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Synthesis of 1,2-Di(phenyl)ethan-1,2-dione through Oxidation of 2-Hydroxy-1,2-Dipheniletanone by using Copper(II) Citrate

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Abstract: 1,2-Di(phenyl)-1,2-dione widely used in chemical and pharmaceutical industries and found as a framework in secondary metabolites can be obtained through oxidation of 2-hydroxy-1,2-diphenylethanone using strong acids, homogeneous, heterogeneous, and metal catalysts. However, these oxidation methods exhibit various drawbacks. This study reported the oxidation of 2-hydroxy-1,2-diphenylethanone by using copper(II) citrate to produce 1,2-di(phenyl)-1,2-dione. The oxidation performed with copper(II) citrate and ammonium nitrate in glacial acetic acid as solvent yielded 1,2-di(phenyl)-1,2-dione in 88% yield higher than the nitric acid method (79% yield). The FTIR, NMR spectriscopies, and mass analysis confirmed the structure of 1,2-di(phenyl)ethane-1,2-dione. The oxidation of 2-hydroxy-1,2-diphenylethanone using copper(II) citrate is proposed by the formation of Cu^+ ions and a resonance-stabilized 2-hydroxy-1,2-diphenylethanone radical resulting in 1,2-di(phenyl)ethane-1,2-dione.

Keywords: 1,2-di(phenyl)ethane-1,2-dione, 2-hydroxy-1,2-diphenylethanone, oxidation, copper(II) citrate

Abstrak: *1,2-Di(fenil)-1,2-dion yang banyak digunakan dalam industri kimia dan obat-obatan serta dijumpai sebagai kerangka senyawa metabolit sekunder dalam beberapa tumbuhan dapat diperoleh melalui oksidasi 2-hidroksi-1,2-difeniletanon menggunakan asam kuat, katalis homogen, katalis heterogen maupun katalis logam. Namun, metode oksidasi tersebut masih menunjukkan berbagai kelemahan. Penelitian ini melakukan oksidasi 2-hidroksi-1,2-difeniletanon dengan tembaga(II) sitrat untuk menghasilkan 1,2-di(fenil)-1,2-dion. Oksidasi yang dilakukan dalam campuran tembaga(II) sitrat dan amonium nitrat dengan pelarut asam asetat glasial menghasilkan 1,2-di(fenil)-1,2-dion dengan yield 88% yang lebih tinggi dari oksidasi dengan asam nitrat dengan yield 79%. Spektroskopi FTIR, NMR, dan analisis massa berhasil menetapkan struktur 1,2-di(fenil)etan-1,2-dion. Mekanisme oksidasi 2-hidroksi-1,2-difeniletanon dengan tembaga(II) sitrat diusulkan melalui pembentukan ion Cu+ dan radikal 2-hidroksi-1,2-difeniletanon terstabilkan resonansi.*

Kata kunci: *1,2-di(fenil)etan-1,2-dion, 2-hidroksi-1,2-difeniletanon, oksidasi, tembaga(II) sitrat*

INTRODUCTION

1,2-di(phenyl)ethane-1,2-dione (Figure 1a) as the simplest diketone consists of two carbonyls and two aromatic rings with the formula $C_{14}H_{10}O_2$. 1,2-di(phenyl)ethane-1,2-dione is a key compound in the manufacture of medicines as well as a precursor in the formation of porphyrins and photoinitiator in polymer synthesis (Chigare *et al.* 2020). 1-(2,5-Dihydroxy-4-methoxyphenyl)-2-phenylene-1,2-dione (Figure 1b) with 1,2-di(phenyl)ethane-1,2-dione framework has been isolated from *Dalbergia latifolia* using 70% ethanol by reflux (Liu *et al.* 2018). *Placolobium vietnamese* produces placovinon B-C containing 1,2-di(phenyl)ethene-1,2-dione skeleton (Figure 1c-d) (Do *et al.* 2022). 1,2-Di(phenyl)ethane-1,2-dione can also be found as a naturally occurring compound of coriaceol, 1,2-(3,5-dimetoxy-4-hydroxyphenyl)ethane-1,2-dione, narceinone, licoagrodion, derrisdion A, sophodibenzoside A, loddigecyinol D, and 1-(4-hydroxyphenyl)-2-(3,5-dihydroxyphenyl)-2-hydroxyethethone (Yayli *et al.* 2021; Yayli *et al.* 2022).

Generally, diketones are produced from oxidation of 1,2-diol or α-hydroxycyclone. Oxidation of 2-hydroxy-1,2-diphenylethanone, an α-hydroxyketone, is an efficient and practical method for the synthesis of 1,2-di(phenyl)ethane-1,2-dione. Various reagents such as nitric acid, Fehling solution, thallium nitrate, bismuth nitrate, and iron(III) nitrate have been employed for the oxidation of 2-hydroxy-1,2-diphenylethanone. Furthermore, iron oxide, aluminum oxide, vanadium trichloride, chromium trioxide, silica-supported manganese dioxide, alumina- or silica-adsorbed ammonium

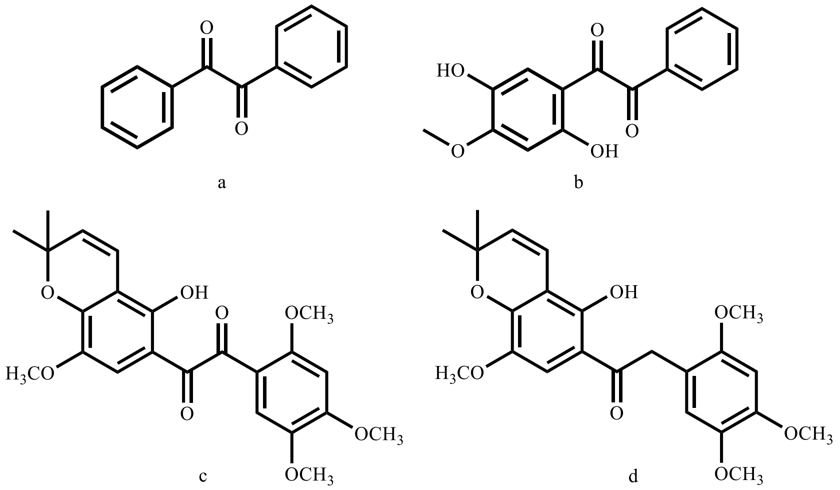

Figure 1. Structure of 1,2-di(phenyl)ethane-1,2-dione (a) and derivatives (b-d).

chlorochromate, alumina or silica gel, and commercial alumina have also been studied to obtain 1,2-di(phenyl)ethane-1,2-dione from 2-hydroxy-1,2-diphenylethanone. Oxidation of 2-hydroxy-1,2-diphenylethanone to 1,2-di(phenyl)ethane-1,2-dione has also bene performed by metal catalyst under reflux conditions using *n*-pentane or *n*-hexane as solvents (Zarnegar & Safari 2015). These methods produce 1,2-di(phenyl)ethane-1,2-dione but they show drawbacks such as long reaction times, low %*yield*, expensive catalysts, harsh reaction conditions because they involve strong acids or metals, and the complexity of work up. Therefore, there is still an opportunity to improve the existing methods or develop other reagents in the oxidation of 2-hydroxy-1,2-diphenylethanone into 1,2-di(phenyl)ethane-1,2-dione. This study reported the oxidation of 2-hydroxy-1,2-diphenylethanone to 1,2-di(phenyl)ethane-1,2-dione by using copper(II) citrate. Copper(II) citrate shows good catalytic activity in the synthesis of 3,4-dihydropyrimidinone through Biginelli reaction (Torres-Méndez & Lopez-Mayorga, 2020). In this study, the oxidation of 2-hydroxy-1,2-diphenylethanone to 1,2-di(phenyl)ethane-1,2-dione was performed with the addition of ammonium nitrate in glacial acetic acid. The nitric acid oxidation of 2-hydroxy-1,2-diphenylethanone was also executed without solvents. The structure of 1,2-di(phenyl)ethane-1,2-dione was elucidated by spectroscopic techniques (FTIR, NMR), and mass analysis.

MATERIALS AND METHOD

Materials

All chemicals were of synthetic quality obtained from commercial suppliers (Sigma-Aldrich or Merck). Technical solvents were distilled before used. Thin-layer chromatography (TLC) plates (Silica Gel 60 F254, Merck) were used for reaction progress and purity check (254/365 nm UV lamp). Melting point was measured by Fisher John *melting point apparatus*. The NMR spectra was recorded on a 500 MHz NMR spectrometer (Agilent). The infrared spectra were obtained from FTIR-8400S spectrometer (Shimadzu). Mass spectrometry analysis was conducted by using LC-MS-MS Xevo G2-S QTof spectrometer (Waters).

Synthesis of 1,2-di(phenyl)ethan-1,2-dione

Nitric acid method

2-Hydroxy-1,2-diphenylethanone (6.875 g, 0.0325 mol) was dissolved in a concentrated nitric acid (35 mL) and the reaction mixture was refluxed (TLC monitor). After 2-hydroxy-1,2-diphenylethanone was completely consumed, the mixture was poured into cold water (100 mL) while stirring at room temperature which was then stored in the refrigerator for 24 hours. The solid was filtered, washed with cold water, and dried. The solid was further recrystallized from ethanol to give 1,2-di(phenyl)ethane-1,2-dione as a yellow solid (5.3895 g, 79%) (Mendes *et al.* 2016).

Copper(II) citrate method

Copper(II) citrate (0.0293 g, 0.09 mmol), ammonium nitrate (1.2638 g, 15.79 mmol), and 2-hydroxy-1,2-diphenyletanone (2.5079 g, 11.82 mmol) were dissolved in glacial acetic acid (8.3 mL). The reaction mixture was refluxed (TLC monitor) and cooled to room temperature while stirring vigorously. The mixture was poured into cold water (20 mL) and stirred again for 5 minutes. The solid was filtered, dried, and purified by recrystallization from ethanol to give 1,2-di(phenyl)ethane-1,2-dione as a white solid (2.1676 g, 88%).

RESULT AND DISSCUSION

Synthesis of 1,2-di(phenyl)ethane-1,2-dione

The synthetic scheme of 1,2-di(phenyl)ethan-1,2-dione is shown in Figure 2. In this study, 1,2-di(phenyl)ethan-1,2-dione was obtained from 2-hydroxy-1,2-diphenylethanone by using nitric acid

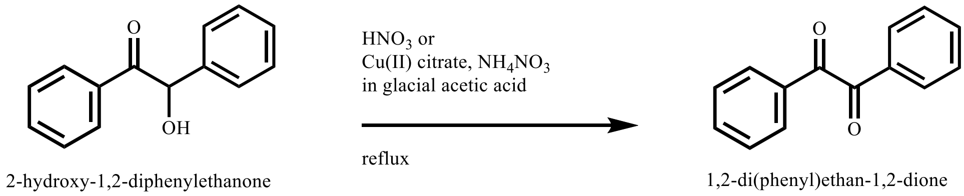

Figure 2.. Synthetic scheme of 1,2-di(phenyl)ethan-1,2-dione.

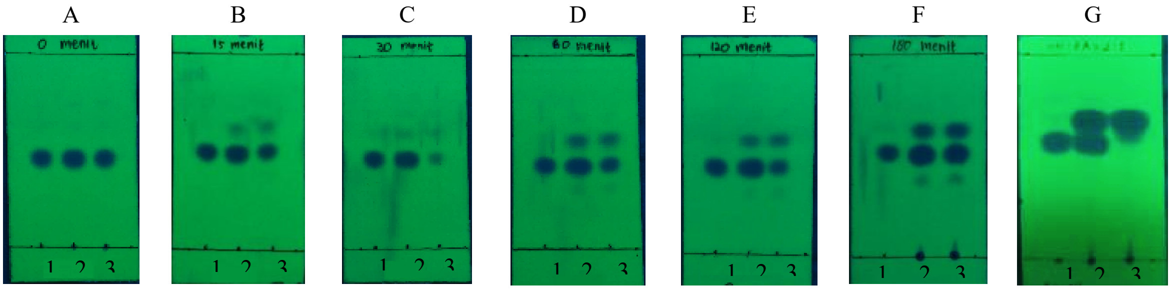

Figure 3. TLC profile of 1,2-di(phenyl)ethan-1,2-dion with nitric acid (n-hexane:ethyl acetate 3:1). 1 = 2-hydroxy-1,2-diphenylethanole, 2 = 2-hydroxy-1,2-diphenylethanol + reaction result, 3 = reaction result. A = 0 minutes, B = 15 minutes, C = 30 minutes, D = 60 minutes, E = 120 minutes, F = 180 minutes, G = 240 minutes.

and copper(II) citrate. The nitric acid oxidation was performed without solvents, while oxidation with copper(II) citrate was carried out in a glacial acetic acid in the presence of ammonium nitrate.

In the nitric acid method, 2-hydroxy-1,2-diphenylethanone was dissolved in the concentrated nitric acid and the reaction mixture was refluxed (Mendes *et al.* 2016). Meanwhile, copper(II) citrate method was performed by dissolving 2-hydroxy-1,2-diphenylethanone, copper(II) citrate, and ammonium nitrate in glacial acetic acid. The reaction mixture was further refluxed so that 2-hydroxy-1,2-diphenylethanone was completely consumed. The reaction progress was monitored by TLC. Figure 3 shows a new spot with a different retardation factor (Rf) in 15 minutes of reaction in the oxidation of 2-hydroxy-1,2-diphenylethanone with nitric acid. A similar trend was also seen in the oxidation of 2-hydroxy-1,2-diphenylethanone using copper(II) citrate (Figure 4). The new spot was becoming more pronounced while the 2-hydroxy-1,2-diphenylethanol stain had disappeared after 240 minutes of reaction. The reaction was subsequently stopped, and the reaction mixture was worked up.

The reaction mixture was then cooled to room temperature and then poured in cold water with stirring. The obtained solid was filtered, washed with cold water, dried, and purified by recrystallization using ethanol. Oxidation of 2-hydroxy-1,2-diphenylethanone with nitric acid produces a yellow solid of 1,2-di(phenyl)ethane-1,2-dione with a mass of 5.3895 gram (79%), while oxidation with copper(II) citrate gives 1,2-di(phenyl)ethane-1,2-dione as a white solid with a mass of 2.1676 gram (88%). The oxidation of 2-hydroxy-1,2-diphenylethanone with copper(II) citrate gives higher yield than with nitric acid. The yield of 1,2-di(phenyl)ethan-1,2-dione produced by oxidation of 2-hydroxy-1,2-diphenylethanone with nitric acid in this study was also lower than that reported by Mendes *et al.* (2016). 1,2-Di(phenyl)ethan-1,2-dione obtained by oxidation of 2-hydroxy-1,2-diphenylethanone using copper(II) citrate in this study has higher yield compared to 1,2-di(phenyl)ethan-1,2-dione resulted from oxidation of 1,2-di(phenyl)ethyne with mercury in THF (52%) (Jung & Deng 2014). A similar profile was also found for 1,2-di(phenyl)ethan-1,2-dione yielded from oxidation of 1,3-di(phenyl)propan-1,3-dione with 2,2,6,6-tetramethylpiperidine oxide in acetic acid (36%) (Zhou *et al.* 2017). Reaction of α-hydroxyacetophenone and bromobenzene in *t*-BuOH with palladium metal as catalyst produces 1,2-di(phenyl)ethan-1,2-dione with similar yield as copper(II) citrate method (Matsuda & Oyama 2020). The yield of 1,2-di(phenyl)ethane-1,2-dione produced by oxidation of 2-hydroxy-1,2-diphenylethanone with copper(II) citrate in this study is lower than 1,2-di(phenyl)ethane-1,2-dione obtained from a reaction of 1,2-di(phenyl)ethene and *tert*-butyl hydroperoxide in toluene/acetonitrile/water catalyzed by ruthenium (91%) (Chen *et al.* 2011).

The purity of 1,2-di(phenyl)ethane-1,2-dione was then checked by TLC (Figure 5). The TLC profile shows a single spot confirming the purity of the synthesized 1,2-di(phenyl)ethane-1,2-dione. This was also supported by melting point test which gave a narrow value of 104-106°C indicating that 1,2-di(phenyl)ethane-1,2-dione is pure.

Structure identification of 1,2-di(phenyl)ethane-1,2-dione

The structure of 1,2-di(phenyl)ethane-1,2-dione was identified by NMR in $CDCl_3$ at 500 MHz. The

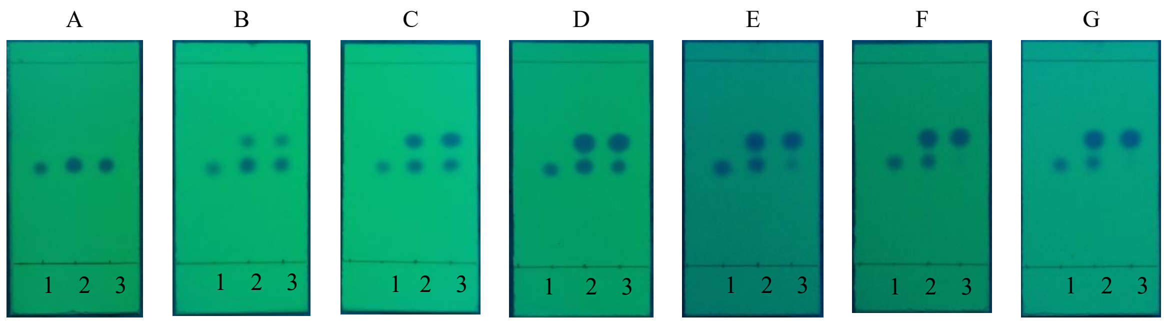

Figure 4. TLC profile of 1,2-di(phenyl)ethan-1,2-dion with copper(II) citrate (n-hexane:ethyl acetate 2:1). 1 = 2-hydroxy-1,2-diphenylethanole, 2 = 2-hydroxy-1,2-diphenylethanol + reaction result, 3 = reaction result. A = 0 minutes, B = 15 minutes, C = 30 minutes, D = 60 minutes, E = 120 minutes, F = 180 minutes, G = 240 minutes.

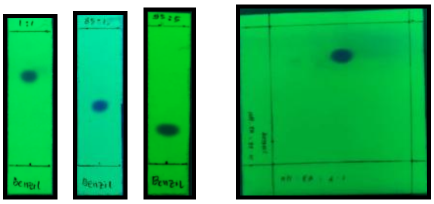

Figure 5. Purity of 1,2-di(phenyl)ethane-1,2-dion by TLC**.** A = n-hexane:ethyl acetate 1:1, B : n-hexane:ethyl acetate 8,5:1,5, C : n-hexane:ethyl acetate 9,5:0,5, D : n-hexane:ethyl acetate 2:1.

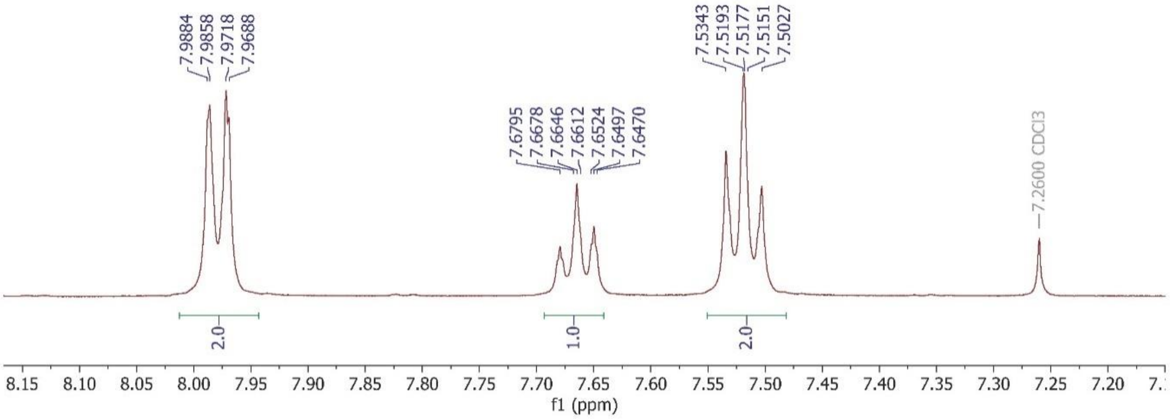

Figure 6. 1H NMR spectrum of 1,2-di(phenyl)ethane-1,2-dione.

1H NMR spectrum (Figure 6) provided aromatic proton signals as triplet at δ 7.52 ppm (*J* = 15.8; 7.5 Hz), triplet at δ 7.66 ppm (*J* = 14.9; 7.45 Hz), and doublet at 7.99 ppm (*J* = 8.4; 1.4 Hz). This result corresponds to the structure of 1,2-di(phenyl)ethane-1,2-dione.

The structure of 1,2-di(phenyl)ethane-1,2-dione was also characterized by FTIR and mass analysis. The FTIR spectrum (Figure 7) provides an absorption band at a wavenumber (ν) of 3064 cm^{-1} suitable for C-H sp^2, ν 1664 cm^{-1} for C=O vibration, ν 1448 cm^{-1} for C=C bond accompanied by strong absorption at ν 719 cm^{-1} and overtone at ν 2000 cm^{-1}. Mass analysis of 1,2-di(phenyl)ethane-1,2-dione gives mass spectrum (Figure 8) showing a peak ion $[M+Na]^+$ at *m/z* 233.0570 with the molecular formula $C_{14}H_{10}O_2Na$ corresponding to the *m/z* for 1,2-di(phenyl)ethane-1,2-dione (calac. *m/z* 233.0578).

Proposed mechanism

The mechanism of oxidation of 2-hydroxy-1,2-diphenylethanone with nitric acid forming 1,2-di(phenyl)ethane-1,2-dione is proposed in Figure 9. 2-Hydroxy-1,2-diphenylethanone reacts with nitric acid to form nitronium ions that become oxidizers on the oxidation of hydroxyl groups into carbonyls. Nitronium ions are reduced to nitric acid (Castilho & Ideia 2016).

The oxidation of 2-hydroxy-1,2-diphenylethanone with copper(II) citrate involves the formation of Cu+ ions resulting from the reaction of copper(II) citrate with 2-hydroxy-1,2-diphenylethanone which is then re-oxidized by ammonium nitrate. This oxidation occurs through two complementary redox reactions. The proposed mechanism for the oxidation of 2-hydroxy-1,2-diphenylethanone with copper(II) citrate as shown in Figure 10 begins with the donation

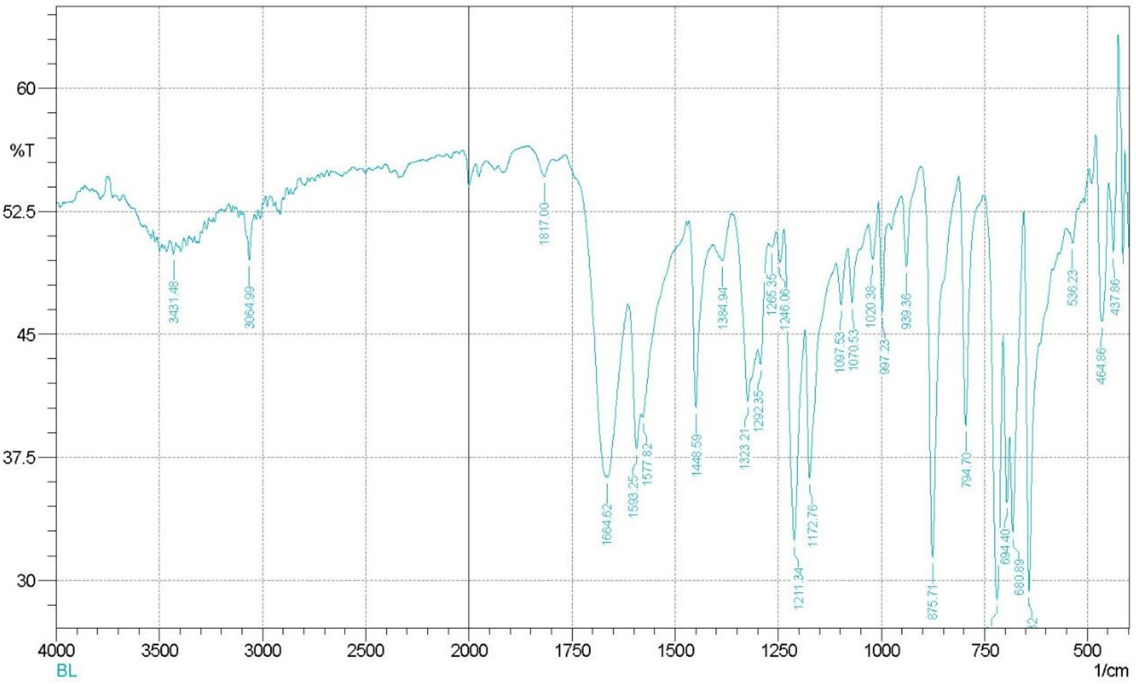

Figure 7. FTIR spectrum of 1,2-di(phenyl)ethane-1,2-dione.

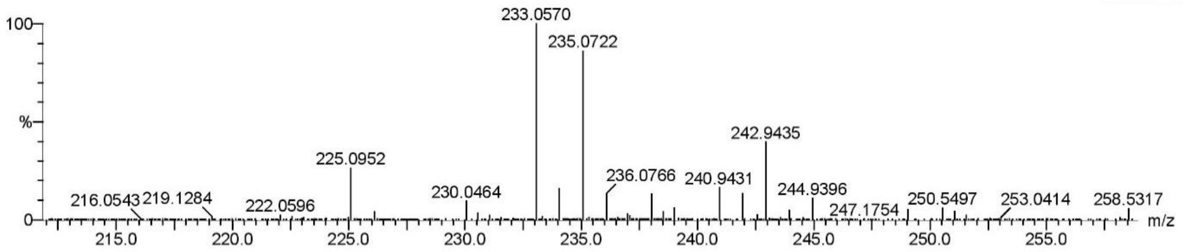

Figure 8. Mass spectrum of 1,2-di(phenyl)ethane-1,2-dione.

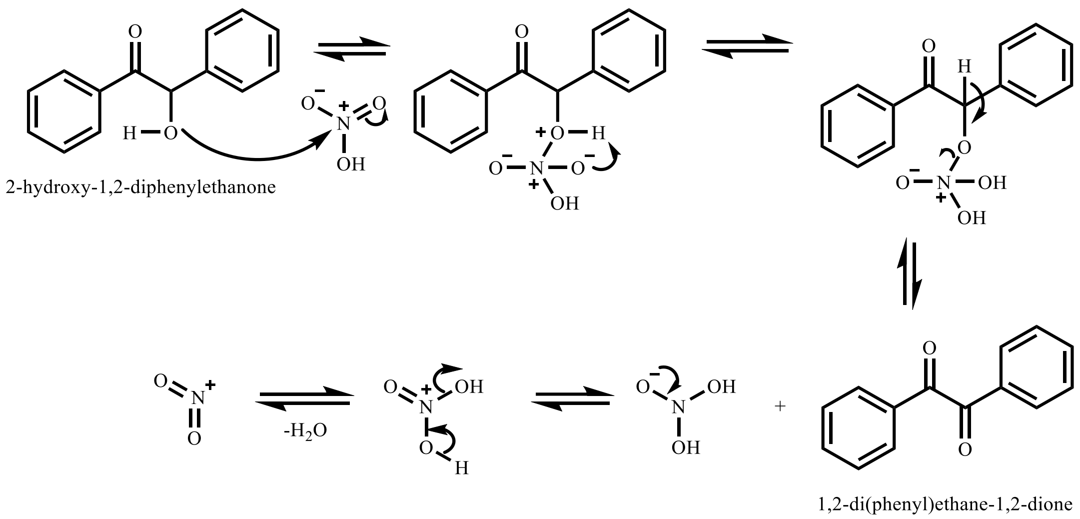

Figure 9. Proposed mechanism of oxidation of 2-hydroxy-1,2-diphenylethanone with nitric acid.

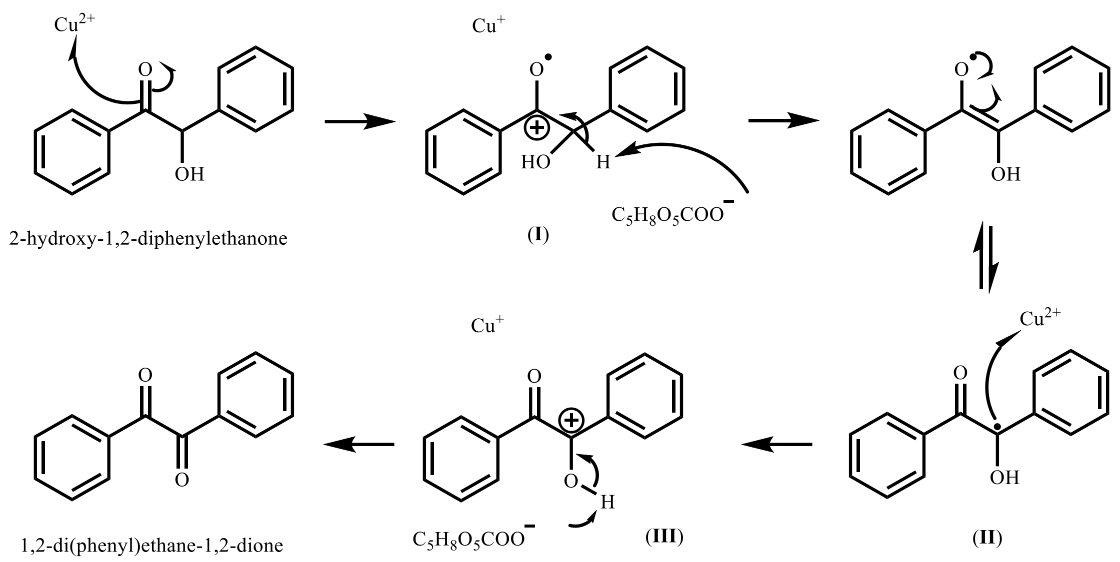

Figure 10. Proposed mechanism of oxidation of 2-hydroxy-1,2-diphenylethanone with copper(II) citrate

of single electron of 2-hydroxy-1,2-diphenylethanone to Cu^{2+} ion producing Cu^{+} ions and 2-hydroxy-1,2-iphenylethanone cation radical. The protonation of these radicals by citric ions forms citric acid and resonance stabilized radical (**II**)**.** The next reaction occurs between Cu^{2+} and radical **II** resulting in a second Cu^{+} ion and a cation of 2-hydroxy-1,2-diphenyletanone (**III**)**.** Next, these cations release protons on other citrate ions and give 1,2-di(phenyl)ethane-1,2-dione. The reoxidation of Cu^{+} ions to Cu^{2+} occurs with the help of ammonium nitrate which acts as an oxidizing agent.

CONCLUSION

1,2-Di(phenyl)ethene-1,2-dione was synthesized from oxidation of 2-hydroxy-1,2-diphenylethanone by using nitric acid and copper(II) citrate. The oxidation of 2-hydroxy-1,2-diphenylethanone with copper(II) citrate yields 1,2-di(phenyl)ethene-1,2-dione in 88% higher than the oxidation with nitric acid (79%). The structure of 1,2-di(phenyl)ethane-1,2-dione has been established by FTIR and NMR spectroscopy and mass analysis.

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