-Tetramethyl-9-aryl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione Derivatives," *Croat. Chem. Acta*, vol. 91, no. 1, 2018, doi: 10.5562/cca3225.
20. L. S. Nirwani, H. M. Ansory, dan A. Nilawati, "Sintesis senyawa 2,4-Dihidroksiasetofenon dan Uji Aktivitasnya sebagai Antioksidan," *J. Farm. Indones.*, vol. 15, no. 1, hlm. 65–70, Mar 2018, doi: 10.31001/jfi.v15i1.356.
21. A. Zare, M. Mokhlesi, A. Hasaninejad, dan T. Hekmat-Zadeh, "Solvent-Free Synthesis of 1,8-Dioxo-octahydroxanthenes and 14-Aryl-14 H -dibenzo[a,j]xanthenes using Saccharin Sulfonic Acid as an Efficient and Green Catalyst," *E-J. Chem.*, vol. 9, no. 4, hlm. 1854–1863, 2012, doi: 10.1155/2012/596862.
22. S. U. Deshmukh, G. K. Kadam, S. U. Shisodia, M. V. Katarina, S. B. Ubale, dan R. P. Pawar, "Efficient synthesis of substituted 1, 8-Dioxo-octahydroxanthene using copper silicate as reusable catalyst," vol. 7, hlm. 5, 2018.
23. P. Sivaguru dan A. Lalitha, "Ceric ammonium nitrate supported HY-zeolite: An efficient catalyst for the synthesis of 1,8-dioxo-octahydroxanthenes," *Chin. Chem. Lett.*, vol. 25, no. 2, hlm. 321–323, Feb 2014, doi: 10.1016/j.ccl.2013.11.043.
24. S. Ammelia, "Analisis Pengaruh Waktu Pemanasan terhadap Perubahan Senyawa Organosulfur dan Persentase Inhibisi Senyawa Antioksidan pada Proses Fermentasi Bawang Hitam dari Bawang Putih (*Allium sativum* L.) dan Bawang Merah (*Allium cepa* L.) dengan Metode Spektrokopi dan Kromatografi," 2019.
25. D. Dhianawaty dan Ruslin, "Kandungan Total Polifenol dan Aktivitas Antioksidan dari Ekstrak Metanol Akar *Imperata cylindrica* (L) Beauv. (Alang-alang)," *Maj. Kedokt. Bdg.*, vol. 47, no. 1, hlm. 60–64, 2015, doi: 10.15395/mkb.v47n1.398.
26. P. Iniyavan, S. Sarveswari, dan V. Vijayakumar, "Synthesis and antioxidant studies of novel bi-, tri-, and tetrapodal 9-aryl-1,8-dioxo-octahydroxanthenes," *Tetrahedron Lett.*, vol. 56, no. 11, hlm. 1401–1406, Mar 2015, doi: 10.1016/j.tetlet.2015.01.162.
27. F. Ekaputri, "Pengaruh Perbandingan Kulit Dan Sari Lemon Dan Konsentrasi Kayu Manis Terhadap Karakteristik Selai Lemon (*Citrus limon burm f.*) Secara Organoleptik," 2018.
28. L. Li-Bin, J. Tong-Shou, H. Li-Sha, L. Meng, Q. Na, dan L. Tong-Shuang, "The Reaction of Aromatic Aldehydes and 1,3-Cyclohexanedione in Aqueous Media," *E-J. Chem.*, vol. 3, no. 3, hlm. 117–121, 2006, doi: 10.1155/2006/686538.