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Research Paper

Modification Structure of Cinnamaldehyde with Primary Amines by Reflux and Sonication Methods in the Presence of Sulfuric Acid as a Catalyst

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Abstract
Cinnamon is one of the most valuable natural resources that sustains life and exists freely in nature. Cinnamaldehyde is the primary compound in cinnamon oil. It has a unique structure that contains a benzene ring, an aldehyde group, and an unsaturated double bond. Cinnamaldehyde has been structurally modified to improve biological activity. In this research, cinnamaldehyde and nitrophenyl amines were reacted with sulfuric acid as a catalyst by refluxing and sonication. UV-Vis Spectroscopy, FT-IR, ^{1}H-NMR, and ^{13}C-NMR were used to validate the chemical structures. Thin-layer chromatography (TLC) revealed a new single spot formed by the reaction of cinnamaldehyde and 4-amino-2-nitrophenol. By refluxing for 2 hours or sonicating for 30 minutes, a novel imine chemical, 4-nitro-2-((3-phenylallylidene)amino)phenol, was effectively synthesized with a yield of 75.21% or 83.71%, respectively. This imine was obtained as a dark red powder with a melting point of 237 °C. Meanwhile, only sonication produced a novel product from the reaction of cinnamaldehyde and 4-nitroaniline. However, the structural elucidation has not yet been performed because the yield was so low. Surprisingly, there was no reaction between cinnamaldehyde and 2,4-dinitroaniline. It was most likely owing to the amine's bulky structure and the presence of two nitro groups in the amine as electron-withdrawing groups that reduced the nucleophilicity of the amine. We demonstrated that sonication is a suitable approach for imine synthesis, as it is commonly utilized in organic compound synthesis protocols.

Keywords
Amines, Cinnamon, Cinnamaldehyde, Imines

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1. INTRODUCTION

Scientists have expanded the use of renewable resources as starting materials for organic synthesis over several decades. A cinnamon plant is one of the renewable resources. Indonesia is well-known for being one of the world's largest cinnamon producers. In 2020, the average cinnamon production was 91.242 tons (Supriana et al., 2022). Cinnamon oil can be made from cinnamon plant parts such as the bark, twigs, and leaves. Cinnamaldehyde, safrole, tannins, resin, calcium oxalate, flavonoids, triterpenoids, and saponins are chemical components found in cinnamon oil. Cinnamaldehyde (C_9H_8O) is the primary compound in cinnamon oil (65%-90.5%) (Gan et al., 2020). Cinnamaldehyde is an aldehyde composed of benzene with a conjugated carbonyl group substituent and an aldehyde group (Doyle and Stephens, 2019; Yaseen and Mohammed, 2020). This chemical is commonly utilized as a starting material for synthetic compounds with biological properties such as antioxidant, antibacterial, anticancer, and antifungal activity (Al Zoubi et al., 2019; Altamimi et al., 2020; Guzman, 2014; Silva et al., 2013). Cinnamaldehyde has also been used as a starting material for synthesizing glyoxylamide compounds as an anionic sensor (Suryanti et al., 2018, 2020a,b).

Imine compounds, also known as Schiff bases (compounds having a C=N functional group), can be synthesized directly from aldehydes or ketones with primary amines via an addition reaction (Hameed et al., 2017; Hussain et al., 2014; Kajal et al., 2013). Aldehyde compounds have influenced the stability of an imine. Furthermore, a conjugated aromatic aldehyde molecule promotes the formation of an imine, which is more stable than a polymerized aliphatic aldehyde. The structural moieties of imine have contributed to many biologically active compounds such as antifungal, antibacterial, antiviral, antioxidant, and anti-inflammatory (Adabiardakani et al., 2012). The reaction of cinnamaldehyde, an aldehyde, and primary amines is expected to form imines.

Sonication is an effective method for increasing the yield of

synthesized chemicals (Akbarzadeh and Safaei-Ghomi, 2020; Basha et al., 2020; Indriyanti and Prahasiwi, 2020). A reaction between dihydropyrimidinone (DHPM) and thione in the presence of tamarind juice as a catalyst produced a product of up to 95% in just 3 mins by sonication (Nazeruddin and Shaikh, 2014), whereas other imines achieved up to 47-97% in 4-15 mins (Wahab et al., 2017). Stirring is also a typical method for imine production. Modifying a vanillin molecule yielded 53% in a 30 mins reaction (Celik et al., 2021). Furthermore, an imine product from 4-dimethylaminobenzaldehyde and 4-amino-2,6-dihydroxypirimidine was effectively synthesized with a yield of 79.5% after 6 hours of stirring (Al Zoubi et al., 2019). Microwave irradiation (1.5 mins) and refluxing (2 hours) were used to synthesize an imine derivative without the use of solvents. The products achieved up to 94 and 76%, respectively (Bekdemir and Efil, 2014). Thiazole-2-imine was generated by microwave for 1.5 mins with a 94% yield; however, reflux for 1.5-2 hours resulted in only 68% of the product (Shaikh et al., 2018).

Cinnamaldehydebenzylamine Schiff base was synthesized in the presence of glacial acetic acid for a 12 hours reflux (Ubani et al., 2015). The results show that sonication is a more efficient method than reflux. It is already considered to have several drawbacks of reflux, including the reaction requiring more solvent, prolonged reaction time, and wasting energy (Omprakash et al., 2015). The acidic condition in imine synthesis is a great protocol since acid provides optimum pH in imine formation (Ubani et al., 2015). Acid catalysts are essential in dramatically raising reaction yields as high as 95% and helping to accelerate reaction.

Acid catalysts have an important role in increasing reaction yields by up to 95% and accelerating the reaction. Previous researches have presented several homogeneous acid catalysts for imine synthesis, including sulfuric acid, hydrochloric acid, and acetic acid (Al Zoubi et al., 2019; Begum et al., 2021; Ubani et al., 2015). Furthermore, some useful transition metal catalysts, such as Cu, Ni, Fe, Zn, Mn, Cr, Cd, dan Co, function as heterogeneous acid catalysts in imine production (Ahmed et al., 2022; Patel et al., 2021). Another acid that can be used in imine production is derived from renewable resources. A natural acid catalyst (also known as a green acid catalyst) has been discovered to produce an imine in the presence of lemon juice, orange juice, and grapefruit juice (Nigam et al., 2023; Wahab et al., 2017).

Hence, no researcher is concerned with imine synthesis using nitrophenyl amine compounds and longer aldehydes like cinnamaldehyde. Therefore, the current work attempted to synthesize imine from cinnamaldehyde and primary amines in the presence of an acid catalyst in two ways: reflux and sonication. Modifying cinnamaldehyde structure with nitrophenylamines, such as 2-amino-4-nitrophenol, 4-nitroaniline, and 2,4-dinitroaniline are expected to improve their biological activity. Nitrophenylamines have been used as starting materials for synthesizing organic compounds with biological activities such as antibacterial, antifungal, and antioxidant (Belghit et al., 2017; Rashdan et al., 2017; Suryanti et al., 2018).

2. EXPERIMENTAL SECTION

2.1 Materials

2.1.1 Chemical

All chemicals were analytical grade from E Merck or Sigma Aldrich. Cinnamaldehyde was obtained from E Merck. Nitrophenylamines, such as 2-amino-4-nitrophenol, 4-nitroaniline, and 2,4-dinitroaniline were provided by Sigma Aldrich. Solvents were purchased from E Merck. Chemicals were used without further purification.

2.1.2 Instrumental

The melting point was determined by a Melting Point Apparatus Digital Merk Omega type MPS-10. UV-visible spectra were recorded by a double-beam Hitachi UH5300 spectrophotometer. Prestige-21 Shimadzu Fourier Transform Infra-Red (FTIR) was used to determine the functional group of imines. ^{1}H-NMR and ^{13}C-NMR spectra were recorded by Nuclear Magnetic Resonance (NMR) Agilent VNMR 500 MHz with DMSO-d6 as a solvent. Other instruments used for the experiment were analytical balance Mettler PB 3000 type ER-182 A, sonication Branson type 1510 (frequency 40 kHz, power 80 W).

2.2 Methods

2.2.1 General Procedure for Imine Synthesis by Refluxing

A mixture of cinnamaldehyde (0.132 g, 1 mmol eq) and nitrophenyl amines (1.2 mmol eq) was placed in a round-bottomed flask with a magnetic stirrer and condenser. The nitrophenylamines used were 0.185 g for 2-amino-4-nitrophenol, 0.166 g for 4-nitroaniline, and 0.220 g for 2,4-dinitroaniline. Then, 30 mL of dichloromethane was added to the flask. The reaction mixture was stirred at 40°C while adding two drops of sulfuric acid. The precipitate was filtered and cooled at room temperature. The product's impurities were removed using dichloromethane (Devidas, 2011).

2.2.2 Reaction between Cinnamaldehyde and 2-amino-4-nitrophenol by Sonication

The procedure was performed according to the previously reported method (Indriyanti and Prahasiwi, 2020). Cinnamaldehyde (0.132 g, 1 mmol eq) and 2-amino-4-nitrophenol (0.185 g, 1.2 mmol eq) were placed in a vial and dissolved in 5 mL of water. This mixture was reacted using ultrasonic irradiation at room temperature for 30 minutes. The obtained red product was washed and recrystallized using aquadest and ethanol.

2.2.3 Reaction between Cinnamaldehyde and 4-nitroaniline or 2,4-dinitroaniline by Sonication

A mixture of cinnamaldehyde (0.132 g, 1 mmol eq) and 4-nitroaniline (0.166 g, 1.2 mmol eq) was placed in a vial. Then, 5 mL of ethanol and two drops of sulfuric acid were added to this solution. The mixture was sonicated at room temperature for 30 minutes. The product was filtered and purified using

hexane: chloroform (3:7) as eluent via column chromatography. Reaction between cinnamaldehyde (0.132 g, 1 mmol eq) and 2,4-dinitroaniline (0.220 g, 1.2 mmol eq) was prepared in 5 mL of ethanol and followed by a similar workup.

3. RESULTS AND DISCUSSIONS

A series of cinnamaldehyde imines derivatives were aimed to synthesis by reacting of a variety of nitrophenylamines, such as 2-amino-4-nitrophenol, 4-nitroaniline, and 2,4-dinitroaniline with cinnamaldehyde. The general reaction scheme for synthesizing imines from cinnamaldehyde and nitrophenylamines is shown in Figure 1. An aldehyde reacts with primary amine through a condensation-addition reaction to form an imine. The reaction will lose water as a coupled product. Imines are synthesised by reacting aldehydes with primary amines in the presence or absence of a catalyst, preferably an acid catalyst. Despite the fact that the reaction will progress more slowly and take longer without a catalyst, it is preferable to add the catalyst throughout the reaction process. Instead of using a catalyst, the moderately acidic state is an excellent technique to produce a better yield.

3.1 Reaction between Cinnamaldehyde and 4-nitroaniline

The reaction between cinnamaldehyde and 4-nitroaniline gave no new synthetic compound by refluxing. On the contrary, the reaction between cinnamaldehyde and 4-nitroaniline gave a yellow solid by sonication. This synthetic compound was purified by column chromatography using hexane: chloroform (3:7) eluent. Thin Layer Chromatography (TLC) using hexane: ethyl acetate (8:2) eluent gave Rf values of cinnamaldehyde, 4-nitroaniline, and the compound synthesized of 0.275; 0.2; and 0.5, respectively. It is confirmed that a new synthetic compound was formed. Nonetheless, the product was not further characterized since it has too few products.

The sonication method is considered in this synthesis route because it has the capacity to produce a greater yield than refluxing. The solvent affects the development of a product in the reflux. A low boiling point solvent such as dichloromethane will decrease the rate of a chemical reaction. That was why the energy was not reached, and the product was not formed because the 4-nitroaniline has a nitro group ($-NO_2$) at the para position. The nitro group is an electron-withdrawing group that influenced the nucleophilicity of the amine group. Herein, the nucleophilicity of the amine group in 4-nitroaniline against the carbon atom of the carbonyl group in cinnamaldehyde will be decreased. We verified that synthesizing imine by sonication can enhance the product in a short-time reaction. Therefore, we modified the structure by adding the other nitro groups in the benzene ring using 2,4-dinitroaniline.

3.2 Reaction between Cinnamaldehyde and 2,4-dinitroaniline

The reaction between cinnamaldehyde and 2,4 dinitroaniline was performed by refluxing or sonication. Compound 2,4-dinitroaniline has two nitro groups (NO_2) in the benzene ring at the ortho and para position. No product was formed by refluxing for 6 hours in reaction with dichloromethane. The evidence clearly showed on the spots in the TLC plate that the Rf value of cinnamaldehyde, 2,4-dinitroaniline, and the synthesized compound was 0.575, 0.525, and 0.525 respectively, using hexane: ethyl acetate (7:3) eluent. Herein is the same case as the above synthesis between cinnamaldehyde and 4-nitroaniline by refluxing. Accordingly, these two reactions are not given a new product and are not further characterized either by refluxing or sonication.

No product formed in this reaction might be due to two nitro groups (NO_2) in the benzene ring of 2,4-dinitroaniline. The nitro group as an electron-withdrawing group affects both the resonance (or mesomeric) effect and inductive effect in the benzene ring. Accordingly, that would encounter the electrophilic substitution reaction during this step. The nitro group would decrease the electron density of the amine and its reactivity. Two nitro groups highly stabilize the amino group (NH_2) in the 2,4-dinitroaniline compound. The 2,4-dinitroaniline compound seems to have a large structure; therefore, no reaction occurs between cinnamaldehyde and 2,4-dinitroaniline. Indeed, the effect of different substituent groups significantly impacts whether the reaction scheme will produce a product.

3.3 Reaction between Cinnamaldehyde and 2-amino-4-nitro phenol

To get the imine that we expected, one of the nitro groups in the para position was modified to be the hydroxyl group by using 4-amino-2-nitrophenol compound. Surprisingly, the amino group has a significant role in forming a product in this route, affecting ring opening on the nitro group. Based on the literature, if the nitro and amino groups are present simultaneously in nitroaniline, then the ring's deactivation is dominant there. As further information, the amino group (ortho and para directing group) will increase the electron density only on the ortho and para positions. In contrast, the nitro group is considered a meta-directing group. The amino group is stronger than the nitro group, as the recorded data show that it affects the π-electron structure of the ring in its benzene derivative (Jezuita et al., 2020). The reaction between cinnamaldehyde and 2-amino-4-nitrophenol produced 4-nitro-2-((3-phenylallylidene)amino)phenol compound.

The product's yield was found to be 75.21% during 2 hours of refluxing. Meanwhile, a higher yield of synthesized product was achieved up to 83.71% for 30 minutes by sonication at room temperature. The reaction of cinnamaldehyde and 2-amino-4-nitrophenol by either refluxing or sonication gave a product with physical characteristics as a dark red solid with a melting point of more than 237 °C. The spots on the TLC plate of the reaction mixture using hexane: ethyl acetate (6:4) eluent showed the Rf value of cinnamaldehyde, 2-amino-4-nitrophenol, and synthesized compound 0.425, 0.45, and 0.275, respectively. The λmax for the cinnamaldehyde and 2-amino-4-nitrophenol was 276 and 400 nm (Figure 2). The absorption of λmax 276 nm indicated a chromophore group

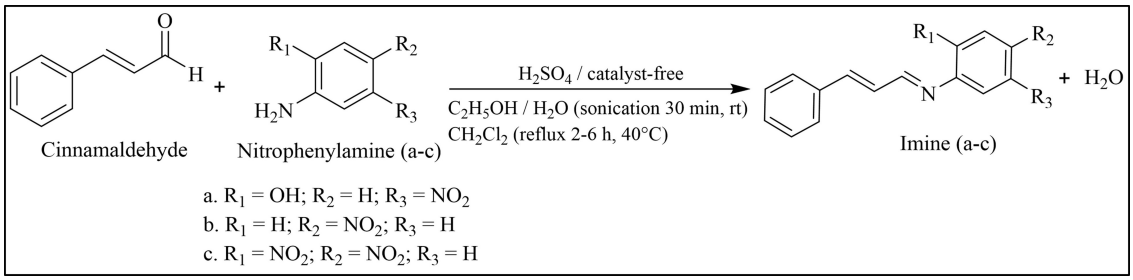

Figure 1. General Reaction Scheme for the Synthesis of Imines from Cinnamaldehyde and Nitrophenylamines

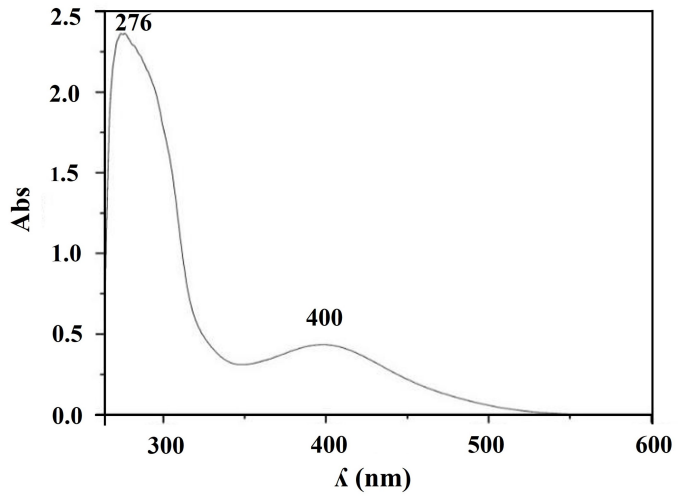

Figure 2. UV-Vis Spectra of Synthesized Product from Cinnamaldehyde and 2-amino-4-nitrophenol in Dimethylformamide (DMF)

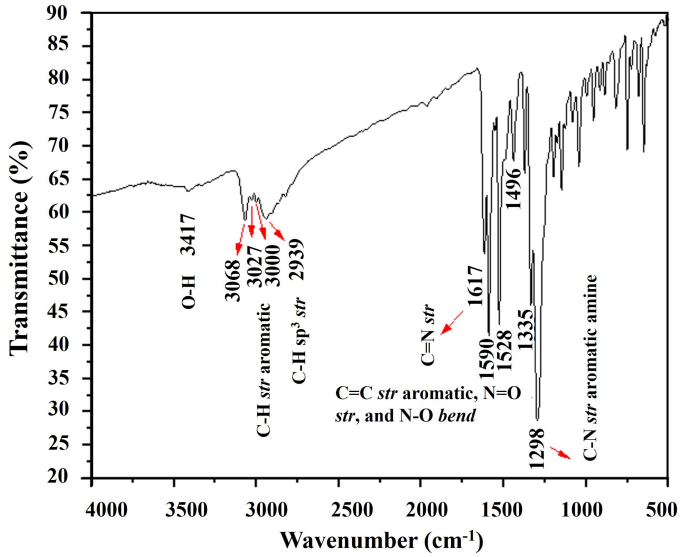

Figure 3. FT-IR Spectra of the Synthesized Compound from Cinnamaldehyde and 2-amino-4-nitrophenol

in benzene with transitions $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$. Meanwhile, the absorption of λmax 400 nm showed a chromophore of the C=N group and the benzene ring with transition $\pi \rightarrow \pi^*$ (Asadi et al., 2011; Ddorovic et al., 2017).

The functional groups of synthesized compound were analyzed by FT-IR spectrophotometer. The FT-IR data is presented in Figure 3 and Table 1. The unique functional group of imine (C=N) showed absorption band at 1617 cm^{-1}, along with O−H group appeared absorption band at 3417 cm^{-1}. This molecule's intramolecular and intermolecular hydrogen bonds can affect a lower absorption shift, broadening absorption peaks. The synthesized compound's hydroxyl group (−OH) showed a vast peak in the IR spectra due to hydrogen bonds between atoms and other atoms in a molecule.

Table 1. FT-IR Peaks of Synthesized Compound from Cinnamaldehyde and 2-amino-4-nitrophenol

Functional Groups	Wavenumber (cm^{-1})
OH	3417
	3068
C−H *str* aromatic	3027
	3000
C−H sp^3 *str*	2939
C=N *str*	1617
C=C *str* aromatic, N=O str, N−O bend	1590-1335
C−N *str* aromatic amine	1298
C=C *str* aromatic, N=O *str*, N−O bend	1590-1335
C−N *str* aromatic amine	1298

The formation of imine from cinnamaldehyde and 2-amino-4-nitrophenol was specifically confirmed by the presence of the proton signal at δ (ppm) 8.58 ppm with a doublet peak, representing 1 proton which is an imine group. All other aliphatic and aromatic protons were observed within the expected regions (Figure 4). To confirm the results in ^{1}H-NMR, we further analyzed the synthesis product, and 15C atoms were detected by ^{13}C-NMR. Considering the data results of this synthesized compound, the possible structure is 4-nitro-2-((3-phenylallylidene)amino)phenol. As mentioned above, the

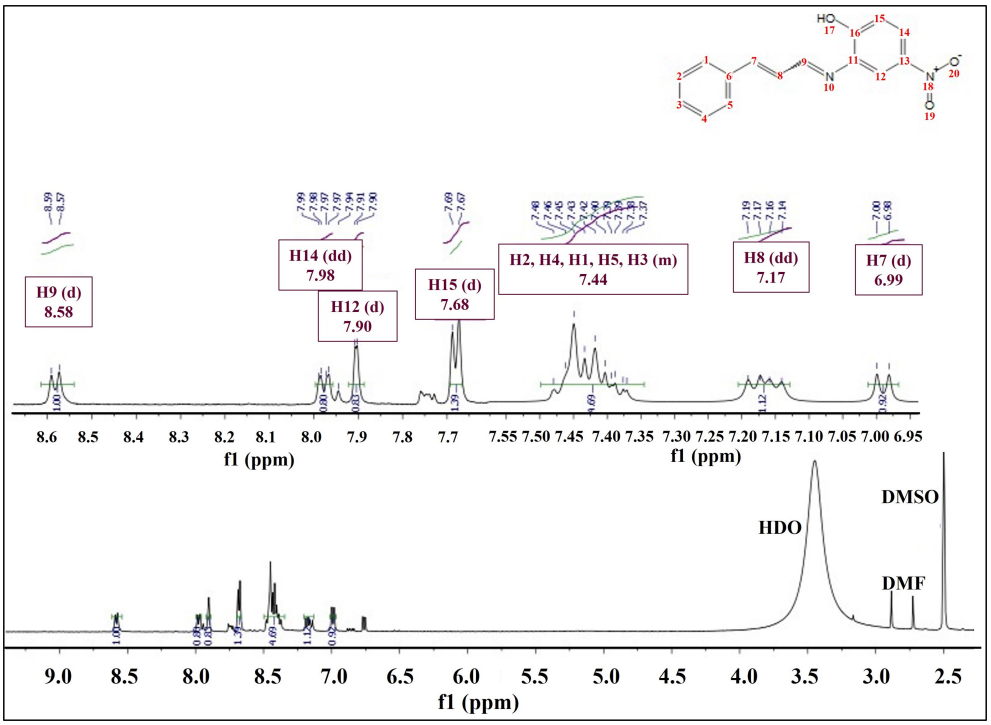

Figure 4. [1]H-NMR Spectra of Synthesized Compound from Cinnamaldehyde and 2-amino-4-nitrophenol (DMSO-d6, 500 MHz)

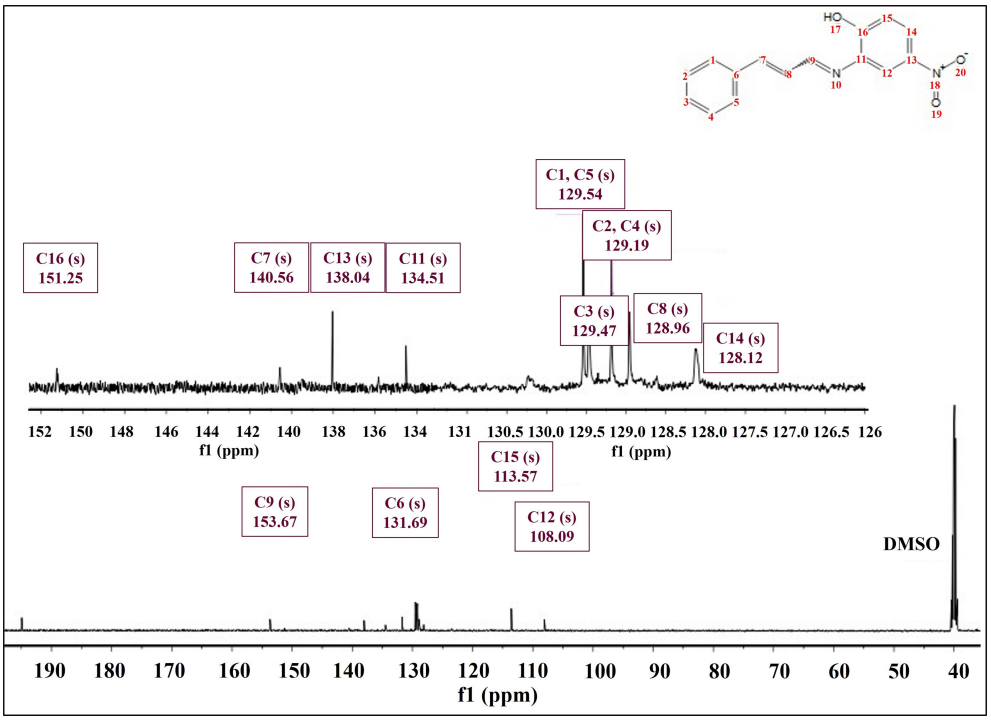

Figure 5. [13]C-NMR Spectra of Synthesized Compound from Cinnamaldehyde and 2-amino-4-nitrophenol (DMSO-d6, 125 MHz)

[13]C-NMR spectra are shown in Figure 5 and Table 2. Column chromatography-free in this reaction exhibited the practical applicability of this developed protocol. Accordingly, the implementation of a catalyst-free condition and water as solvent

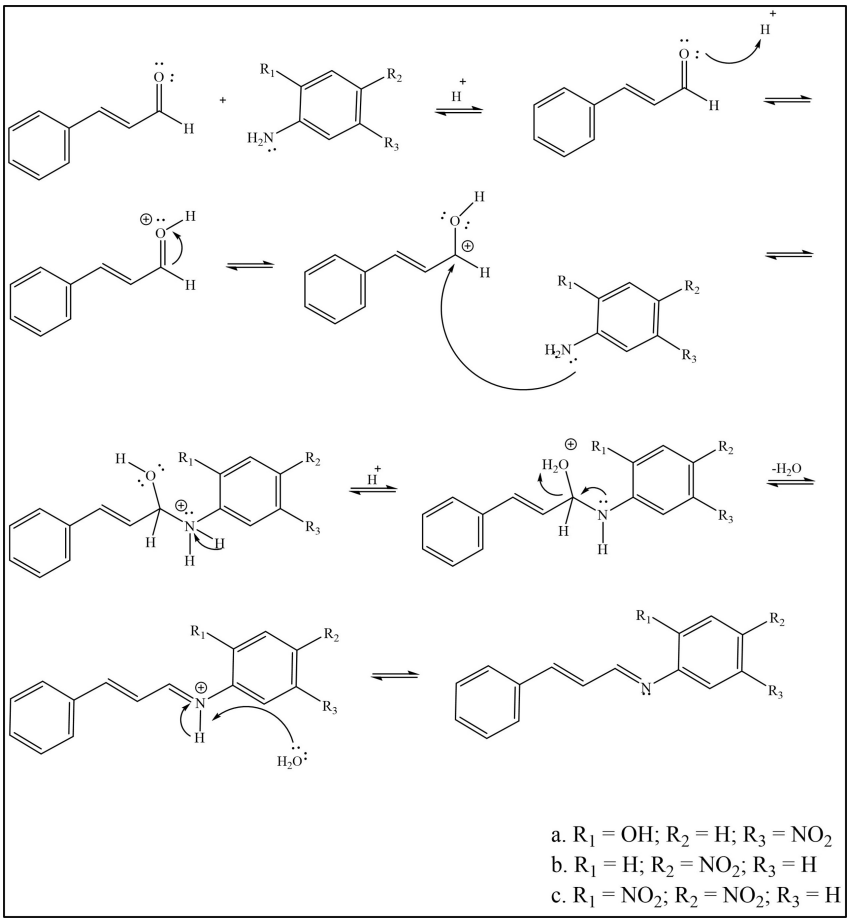

Figure 6. Proposed Mechanism for Synthesis of Imines from Cinnamaldehyde and Nitrophenylamine Compounds

Table 2. ^{13}C-NMR and ^{1}H-NMR of Synthesized Compound from Cinnamaldehyde and 2-amino-4nitrophenol (DMSO-d6, 500 MHz)

Atom Position	δ_C (ppm)	Carbon Type	δ_H (ppm)	Proton Type
1	129.54	Aromatic	7.50-7.35 (m, 5H)	Aromatic
2	129.19		7.50-7.35 (m, 5H)	
3	129.47		7.50-7.35 (m, 5H)	
4	129.19		7.50-7.35 (m, 5H)	
5	129.54		7.50-7.35 (m, 5H)	
6	131.69	Alkene	-	Alkene
7	140.56	Imine	6.99 (d, J=9.0 Hz, 1H)	Imine
8	128.96		7.17 (dd, J= 16.0; 9.0 Hz, 1H)	
9	153.67		8.58 (d, J= 8.9 Hz, 1H)	
10	-	Aromatic	-	Aromatic
11	134.51		-	
12	108.09		7.90 (d, J= 2.7 Hz, 1H)	
13	138.04		-	
14	128.12		7.98 (dd, J= 8.9; 2.7 Hz, 1H)	
15	113.57		7.68 (d, J= 7.5 Hz, 1H)	

also improved the synthesis of cinnamaldehyde and 2-amino-4-nitrophenol significantly in a shorter time reaction.

Using sonication for synthesizing imine will enhance the product yield much higher than the conventional method (re-

flux) caused by ultrasound cavitation existence. The cavitation bubbles had a significant role in the reaction. The cavitation bubbles were formed via sonication during the water reaction. They collapse, break down, and release intense heat and pressure energy around the system. Thus, the reactants are dispersed in the liquid medium, activating the molecules to accelerate the reaction. The proof for the outcome is that we acquired a greater product yield using sonication in a shorter reaction time; nevertheless, reflux required up to 2 hours of imine reaction here. In this context, the synthesis approach decreases the usage of solvents (no solvent is required), whereas the standard method requires more solvents in the reactions. Sonication is a convenient, efficient, and fast procedure. Because of the advantages of sonication, this method is extremely important for the long-term development of organic synthesis.

The reaction investigated here, the synthesis of imine, depends on the acidity (pH) of the catalyst. The optimal condition for imine reaction is generally most excellent around a pH of 3-4. The mechanism involved in forming imine from cinnamaldehyde and nitrophenylamine under acidic conditions is illustrated in Figure 6. Initially, hydrogen protonation provided by an acidic catalyst) towards the oxygen electron increased the aldehyde's carbonyl carbon's reactivity. Carbonyl carbon behaves as an electrophile capable of undergoing addition reactions. First, a nucleophilic attack reaction occurs, in which a nitrogen atom from the main amine attacks the carbon carbonyl via an addition reaction, forming a tetrahedral intermediate. Concerning the requirement to convert O−H into a much better-leaving group, more proton transfer is required. The final step, eliminating O−H by removing H_2O, would produce an imine, preventing the reverse reaction. That is the only way to drive the imine reaction. Using a sulfuric acid catalyst at a high pH will not be sufficient to protonate the hydroxyl group in the intermediate, allowing for removal as H_2O.

4. CONCLUSIONS

In summary, a high yield of imine was achieved by reacting cinnamaldehyde and 2-amino-4-nitrophenol in acidic conditions. The new imine compound of 4-nitro-2-((3-phenylallylidene)amino)phenol was obtained as a dark red solid and was confirmed by UV-Vis, FT-IR, ^{1}H-NMR, and ^{13}C-NMR. The sonication method showed an advantage for enhancing the yield up to 83.71% with a melting point of 237 °C for 30 minutes. Conversely, the reaction between cinnamaldehyde and two nitrophenylamine compounds did not form any product by refluxing. The new imine compound was probably produced by sonication in the reaction between cinnamaldehyde and 4-nitroaniline. Nonetheless, sonication methods still have to be improved for synthesizing imines.

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