The Open Materials Science Journal

Content list available at: www.benthamopen.com/TOMSJ/

DOI: 10.2174/1874088X01812010058, 2018, *12*, 58-67

RESEARCH ARTICLE

Effect oF β-Alanine on The Preparation of 4-Ethoxy-Cinnamic Acid

N. T. Hoai[1,*], Tran Thi Yen Ngoc[1], Nguyen Dang Nam[2], Tran Thu Thuy[1], Cao Thi Thu Trang[1], Nguyen Duy Hai[1] and Truong Khoi Nguyen[1]

[1]Petroleum Department, PetroVietnam University, Long Toan Ward, Ba Ria–Vung Tau, Vietnam
[2]Institute for Basic and Applied Research, Duy Tan University, Ho Chi Minh City 700000, Vietnam

Received: April 2, 2018 Revised: June 16, 2018 Accepted: June 20, 2018

Abstract:

Objective:

Cinnamic acid and its derivatives have a numerous potential applications in many different fields such as pharmacy, organic "building blocks", and corrosion inhibitors.

Method:

It is well-known that Verley-Doebner modification is a high efficient method for the preparation of cinnamic acid derivaties, especially with the compounds containing electron-donating subtituents at para position in aromatic ring. In this paper, 4-ethoxy-cinnamic acid was synthesized according to Verley-Doebner reaction with the use of pyrine acting as catalyst and solvent. The effect of the β-alanine concentration on the conversion of the starting material of 4-ethoxy-benzaldehyde was thoroughly investigated using high performance liquid chromatography. The results showed that consuming of 8% of β-alanine would convert 100% of 4-ethoxy-benzaldehyde to 4-ethoxy-cinnamic acid.

Result:

The structure of the obtained 4-ethoxy-cinnamic acid was also confirmed using Fourier transform infrared spectroscopy, Raman spectroscopy, and Gas chromatography-Mass spectroscopy.

Cinnamic acid and its derivatives have numerous potential applications in many different fields such as pharmacy, organic "building blocks", and corrosion inhibitors. It is well-known that Verley-Doebner modification is a high efficient method for the preparation of cinnamic acid derivaties, especially with the compounds containing electron-donating subtituents at para position in aromatic ring. In this paper, 4-ethoxy-cinnamic acid was synthesized according to Verley-Doebner reaction with the use of pyrine acting as catalyst and solvent. The effect of the β-alanine concentration on the conversion of the starting material of 4-ethoxy-benzaldehyde was thoroughly investigated using high performance liquid chromatography. The results showed that consuming 8% of β-alanine would convert 100% of 4-ethoxy-benzaldehyde to 4-ethoxy-cinnamic acid. The structure of the obtained 4-ethoxy-cinnamic acid was also confirmed using Fourier transform infrared spectroscopy, Raman spectroscopy, and Gas chromatography-Mass spectroscopy.

Keywords: 4-Ethoxy-cinnamic acid, Verley-Doedner modification, Corrosion inhibitor, Cinnamic acid, β-Alanine, Raman spectroscopy.

1. INTRODUCTION

Cinnamic acid is an anti-bacteria and anti-mould organic compound which has been widely used in cosmetic and food industries. In particular, its derivatives are also the vital source of pharmaceutical products which can be applied in the high pressure treatment and tumor inhibition [1–4]. Beside the application in pharmaceutical field, cinnanic acid and its derivatives have been also used as "building blocks" for the synthesis of photo-sensitive polymers due to the

---

[*] Address for correspondence to this auther at the Petroleum Department, PetroVietnam University, Long Toan Ward, Ba Ria–Vung Tau, Vietnam; E-mail: hoaito@pvu.edu.vn

corrosion inhibitors [5 - 15].

The preparation of cinnamic acid was pioneered by the work of Perkin' group which is well-known as Perkin reaction [16]. In this reaction, benzaldehyde reacted with malonic anhydride in the presence of sodium acetate or potasium acetate as catalyst. In order to obtain a rather good conversion of benzadehyde, long reaction time (8 h) and high temperature (180 °C) should be applied [16]. This reaction is unsuitable for the synthesis of cinnamic acid derivatives with electron-donating substituents in the aromatic ring. For example, the yields of 4-methoxy-cinnamic acid and 4-ethoxy-cinnamic acid were 30% and 36%, respectively. In order to obtain relatively good yields of cinnamic acid derivaties with electron-donating subtituents at the *para* position in the aromatic ring, many literatures have focused on the Knoevenagel modification using malonate ester, malonic acid or acetic acid insteads of malonic anhydride [17–24]. Different types of catalysts including acidic and basic catalysts were used in this approach, which showed a prospective potential for the synthesis of many types of cinnamic acid derivaties, especially compounds with the electron-donating subtituents at *para* position in the aromatic ring. For intance, when carrying out the reation between 4-methoxy-benzaldehyde with acetic acid in the solvent of *N*-methyl-2-pyrrolidone using boron-based catalysts ($NaBH_4$, BBr_3, or LiB_4O_7) [17–19] at 180-190 °C for 12 hours, the yield of 4-methoxy-cinnamic acid was in the range of 53–64%. In other literatures, microwave was applied instead of tradditional heating, which reduced the reaction time to several minutes and yielded high percentage of 4-methoxy-cinnamic acid [20–24]. Recently, Verley-Doebner modification with the use of malonic acid and β-alanine as co-catalyst in the presence of pyridine showed a great potential for the preparation of a wide range of cinnamic acid derivatives [25–29]. In this article, we also used Verley-Doebner modification for the preparation of 4-ethoxy-cinnamic acid with thoroughly investigation of the effect of β-alanine concentration on the conversion of 4-ethoxy-benzaldehyde which has not yet been mentioned in the literature. In addition, with the proposed experiment procedure, the yield of 4-ethoxy-cinnamic acid was high (>98.2%) with the short reaction time.

2. MATERIAL AND METHODS

2.1. Material

4-Ethoxy-benzaldehyde, malonic acid, β-alanine, and pyridine were purchased from Sigma-Aldrich, Singapore. Concentrated HCl, ethanol were supplied by Xilong Chemical, China. Acetonitrile at HPLC grade was provided by Scharlab, Spain.

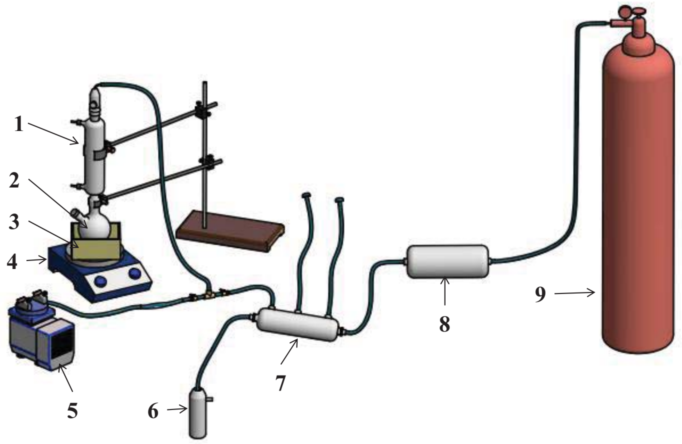
2.2. Preparation of 4-Ethoxy-cinnamic Acid

The experiment was set up followed the Scheme. (**1**) in which all of the reactions were carried out under nitrogen atmosphere. A typical reaction (Scheme. **2**), Run 1 of Table **1** was described as follows. To a 100 mL of two neck round-bottom flask were added 1853 mg of malonic acid (17.8 mmol) and 51.3 mg of β-alanine (0.58 mmol). The solid mixture was then kept for overnight under reduced pressure using vacuum pump. The vacuum atmosphere was then switched to nitrogen atmosphere thoroughly with at least three cycles of vacuuming and purging nitrogen. To the above solid mixture were added 1.00 mL of 4-ethoxy-benzaldehyde (7.20 mmol) and 3.20 mL of pyridine (39.7 mmol) under nitrogen atmosphere. The reaction mixture was then heated to the reflux condition (120 °C) using oil bath and hotplate. During reaction period, samples were taken for high performance liquid chromatography measurements at 0, 1, 2, 3, 4, 5, 7, 10, 15, and 30 mins for investigating conversion of 4-ethoxy-benzaldehyde. Reaction was stopped at 30 min and the reaction mixture was then cooled to room temperature. 5 mL of concentrated HCl was then slowly added to the mixture which was placed in ice water. The precipitated white crystals were filtered, washed with cold water and dried under vacuum for overnight (98.2% yield). For analysis, white crystals were recrystallized twice using ethanol and water.

Table 1. Experimental Condition for the Preparation of 4-Ethoxy-Cinnamic Acid and 4-Propoxy-Cinnamic Acid.

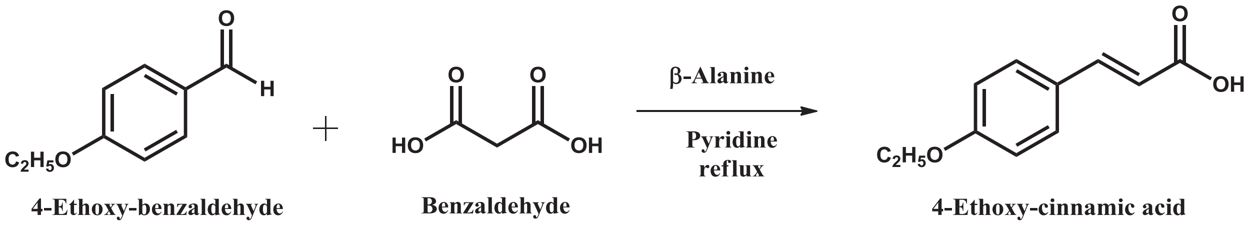
Run	4-Ethoxy-Benzadehyde / Mol	Malonic Acid / Molar	Pyridine / Molar	β-Alanine[a] / %
1	7.20	17.8	39.7	8
2	7.20	17.8	39.7	4
3	7.20	17.8	39.7	2

[a] % β-alanine = (molar of β-alanine/ molar of 4-ethoxy or propoxy-benzadehyde)*100%



1: condensor; **2**: round-flask; **3**: oil bath; **4**: hot plate; **5**: vacuum pump;
6: bubble trap; **7**: intermediate tank; **8**: drying tube; **9**: nitrogen tank.

Scheme. (1). Experimental set up.



Scheme. (2). Preparation of 4-ethoxy-cinnamic acid.

2.3. Investigation on the Conversion of 4-Ethoxy-Benzaldehyde Using High Performance Liquid Chromatography

The conversion of 4-ethoxy-benzaldehyde was investigated using High Performance Liquid Chromatography (HPLC) measurements at different reaction times of 0, 1, 2, 3, 4, 5, 7, 10, 15 and 30 mins. 10 µL of samples at a certain time were diluted with 1 mL of ethanol. The mixtures were then applied for HPLC analysis with the mobile phase of the acetonitrile/water mixture (60/40 v/v), flow rate of 1 mL/min, C18 column, 1 µL of injected volume, and UV detector at 254 nm. The peaks appear at 2.39 min in the spectra of HPLC corresponding to 4-ethoxy-benzadehyde. The conversion of 4-ethoxy-benzadehyde was calculated using the following equation:

$$Conv_{ethoxy} = (1 - A^{t}_{2.39} / A^{0}_{2.39}) \qquad \textbf{(1)}$$

Where $Conv_{ethoxy}$: Conversion of 4-ethoxy-benzadehyde; $A_{2.39}$ and $A^{t}_{2.39}$: peak areas of 4-ethoxy-benzadehyde at 0 and t min, respectively.

2.4. Measurements

Fourier Transform Infrared Spectroscopy (FT–IR) was measured under KBr pellets using Bruker's VERTEX 70 at a resolution of 2 cm^{-1}. Raman measurements were carried out using Horiba XploRA laser 785 nm. Gas chromatography–Mass spectroscopy (GC–MS) was carried out using Agilent 7890B for GC and Agilent 5977A for MS with the mobile phase at 1 mL/min of flow rate.

3. RESULTS AND DISCUSSION

3.1. Effect of β-Alanine Concentration on the Conversion of 4-Ethoxy-Benzaldehyde

In this paper, the conversion of 4-ethoxy-benzadehyde was thoroughly investigated using HPLC measurements.

HPLC profiles at different reaction conditions with different amounts of β-alanine were described in Fig. (**1a**, **b**, **c**). The peaks at 1.87 min and 2.39 min correspond to the desired product of 4-ethoxy-cinnamic acid and the reactant of 4-ethoxy-benzadehyde, respectively. In the case of using 2% of β-alanine Fig. (**1a**), the reactant remained at high level in the reaction mixture even at long reaction time, indicating the used amount of β-alanine was insufficient. The amount of β-alanine was therefore increased to 4% leading to a better result shown in Fig. (**1b**); however, 4-ethoxy-benzadehyde still remained after 30 min of reaction time. In the case of using 8% of β-alanine Fig. (**1c**), the 4-ethoxy-benzadehyde was completely consumed after 5 min of reaction time. The results showed in Fig. (**1d**) obviously demonstrated that the amount of β-alanine affected the conversion of 4-ethoxy-benzadehyde. In particular, when using 2% of β-alanine, the conversion of 4-ethoxy-benzadehyde was below 45% and required 30 min to reach maximum value of 42.8%. When increasing β-alanine concentration to 4%, the conversion of 4-ethoxy-benzadehyde went up to 87.9% and required less time (15 mins) to reach maximum value as compared with the case of using 2% β-alanine. In the case of using 8% β-alanine, the conversion of 4-ethoxy-benzadehyde reached 100% rapidly after 5 min of reaction time.

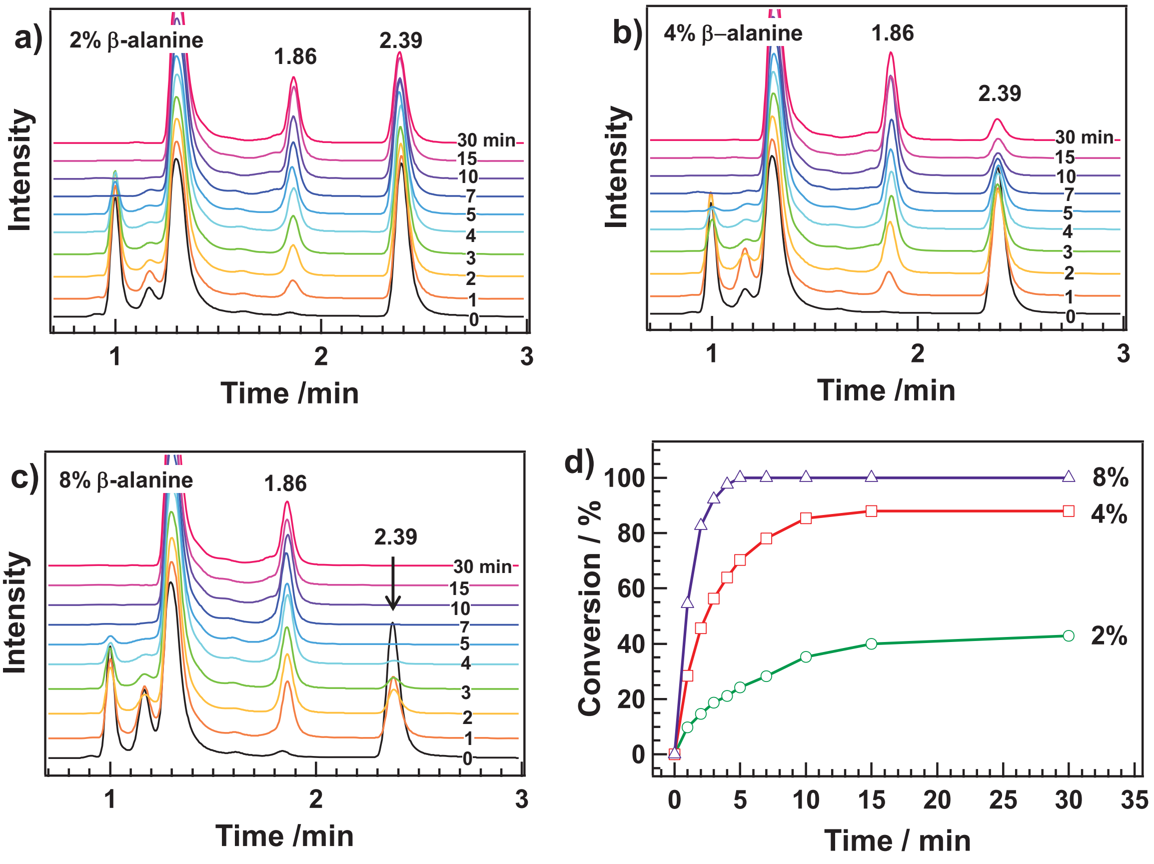


Fig. (1). The high performance liquid chromatography spectra of reaction samples at different β-alanine concentration: **a**) 2% β-alanine, **b**) 4% β-alanine, **c**) 8% β-alanine; **d**) Effect of β-alanine concentration on the conversion of 4-ethoxy-benzaldehyde.

3.2. Characterization of 4-Ethoxy-Cinnamic Acid

The obtained product of 4-ethoxy-cinnamic acid was recrystallized twice using ethanol and water for characterization. The FT-IR and Raman spectra of 4-ethoxy-cinnamic acid were showed in Fig. (**2**) in the wavenumber region of 3500–2000 cm^{-1} Fig. (**2a**) and 2000–400 cm^{-1} Fig. (**2b**) and the vibration assignments were described in Table **2** followed the literatures [30, 31].

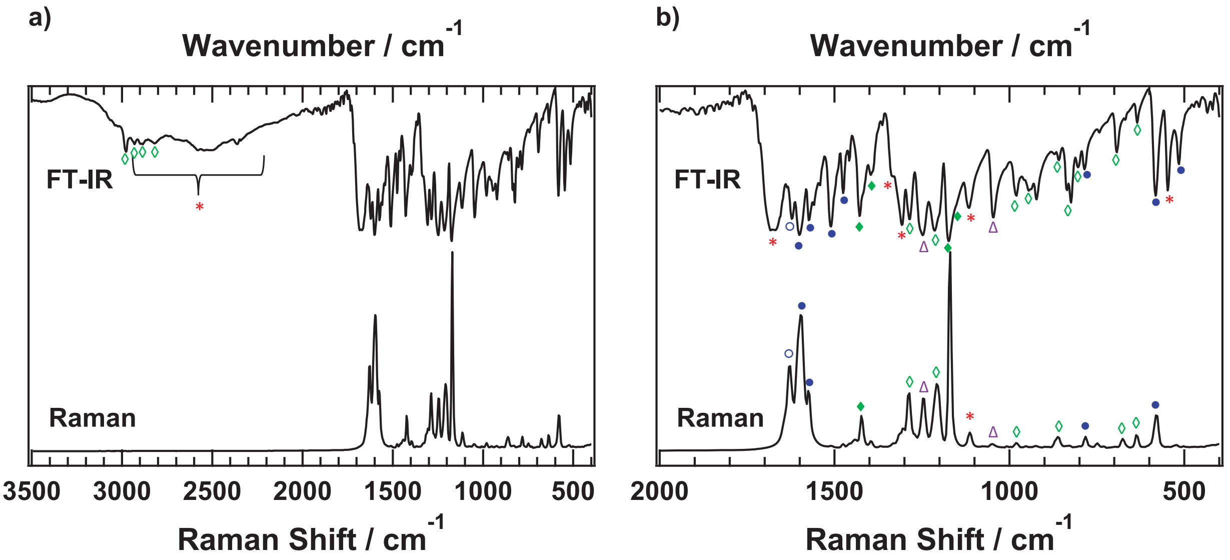


Fig. (2). FT–IR spectroscopy of 4-ethoxy-cinnamic acid at the region of **a**) 3500–400 cm^{-1} and **b**) 2000–200 cm^{-1}. Asterisks: vibrations of carboxylic; Closed circle: C–C virbations in phenyl; Open circle: C–C vibrations in double bond; Open diamond: C–H vibrations; Closed diamond: CH_2 and CH_3 vibrations; Open triangle: ether vibrations

Table 2. Ft-ir and Raman Assignment for 4-Ethoxy-Cinnamic Acid.

Assignments	FT-IR	Raman	Assignments	FT-IR	Raman
νC–H (aryl)	3037 vw	-	β=C–H	1213 vs	1208 m
γOH	3200-2600 w, br	-	ωCH_3	1174 vs	1169 vs
νC–H (sp^3)	2974 m 2928 m 2887 m	-	ρCH_2	1157 m	-
νC=O	1676 vs	-	βO–H	1117 s	1114 w
νC=C (alkene)	1622 s	1626 s	νO–CH_2	1045 s	1049 w
νC–C (aryl)	1600 vs	1597 vs	γ=C–H (trans)	980 s	981 w
νC–C (aryl)	1573 s	1575 m	βC–H	942 m	
νC–C(aryl)	1510 vs		γC–H	858 w	861 w
νC–C (aryl)	1475 s		γC–H (para-di-substitution)	835 s	-
δCH_2	1427 s	1423 m	γC–H	802 m	-
δCH_3	1396 m	-	βC–C–C	785 m	782 w
νC–OH	1335 s	-	γC–H	743 vw 692 m 673 vw	749 vw 672 vw
νC–COOH	1308 vs	-	βC–C–C	582 s	580 m
β=C–H	1285 s	1287 m	γO–H	547 s	-
νC–O(CH_2)	1248 vs	1246 m	βC–C–C	515 m	-

[a] ν–stretching; β–in-plane bending; δ–deformation; ρ–rocking; γ–out-of-plane bending; ω–wagging. [b] vw: very weak; w: Weak; m: Medium; A: strong; *vs:* very strong; br: Broad.

3.2. Vibrations of Carboxylic Acid

The broad band in the range of 3200–2600 cm^{-1} in FT-IR spectrum is characteristic for the vibration of O–H stretching in carboxylic acid. Other strong peak appears at 1676 cm^{-1} was assigned for the C=O stretching mode. This peak is strong in FT-IR spectrum but completely absented in Raman spectrum. The peak at 1335 cm^{-1} is assigned for C–O stretching. The C–COOH stretching vibration was confirmed with the peak appearing very strong at 1308 cm^{-1} in the FT-IR spectrum. The OH in-plane bending vibration appears with strong intensity at 1117 cm^{-1} in the FT-IR spectrum, while OH out-of-plane bending shifted to lower wavenumber at 547 cm^{-1}. All of the peaks corresponding to the vibrations of carboxylic acid are marked by red asterisks in (Fig. **2**).

3.3. Vibrations of –C=C– and C–C

The vibration of C–C stretching in phenyl ring is obviously observed both in FT-IR and Raman spectra with the intensity ranging from weak to very strong which are marked by closed blue circles in the Fig. (**2**). These peaks appear in the region of 1650–1100 cm^{-1}. In FT-IR spectrum they can be seen at 1600, 1573, 1510, and 1475 cm^{-1}, whereas at 1597, 1575 cm^{-1} in Raman spectrum. Other characteristic vibration of C–C bond in phenyl ring is CCC in-plane-bending, which appears in FT-IR spectrum at 785, 582, and 515 cm^{-1}. For C=C stretching in double bond, the characteristic peaks appear very strong in both FT-IR and Raman spectra; specifically at 1622 cm^{-1} in FT-IR spectrum and at 1626 cm^{-1} in Raman spectrum, which are marked by open blue circles in the (Fig. **2a**).

3.4. Vibrations of C–H

The characteristic vibrations of C–H in phenyl and double bond are stretching, in-plane bending and out-of-plane bending, which are marked by open green diamonds in the Fig. (**2**). The stretching mode shows weak peak in FT-IR spectrum at 3037 cm^{-1}. The in-plane C–H bending mode in phenyl ring appears at 942 cm^{-1} in FT-IR spectrum. The out-of-plane C–H bending vibrations in phenyl ring appear at 858, 835, 802, 743, 692, and 673 cm^{-1} in FT-IR spectrum and at 861, 749, 672 cm^{-1} in Raman spectrum. The peak observed at 835 cm^{-1} is characteristic peak for the di-substituent at para position of phenyl ring. For the vibrations of C–H in double bond, in-plane bending and out-of-plane bending modes were observed. Specifically, the in-plane bending mode of C–H in double bond appears very strong at 1285 and 1213 cm^{-1} in FT-IR spectrum and medium at 1246 and 1208 cm^{-1} in Raman spectrum. Whereas, the out-of-plane bending of C–H in double bond appeared at 980 cm^{-1} in FT-IR spectrum and 981 cm^{-1} in Raman spectrum. These are characteristic peaks for the *trans* isomer of 4-ethoxy-cinnamic acid.

3.5. Vibration of CH_3 and CH_2

The vibrations modes of CH_3 and CH_2 in 4-ethoxy-cinnamic acid are CH_3 and CH_2 deformation, CH_2 rocking, and CH_3 wagging which are marked by closed green diamond in the Fig. (**2**). The CH_2 deformation appeared strongly at 1427 cm^{-1} in FT-IR spectrum, whereas CH_3 deformation appeared at 1396 cm^{-1} in FT-IR spectrum. The CH_2 rocking vibration is confirmed with the medium peak at 1157 cm^{-1} in FT-IR spectrum. The CH_3 wagging mode is the characteristic vibration of CH_3 and appears strongly both in FT-IR and Raman spectra at 1174 cm^{-1} and 1169 cm^{-1}, respectively.

3.6. Vibrations of Ather

The structures of 4-ethoxy-cinnamic acid consist of ether linkages between ethoxy and phenyl, which lead to two stretching vibration modes of $\nu C–OCH_2$ and $\nu O–CH_2$ which are marked by open purple triangles in the Fig. (**2**). $\nu C–OCH_2$ appears in FT-IR spectrum with high intensity at 1248 cm^{-1}, while in Raman spectrum at 1246 cm^{-1}. These vibrations are also present in the Raman spectrum at 1246 cm^{-1}. In contrast, the $\nu O–CH_2$ vibration is observed in the FT-IR and Raman spectra at 1045 cm^{-1} and 1049 cm^{-1}, respectively.

3.7. GC-MS Measurements

The structure of 4-ethoxy-cinnamic acid was further confirmed using GC–MS measurement and the result is shown in Fig. (**3**). According to literature [32], the fragmentation of cinnamic acid in the ion source should lead to positively charged ions; hence m/z values in Fig. (**3**) are equal to the molecular mass of corresponding ions. The chemical composition of 4-ethoxy-cinnamic acid ($C_{11}H_{12}O_3$) was confirmed by checking the isotope ratios of $(M+1)^+$ and M^+ of 4-ethoxy-cinnamic acid. The existence of $(M+1)^+$ isotopes at *m/z* = 193 in Fig. (**3**) is attributed to the contribution of natural abundance of ^2H, ^{13}C or ^{17}O isotopes to chemical molecules of 4-ethoxy-cinnamic acid. The isotope ratios of $(M+1)^+$ and M^+ of 4-ethoxy-cinnamic acid was theoretically calculated using the below equation:

$$(M+1)^+/M^+ = n_C * p_{^{13}C} + n_H * p_{^2H} + n_O * p_{^{17}O} \tag{2}$$

Where:

n_H: number of H atoms in chemical molecules;

n_O: number of O atoms in chemical molecules;

p_{13C}: natural abundance of ^{13}C (1.08%);

p_{2H}: natural abundance of ^{2}H (0.015%); and

p_{17O}: natural abundance of ^{17}O (0.04%).

The theoretical isotope ratio of $(M+1)^+$ and M^+ for 4-ethoxy-cinnamic acid calculated from equation (2) is 12.18%. The observed isotope ratio of 4-ethoxy-cinnamic acid was calculated based on the intensity of the peak at *m/z* = 193 divided by that of the peak at *m/z* = 192 in Fig. (**3**). The results show that the calculated ratio was completely matched to the observed one for 4-ethoxy-cinnamic acid. Therefore, the chemical composition of 4-ethoxy-cinnamic acid ($C_{11}H_{12}O_3$) was confirmed.

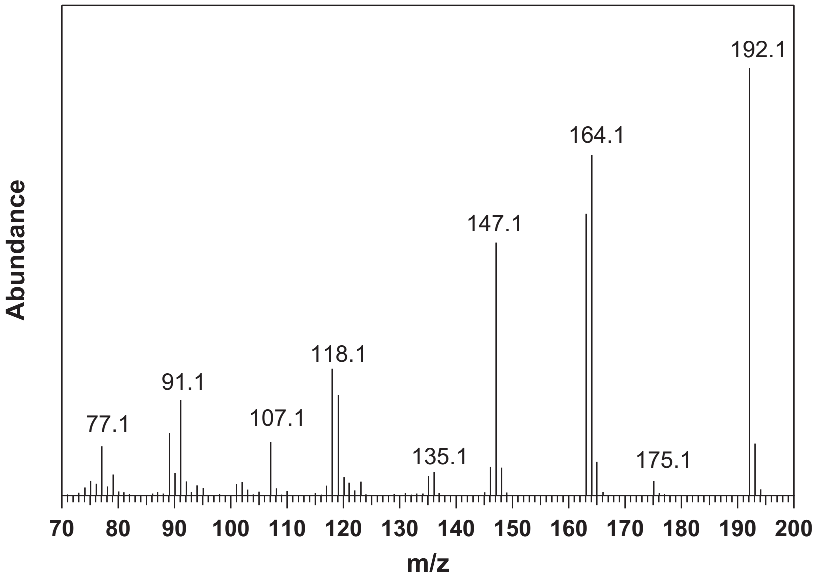
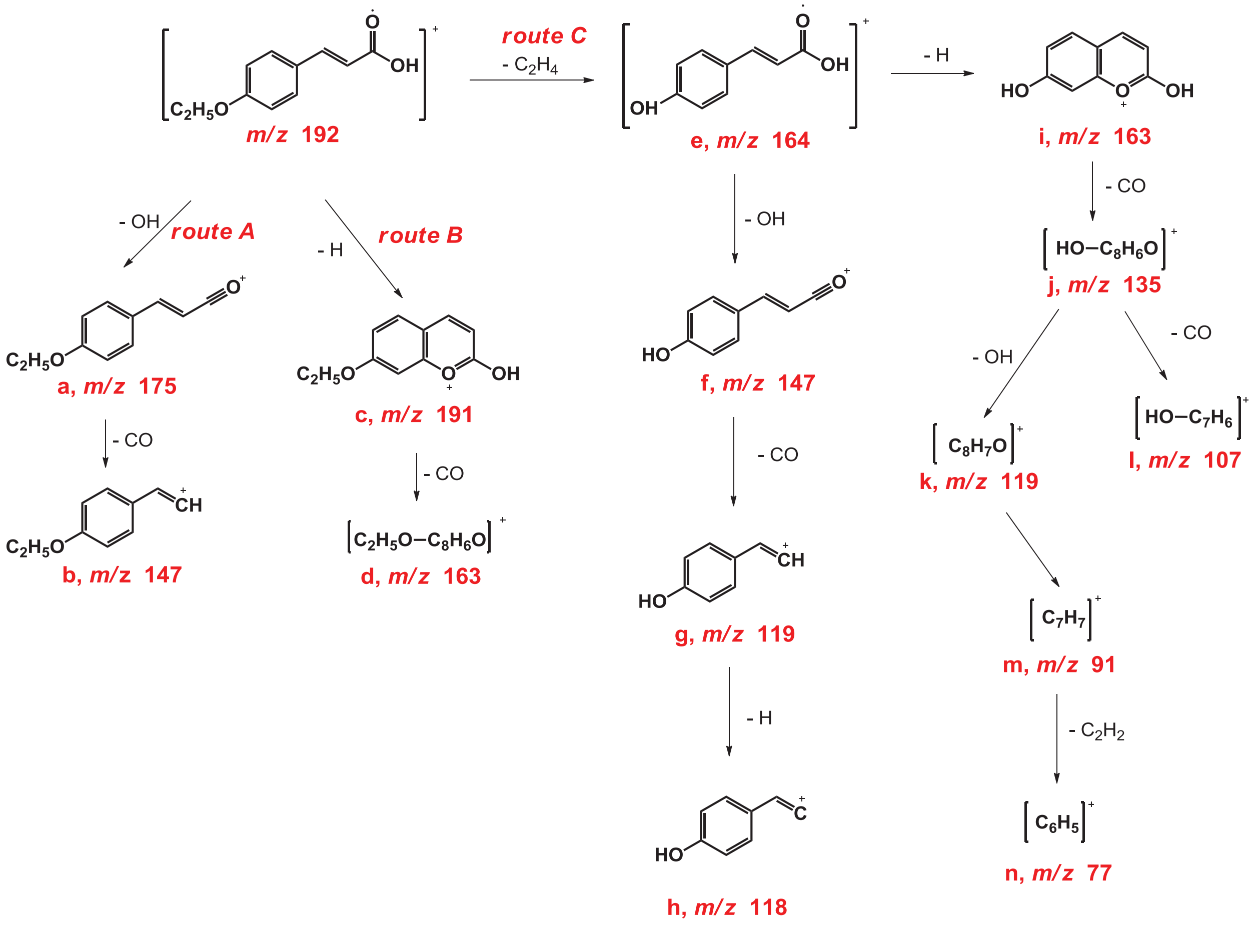


Fig. (3). GC–MS spectrum of 4-ethoxy-cinnamic acid.

The fragmentation of 4-ethoxy-cinnamic acid was initiated from the “mother” ions as showed in Scheme. (**3**). According to the previous literature [30], the fragmentation route should be classified *via* three competitive pathways: i) cleavage of OH from carboxylic acid group (route A); ii) elimination of H in phenyl ring and ring-closing (route B) and iii) elimination of C_2H_4 of ethoxy group forming 4-hydroxy-cinnamic acid ions (route C). For route A, *a* ion at the *m/z* = 175 appeared with very low intensity. The further fragmentation of this ion to *b* ion should result in the appearance of the peaks at *m/z* = 147 in Scheme. (**3**). Here, the *m/z* at 147 in Scheme. (**3**) should be investigated whether it can be assigned for *b* ion. The isotope ratio of $(M+1)^+$ and M^+ of *b* ion was calculated theoretically based on equation (2) and compared with one obtained from the ratio of the observed intensity of the peaks at *m/z* = 148 and 147 in Fig. (**3**). The result shows that the calculated isotope ratio based on *b* ion was different from the observed ratio. Therefore, the peak at *m/z* = 147 should not be assigned for *b* ion. Actually, in route C, there is the *f* ion with *m/z* = 147 and its isotope ratio was fitted with the observed ratio in Fig. (**3**). Hence, the peak at *m/z* = 147 in Scheme. (**3**) should be assigned for *f* ion in route C.

For route B, the peaks at 191 corresponding to *c* ion and their “children” ions of *d* (*m/z* = 163) should appear in Fig. (**3**); however, its observed isotope ratio was not assigned for *d* ion. The fragmentation *via* Route C undergoes the elimination of C_2H_4 from the structures of 4-ethoxy-cinnamic acid leading to the formation of 4-hydroxy-cinnamic acid ion. This route was strongly confirmed by the appearance of the peak at *m/z* = 147 in Fig. (**3**) with strong intensity, which should be assigned for *f* ion. Interestingly, the theoretical isotope ratio of *f* ion was in agreement with the observed ratio calculated from the intensity of the peaks at *m/z* = 148 and 147 in Fig. (**3**). All other “children” ions belonging Route C fragmentation appear in Fig. (**3**) at *m/z* = 147, 135, 119, 107, 91, and 77. Moreover, the GC-MS profile of 4-ethoxy-cinnamic acid in Fig. (**3**) in the *m/z* region of 75-164 was similar to that of 4-hydroxy-cinnamic acid which was reported in the literature [32].



Schema. (3). Fragmentation routes of ionized 4-ethoxy-cinnamic acid.

CONCLUSION

The effect of β-analine concentration on the conversion of 4-ethoxy-benzaldehyde converting to 4-ethoxy-cinnamic acid was obviously shown. High performance liquid chromatography was proved that it was a straight forward method to investigate the conversion of 4-ethoxy-benzadehyde. In order to acquire 100% conversion within short reaction time, 8% of β-alanine should be applied. In this article, the structure of the obtained 4-ethoxy-cinnamic acid was also confirmed thoroughly using Fourier transform-Infrared Spectroscopy, Raman spectroscopy, and Gas chromatography-Mass Spectroscopy. It is clearly demonstrated in the FT-IR and Raman spectra that the vibrations of all functional groups including COOH group, phenyl ring, trans isomer of double bond, CH_2 and CH_3 groups, and ether bonds in 4-ethoxy-cinnamic acid were observed. The MASS results indicated that 4-ethoxy-cinnamic acid underwent the fragmentation route *via* the elimination of C_2H_4 of ethoxy group forming 4-hydroxy-cinnamic acid ions.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This research was funded by PetroVietnam University under grant number GV1604.

REFERENCES

[1] Aragón-Muriel A, Polo-Cerón D. Synthesis, characterization, thermal behavior, and antifungal activity of La(III) complexes with cinnamates

and 4-methoxyphenylacetate. J Rare Earths 2013; 31: 1106-13.
[http://dx.doi.org/10.1016/S1002-0721(12)60412-8]

[2] Brozic P, Golob B, Gomboc N, Rizner TL, Gobec S. Cinnamic acids as new inhibitors of 17β-hydroxysteroid dehydrogenase type 5 (AKR1C3). Mol Cell Endocrinol 2006; 248(1-2): 233-5.
[http://dx.doi.org/10.1016/j.mce.2005.10.020] [PMID: 16337332]

[3] Liu L, Hudgins WR, Shack S, Yin MQ, Samid D. Cinnamic acid: A natural product with potential use in cancer intervention. Int J Cancer 1995; 62(3): 345-50.
[http://dx.doi.org/10.1002/ijc.2910620319] [PMID: 7628877]

[4] Sharma P. Cinnamic acid derivatives: A new chapter of various pharmacological activities. J Chem Pharm Res 2011; 3: 403-23.

[5] Matsusaki M, Kishida A, Stainton N, Ansell CWG, Akashi M. Synthesis and characterization of novel biodegradable polymers composed of hydroxycinnamic acid and D,L-lactic acid. J Appl Polym Sci 2001; 82: 2357-64.
[http://dx.doi.org/10.1002/app.2085]

[6] Nagata M, Hizakae S. Synthesis and characterization of photocrosslinkable biodegradable polymers derived from 4-hydroxycinnamic acid. Macromol Biosci 2003; 3: 412-9.
[http://dx.doi.org/10.1002/mabi.200350011]

[7] Pinazzi CP, Fernandez A. Synthesis of new photocrosslinkable polymers derived from cinnamic acid. ACS Symposium Series. 37-51.
[http://dx.doi.org/10.1021/bk-1976-0025.ch004]

[8] Thi TH, Matsusaki M, Shi D, Kaneko T, Akashi M. Synthesis and properties of coumaric acid derivative homo-polymers. J Biomater Sci Polym Ed 2008; 19(1): 75-85.
[http://dx.doi.org/10.1163/156856208783227668] [PMID: 18177555]

[9] Battouti ME. Cinnamic acid derivatives as inhibitors for dissolution of copper in phosphoric acid. Anti-Corros Methods Mater 1995; 42: 15-8.
[http://dx.doi.org/10.1108/eb007376]

[10] Blin F, Koutsoukos P, Klepetsianis P, Forsyth M. The corrosion inhibition mechanism of new rare earth cinnamate compounds-Electrochemical studies. Electrochim Acta 2007; 52: 6212-20.
[http://dx.doi.org/10.1016/j.electacta.2007.04.001]

[11] Blin F, Leary SG, Deacon GB, Junk PC, Forsyth M. The nature of the surface film on steel treated with cerium and lanthanum cinnamate based corrosion inhibitors. Corros Sci 2006; 48: 404-19.
[http://dx.doi.org/10.1016/j.corsci.2005.01.009]

[12] Blin F, Leary SG, Wilson K, Deacon GB, Junk PC, Forsyth M. Corrosion Mitigation of Mild Steel by New Rare Earth Cinnamate Compounds. J Appl Electrochem 2004; 34: 591-9.
[http://dx.doi.org/10.1023/B:JACH.0000021932.87043.7b]

[13] Nam ND, Mathesh M, Hinton B, Tan MJY. Rare earth 4-hydroxycinnamate compounds as carbon dioxide corrosion inhibitors for steel in sodium chloride solution. J Electrochem Soc 2014; 161: C527-34.
[http://dx.doi.org/10.1149/2.0231412jes]

[14] Seter M, Girard GMA, Lee WW, *et al.* The influence of organic structure and rare earth metal cation on the corrosion efficiency observed on AS1020 steel compared with La(4OHCin)$_3$. AIMS Materials Science 2015; 2: 1-15.
[http://dx.doi.org/10.3934/matersci.2015.1.1]

[15] Vrsalović L, Gudić S, Kliškić M, Oguzie EE, Carev L. Inhibition of copper corrosion in NaCl solution by caffeic acid. Int J Electrochem Sci 2016; 11: 459-74.

[16] Johnson JR. Perkin reaction and related reactions. Org React 1942; 1: 210-65.

[17] Chiriac CI, Tanasa F, Onciu M. A new direct synthesis of cinnamic acids from aromatic aldehydes and aliphatic carboxylic acids in the presence of sodium borohydride. Tetrahedron Lett 2003; 44: 3579-80.
[http://dx.doi.org/10.1016/S0040-4039(03)00529-X]

[18] Chiriac CI, Tanasa F, Onciu M. A novel approach in cinnamic acid synthesis: Direct synthesis of cinnamic acids from aromatic aldehydes and aliphatic carboxylic acids in the presence of boron tribromide. Molecules 2005; 10(2): 481-7.
[http://dx.doi.org/10.3390/10020481] [PMID: 18007319]

[19] Chiriac CI, Tanasa F, Nechifor M. A new alternative method for the synthesis of cinnamic acids from aromatic aldehydes and zinc acetate. Rev Roum Chim 2008; 53: 833-6.

[20] Gupta M, Wakhloo BP. Tetrabutylammoniumbromide mediated knoevenagel condensation in water: Synthesis of cinnamic acids. ARKIVOC 2007; 94-8.

[21] Gopalakrishnan M, Sureshkumar P, Kanagarajan V, Thanusu J, Thirunavukkarasu S. Dry media reaction procedure for synthesis of α,β-unsaturated acids, α-cyanoacrylonitriles and α-cyanoacrylates *via* knoevenagel condensation using $NaHSO_4 \cdot SiO_2$ catalyst. Korean Chem Soc 2007; 51: 346-51.
[http://dx.doi.org/10.5012/jkcs.2007.51.4.346]

[22] Kumar SD, Sandhu JS. Alum [$KAl(SO_4)_2.12H_2O$]: An efficient, novel, clean, catalyst for Doebner Knoevenagel reaction for the efficient production of α,β-unsaturated acids. Indian J Chem 2011; 50B: 1479-8.

[23] Pellón RF, Mamposo T, González E, Calderón O. Synthesis of cinnamic acid derivatives using ethanol as solvent or microwave assisted method. Synth Commun 2000; 30: 3769-74.
[http://dx.doi.org/10.1080/00397910008087005]

[24] Ogata Y, Tsuchida M. Kinetics of the Knoevenagel condensation of benzaldehydes with diethyl malonate. J Am Chem Soc 1959; 81: 2092-4.
[http://dx.doi.org/10.1021/ja01518a016]

[25] Morais GR, Watanabe M, Tanaka Y, Thiemann T. Simple amidation of unprotected phenol-containing 2-alkenoic acids. J Chem Res 2005; 29: 802-7.
[http://dx.doi.org/10.3184/030823405775146889]

[26] Zhang W, Xu W, Liu M, Yan Y, Sun Y, Zhang Sh. Synthesis of cinnamic acid derivatives in a water-insoluble ionic liquid. J Chem Res 2011; 35: 723-5.
[http://dx.doi.org/10.3184/174751911X13236869868941]

[27] Keuseman KJ, Morrow NCA. “Green” Approach to synthesis of *trans*-4-methoxycinnamic acid in the undergraduate teaching laboratory. Chem Educ 2014; 19: 347-50.

[28] Kolb KE, Field KW, Schatz PF. A One-step synthesis of cinnamic acids using malonic acid: The verley-doebner modification of the Knoevenagel condensation. J Chem Educ 1990; 67: A304-5.
[http://dx.doi.org/10.1021/ed067pA304]

[29] Rudyanto M, Hartanti L. Synthesis of some cinnamic acid derivatives: Effect of groups attached on aromatic ring to the reactivity of benzaldehyde. Indo J Chem 2008; 226-30.

[30] Arjunan V, Anitha R, Marchewka MK, Mohan S, Yang H. Conformational, structural, vibrational, electronic and quantum chemical investigations of cis-2-methoxycinnamic acid. J Mol Struct 2015; 1080: 122-36.
[http://dx.doi.org/10.1016/j.molstruc.2014.09.083]

[31] Arjunan V, Anitha R, Thenmozhi S, Marchewka MK, Mohan S. Potential energy profile, structural, vibrational and reactivity descriptors of trans-2-methoxycinnamic acid by FTIR, FT-Raman and quantum chemical studies. J Mol Struct 2016; 1113: 42-54.
[http://dx.doi.org/10.1016/j.molstruc.2016.02.034]

[32] Schaldach B. Griitzmacher HFr. The fragmentations of substituted cinnamic acids after electron impact. Org Mass Spectrom 1980; 15: 175-81.
[http://dx.doi.org/10.1002/oms.1210150404]