Addition reaction of methyl cinnamate with 2-amino-4-nitrophenol

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Abstract. A novel compound which have one N-H fragment and nitrophenyl group has been designed and synthesized from cinnamaldehyde. The reaction was conducted in 3 step reactions to give the final product. Firstly, cinnamaldehyde was converted into cinnamic acid, which was then esterified with methyl alcohol to obtained methyl cinnamate. The last step was the addition reaction between methyl cinnamate and 2-amino-4-nitrophenol to give a cinnamaldehyde derivative, namely methyl-3-(2-hidroksi-5-nitrophenyl amino)-3-phenylpropanoate.

1. Introduction
Cinnamomum Verum J. Presl belongs to the Lauraceae family. Cinnamon is a good source of polyphenol compounds where over 300 volatile compounds were found in essential oils of cinnamon [1-2]. Oils and extracts from cinnamon have good antioxidant activity, which is ascribed to the presence of phenolic and polyphenolic compounds [3]. Cinnamaldehyde (3-phenyl-2-propanal) is the major component which present in cinnamon oil or cinnamon bark extract [4]. This compound having various substituents on the aromatic ring are useful for starting material in synthesizing of its derivatives.

Peralta-Dominguez et al. have established applications of organic molecules based on cinnamaldehyde for colorimetric chemosensors. A Schiff base derivative of cinnamaldehyde, 4-chloro-2-[(3-(4-(dimethylamino)phenyl)allyl-dene)amino]phenol has been synthesized and demonstrated to be a sensitive colorimetric Ni$^{2+}$ sensor in aqueous solution, where the presence of Ni$^{2+}$ into the sample solution produced a rapid color change from faded yellow to deep orange [15].

Suryanti et al. have demonstrated colorimetric anion sensors based on N-acetyl glyoxylic amides. These compounds were synthesized by one-step ring-opening reactions of N-acetylation with 4-nitrophenyl and 2,4-dinitrophenyl amines. These sensors contain two NH groups as anion binding sites and a nitrophenyl moiety as a signaling unit, where visible color changes occurred upon the addition of fluoride and cyanide anions. These anions formed hydrogen bonding interactions with the compounds and triggered deprotonation of those compounds [16]. Suryanti et al. also have reported the synthesized of another series of N-acetyl glyoxylic amides having N-H fragments [17]. In addition, series of N-octanoyl glyoxylic amides and oxalyl-bis-glycosylamines have been synthesized by ring opening of N-octanoyl isatins and bis-acylisatins, respectively, with a range of amines and amino acid alkyl esters [18-19]. These findings prompted us to synthesize novel compounds containing N-H
fragment and nitrophenyl group. This present research was focused on the design and develop of target compound using cinnamaldehyde as starting material.

2. Materials and Methods

2.1. Chemistry

Reagents and solvents were purchased from commercial suppliers. All solvents employed were of analytical grade and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) on TLC silica gel 60 F254. Melting points were determined by an open tube capillary method using Stuart SMP 10 melting point apparatus and uncorrected. All spectrometric analyzes were carried out at the Faculty of Mathematics and Natural Sciences Laboratory Facilities, Sebelas Maret University. UV-Vis spectra were recorded on a UV-Vis Shimadzu Lambda 25 spectrophotometer at room temperature. IR spectra were recorded as KBr pellets on Shimadzu type FT-IR 8201 PC spectrophotometer. 1H NMR dan 13C NMR spectra were measured with an Agilent VNMR 400 MHz instrument at 25°C. Signals were recorded in parts per million (δ) downfield from TMS as an internal standard, and J values are given in Hz.

2.2. Procedures of compounds preparation

2.2.1. Synthesis of cinnamic acid 2

Cinnamaldehyde (2.46 g), diethyl ether (100 mL), four drops of polysorbate 20 and water (100 mL) were placed and stirred in round bottom flask. CrO3 (7.9 g) was added slowly and the reaction mixture was then stirred for 6 h. The mixture was cooled with ice in 4-5°C and then left at room temperature. The mixture was extracted with diethyl ether. The organic phase was collected, dried over MgSO4 and evaporated to dryness affording a white powder of 64.9% yield and m.p. 125°C. UV(EtOH): λmax 201 (5715 cm⁻¹ M⁻¹), 210 (4375), 267 (2086); IR (KBr): υmax 3462, 3068, 3028, 2835, 1683, 1630, 1576, 1492, 1449, 1423, 1344, 1315, 1287, 1226, 1175, 933, 871, 765, 705; 1H NMR (400 MHz, CDCl3): δ 6.46 (dd, ArCHC=H, J = 16.0, 7.7 Hz, 1H), 7.26 (d, COOH, J =7.7 Hz, 1H), 7.39 (m, 3 x ArH, 3H), 7.56 (dd, 2 x ArH, J = 9.7 Hz, 2H), 7.80 (dd, ArCH=CH, J =5.9 Hz, 1H). 13C NMR (100 MHz, CDCl3): δ 117.2 (ArCH=CH), 128.0 (2 x ArC), 128.9 (2 x ArC), 130.3 (ArC), 134.0 (ArC), 144.9 (ArCH=CH), 171.8 (COOH).

2.2.2. Esterification of cinnamic acid 2 with methanol

Cyncamic acid (0.67 g) and methanol (10 mL) were placed in a round bottom flask. Two drops of saturated H2SO4 was added and the reaction mixture was heated under reflux for 6 hours. After cooling, the reaction mixture was evaporated to dryness affording a dark brown liquid of 42% yield and b.p. 33°C. UV(EtOH): λmax 202 (7909 cm⁻¹ M⁻¹), 211 (4672), 269 (2441); IR (KBr): υmax 3413, 3028, 2927, 2854, 1715, 1634, 1493, 1450, 1314, 1279, 980, 868, 767, 701; 1H NMR (400 MHz, CDCl3): δ 3.81 (s, OCH3, 3H), 6.44 (d, ArCHCH=H, J =16 Hz, 1H), 7.38 (m, 3 x ArH, 3H), 7.52 (m, 2 x ArH, 2H); 7.68 (dd, ArCH=CH, J=5.9 Hz, 1H). 13C NMR (100 MHz, CDCl3): δ 51.7 (C OOCH3), 109.6 (ArCHC=H2), 109.7 (ArC=HCH2), 117.1 .

2.2.3. Reaction of methyl cinnamate 3 and 2-amino-4-nitrophenol 4

Methyl cinnamate (1 mmol) and 2-amino-4-nitrophenol (1.2 mmol) were reacted in 25 mL dichloromethane. The reaction mixture was refluxed for 48 h. After cooling, the reaction mixture was evaporated to dryness affording a yellowish brown gel of 68% yield and m.p. 10°C. UV(acetone): λmax 328 (9091 cm⁻¹ M⁻¹), 375 (10014); IR (KBr): υmax 3531, 3375, 3306, 2952, 1709, 1693, 1632, 1525, 1499, 1451, 1336, 1294, 1204, 1172, 1079, 1039, 979, 876, 769, 746; 1H NMR (400 MHz, CD3OD): δ 3.61 (s, OCH3, 3H), 6.50 (d, ArCH=CH, J=16 Hz, 2H), 6.74 (m, ArCH=CH, J=8.7 Hz, 1H), 7.36 (dd, 3 x ArH, J=10.9, 8.1 Hz, 3H), 7.51 (dd, Ar=CH=CH, J=10.9, 8.1 Hz, 1H), 7.57 (m, 3 x ArH, 3H), 7.66 (m, ArH, 1H); 13C NMR (100 MHz, CD3OD): δ 50.7 (COOCH3), 109.6 (ArCH=CH2), 109.7 (ArCH=CH2), 117.1.
127.8, 128.6, 130.1, 135.5, 134.2 (6 x ArC), 112.8, 114.7, 114.8, 140.9, 144.8, 151.1, (6 x CHNO\textsubscript{2}OH), 167.7 (C\textsubscript{6}OOCH\textsubscript{3}).

3. Results and Discussion

Scheme 1 summarizes the reaction steps occurred in this work, where the reaction was conducted in 3 step reactions to give the final product.

![Scheme 1](image)

Scheme 1. Reagents and conditions: (i). (C\textsubscript{2}H\textsubscript{5})\textsubscript{2}O, H\textsubscript{2}O, polysorbate 20, CrO\textsubscript{3}, 6 h, r.t. (ii). CH\textsubscript{3}OH sat. HCl, reflux, 6 h. (iii). CH\textsubscript{2}Cl\textsubscript{2}, reflux, 48 h.

3.1. Synthesize of cinnamic acid 2

Compound 2 was prepared by reacting of cinnamaldehyde 1 with chromium trioxide (CrO\textsubscript{3}) in diethyl ether and water in the presence of polysorbate 20 as phase transfer catalyst. The chromium trioxide in water forms chromic acid (H\textsubscript{2}CrO\textsubscript{4}) which would then oxidized the cinnamaldehyde to cinnamic acid 2 as a white powder in 64.9% yield.

The \textsuperscript{1}H NMR spectrum of compound 1 in CDCl\textsubscript{3} exhibited the singlet resonance for the aldehyde proton (-COH) at 9.69 ppm, whereas the \textsuperscript{13}C NMR spectrum of the compound 2 in CDCl\textsubscript{3} exhibited the singlet resonance for the carboxylic proton (-COOH) at 7.26 ppm. In addition, proton shifts were observed in the \textsuperscript{1}H NMR spectra of the compounds 1 and 2. The resonances for –CH=CH- in the \textsuperscript{1}H NMR spectrum of compound 1 were observed at 6.72 and 7.56 ppm, whereas in the \textsuperscript{1}H NMR spectrum of compound 2 were observed at 6.46 and 7.80 ppm, respectively. The resonance for the carboxylic carbonyl (-COOH) of compound 2 was also confirmed by \textsuperscript{13}C NMR spectroscopy spectrum which showed a peak at 171 ppm, whereas compound 1 exhibited a peak at 193 ppm for aldehyde carbonyl (-COH). Moreover, the resonances for –CH=CH- in the \textsuperscript{13}C NMR spectrum of compound 1 were observed at 152 and 131 ppm, whereas in the \textsuperscript{1}H NMR spectrum of compound 2 were observed at 117 and 146 ppm, respectively.

3.2. Esterification of cinnamic acid 2 with methanol

Compound 3 was synthesized in 42% yield by stirring of a mixture of compound 2 and methanol under reflux for 6 hours in the presence of saturated HCl. The analysis of compound 3 by \textsuperscript{1}H NMR spectroscopy revealed the presence of new methyl protons at 3.81 ppm. The new resonance for this –CH\textsubscript{3} was also indicated by \textsuperscript{13}C NMR spectroscopy spectrum which showed a peak at 51 ppm.
3.3. Reaction of methyl cinnamate 3 and 2-amino-4-nitrophenol 4

The reaction of compound 3 with 2-amino-4-nitrophenol 4 in dichloromethane under reflux for 48 hours resulted in the formation of compound 5 as a yellowish brown gel in 68% yield. Figure 1 and 2 showed the $^1$H NMR and $^{13}$C NMR spectra of compound 5, respectively. The resonances for $–$CH=CH$–$ in the $^1$H NMR spectrum of compound 3 were observed at 6.44 and 7.68 ppm for one proton each. Conversely, the $^1$H NMR spectrum of compound 5 exhibited peaks at 6.50 ppm for two protons and 7.80 ppm for one proton. In addition, resonances for $–$CH=CH$–$ in the $^{13}$C NMR spectrum of compound 3 were observed at 167 and 117 ppm. As shown in the $^{13}$C NMR spectrum of compound 5, these peaks were shifted to 169.6 and 109.7 ppm. Analysis of compound 5 by $^1$H NMR spectroscopy revealed additional peak at 7.36 ppm for additional aromatic protons which integrated for three protons in total. Furthermore, additional six aromatic carbons were also observed in $^{13}$C NMR spectrum of compound 5 at 112.8, 114.7, 114.8, 140.9, 144.8 and 151.1 ppm. These results indicated that the addition product of compound 5 was obtained in this reaction. Compound 5 contains one N-H fragment and nitrophenyl group as we expected which might be useful for the future application.

![Figure 1. $^1$H NMR spectrum of compound 5.](image1)

![Figure 2. $^{13}$C NMR spectrum of compound 5.](image2)

In contrast to the above reaction, the reaction between methyl cinnamate 3 with 4-nitroaniline 6 and 2,4-dinitroaniline 7 were proved unsuccessful in producing desired products. The reaction between compound 3 and 4-nitroaniline 6 resulted in the formation of cinnamic acid 2, whereas the starting...
material 3 and 2-4-dinitroaniline 7 were found by TLC to remain unreacted in the reaction of compound 3 and 2-4-dinitroaniline 7. The difficulty encountered in the reaction of compound 3 with 4-nitroaniline 6 was unexpected as the previously described compound 5 was readily obtained from compounds 3 and 4 in a one-step reaction (Scheme 1). The difficulty in the reaction between compound 3 and 2,4 dinitroaniline 7 can possibly be explained by the desired product offering steric hindrance which could prevent the addition reaction from occurring.

4. Conclusion
The addition reaction occurred between methyl cinnamate and 2-amino-4-nitrophenol. The reaction was conducted in 3 step reactions to give the final product from cinnamaldehyde as starting material. Firstly, cinnamaldehyde was converted into cinnamic acid, which was then esterified with methanol to have methyl cinnamate. The last step was the addition reaction between methyl cinnamate and 2-amino-4-nitrophenol to give methyl-3-(2-hidroksi-5-nitrophenyl amino)-3-phenylpropanoate as a yellowish brown gel in 68% yield.

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