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Epoxide and Hydroperoxide Derived from Naturally Cinnamaldehyde and its Schiff Base Derivatives

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Thermal and photo epoxidation, photooxygenation reactions of cinnamaldehyde may be useful tool for the design of drugs to act as potent chemopreventation and anticancer agents. *trans*-Cinnamaldehyde was isolated from essential oil of cinnamon (*Cinnamonum verum*). It was subjected to oxidation reactions either photochemically with hydrogen peroxide or thermally with 3-chloro-peroxybenzoic acid. Schiff base derivative was synthesized through condensation reaction with aniline. It subjected to photooxidation reaction in the presence of tetraphenylporphin as singlet oxygen sensitizer. photochemically oxidation reaction gave the corresponding epoxy derivative together with *cis*-isomerisation. Whereas, thermally oxidation reaction resulted the corresponding epoxy derivative together with cinnamic acid. In addition, photooxidation reaction of Schiff base derivative led to 1-phenyl-3-phenyliminopropen-1-yl hydroperoxide through endoperoxide derivative. The primary tested of hydroperoxide derivative showed a moderate degree of DNA degradation. *trans*-Cinnamaldehyde and its derivatives can act as antioxidants. They were trapped the reactive oxygen species (ROS) to give the intermediated epoxides and hydroperoxide derivatives, which could be alkylated or damage DNA, proteins and other biological species

Keywords: Photooxygenation, Epoxidation, *trans*-Cinnamaldehyde, Schiff base, Tetraphenyl porphin.

INTRODUCTION

Light can be considered as an ideal reagent for environmentally friendly, 'green' chemical synthesis; unlike many conventional reagents, light is non-toxic, generates no waste, and can be obtained from renewable sources. Nevertheless, the need for high-energy ultraviolet radiation in most organic photochemical processes has limited both the practicality and environmental benefits of photochemical synthesis on industrially relevant scales. Photochemistry can serve as a valuable green chemical application since light can be considered as an ideal reagent[1]. However, despite obvious advantages in terms of selectivity and sustainability, the photochemical production of chemicals on industrial scales remains rare[2]. To overcome this neglect, we are studying selected photochemical reactions with moderately concentrated sunlight. Furthermore, we are investigating photochemical transformations for the production of hydroperoxide and epoxide which may be useful as future pharmaceuticals or agrochemicals. Many naturally occurring alkenylbenzene derivatives, usually relatively simple allyl- or propenylbenzene have been identified as components of numerous plants or their essential oils[3,4], which was used as natural flavoring and fragrance chemicals. *trans*-Cinnamaldehyde (**1a**) is an aromatic aldehyde and main component of bark extract of cinnamon (*Cinnamomum verum*)[5]. It is present in essential oils of many plants and are proved to be active against many pathogenic bacteria[6,7], fungi[7,8] and viruses[9]. Microbial metabolism of phenylpropenoids involves oxidation of the side chain to carboxylic acid prior to hydroxylation and cleavage of the benzene ring, for example cinnamaldehyde is oxidized to cinnamic acid by Eilerman[10].

The oxidation process is enhanced by heat, irradiation[11] or in the presence of catalysts[12]. Zanardi *et. al.*[13] reported that oxidation of cinnamaldehyde (**1**), with (2R,5R)-2,5-dimethylthiolane give epoxy derivative **2**. Wright and Abbot[14] found that analogous reaction with alkaline peroxide thermally lead to form **2**. Hu *et al.*[15] found that oxidation reaction with hydrogen peroxide thermally in the presence of cyclodextrins (CDS) formed epoxy-cinnamaldehyde, which undergoes further reaction by ring opening and side chain cleavage to yield benzaldehyde, where that epoxide derivatives (**2**) could not be isolated. Furthermore, phenylpropenoides were trapped the activated oxygen species *in vivo* to give the intermediated epoxides and hydroperoxide derivatives, which could be alkylated or damage DNA, proteins and other biological species[16,17]. Taking into account important activities of plant phenyl-propenoides and contradictory published data on epoxidation of *trans*-cinnamaldehyde (**1a**), we studied the oxidation reaction of *trans*-

cinnamaldehyde (**1a**) under different conditions (thermal and photochemical).

EXPERIMENTAL

IR spectra were performed on a Perkin-Elmer 16 FPC FT-IR spectrophotometer as thin films. ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ solution on a Brucker AVANCE D.P.X. 400 MHz apparatus. GCMS were determined by Joel JMS 600H, GC Hewlett Packerd, HP 6890 Series, with capillary column (30 × 0.32 mn × 0.25 mm) HP-5 cross linked 5 % dimethyl polysiloxane. A sodium lamp (Phillips G/5812 SON) was used for photo-irradiation reactions. Thin layer chromatography (TLC) and preparative layer chromatography (PLC): Polygram SIL G/W 254, Mecherey-Nagel. A rotatory evaporator (at 20 °C/15 torr) was used to remove the solvents.

General epoxidation procedures of natural volatile aromatic compounds

Method A: Epoxidations photochemically using hydrogen peroxide: A solution of H_2O_2 (2.5 mL, 50 %) was added cautiously dropwise over 5 min to a stirred solution **1a** (5 mmol) in C_2H_5OH (25 mL) at 0 ºC. The mixture was irradiated using sodium lamp in an atmosphere of nitrogen. The reaction mixture was evaporated under reduced pressure at room temperature to give the gummy material. Chloroform (25 mL) was added to the crude product. The combined extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give crude product, which was purified by column chromatography on silica gel adsorbent. Elution of the column with the solvent mixture of petroleum ether 60-80 ºC and diethyl ether (9:2) to give the epoxide derivative and *cis*-cinnamaldehyd[18].

Method B: Thermally epoxidations using *m*-chloroperbenzoic acid: A solution of *m*-chloroperbenzoic acid (10 mmol, 80 %) was added cautiously dropwise over 15 min to a stirred solution **1a** (5 mmol) in $CHCl_3$ (25 mL) at 0 ºC. The mixture was stirred in an atmospheric nitrogen at room temperature (TLC, peroxide test by KI, 10 %), after carefully washed with a saturated aqueous solution of $NaHCO_3$ (3 × 10 mL), then with distilled water (3 × 10 mL). The organic layers were separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure at room temperature. The crude residue product was purified by column chromatography on silica gel adsorbent. Elution of the column with the solvent mixture of petroleum ether 60-80 ºC and ether (9:2) to give the epoxide derivative and cinnamic acid[18].

General photooxygenation of aromatic compounds

Photosensitized oxygenation of Schiff base (4) with tetraphenylporphin: A solution of **4** (10 mmol in chloroform) in the presence of tetraphenylporphin (TPP) as singlet oxygen sensitizer was irradiated externally by means of sodium lamp at -5 ºC. During the irradiation a continuous stream of dry oxygen gas was allowed to pass through the reaction mixtures at a slow rate to avoid evaporation of solvent. The solvent was evaporated at 20 ºC/15 Torr. The crude products were purified by column chromatography on silica gel adsorbent by eluting with a mixture of petroleum ether 60-80 ºC and ether (9: 2) to give hydroperoxide derivative[18].

3-Phenyl-2-propenal [*trans*-cinnamaldehyde] (1a): R_f = 0.41, Colourless oil, C_9H_8O (M 132.154). IR spectrum, (KBr, ν_{max}, cm^{-1}): 3008, 2928, 2847, 1747, 1677, 1629, 1473, 1241, 1165. ^{1}H NMR spectrum, δ, ppm: 6.69 dd (1H, 2′- H, *J* = 8,16 Hz) 7.36-7.5 comp. pat. (5H, phenyl protons), 7.57d (1H, 3′-H, *J* = 8 Hz), 9.68 (1H, CHO, *J* = 8 Hz). ^{13}C NMR spectrum, δ ppm: 128.4 (C4), 128.6 (C3, C5), 129.1 (C2, C6), 131.2 (C3′), 134 (C1), 152.7 (C2′), 189.9 (CHO), *m/z* 132 (M^+).

***cis*-Cinnamaldehyde (1b):** R_f = 0.5, Colourless oil, C_9H_8O (M 132.154). IR spectrum of **1b** had an absorption bands as in the case of **1a**. ^{1}H NMR spectrum, δ, ppm: 6.2 dd (1H, 2′- H, *J* = 4.12 Hz) 7.23-7.34 comp.pat. (5H, phenyl protons), 7.57d (1H, 3′-H, *J* = 12 Hz), 9.7d (1H, CHO, *J* = 4 Hz). The other protons spectra as in the case of **1a**.

3-Phenyl-2,3-epoxypropanal or (3-phenyl-oxirane-2-carbaldehyde) cinnamaldehyde epoxide (2): Colourless oil, $C_9H_8O_2$ (M 148.154). IR spectrum, (KBr, ν_{max}, cm^{-1}): 3007, 2925, 1752, 1675, 1619, 1450, 1163. ^{1}H NMR spectrum, δ, ppm: 3.55 comp. pat. (1H, 2-H) 3.69 comp.pat. (1H, 3′-H)), 7.2-7.4 comp. pat. (5H, phenyl protons), 9.76 d (1H, CHO, J = 8 Hz). ^{13}C NMR spectrum, δ ppm: 41 ($C^{2'}$), 62 ($C^{3'}$), 126.3 (C^2), 126,4 (C^6), 129.5 (C^3), 129.6 (C^4), 129.7 (C^5), 137.3 (C^1), 190 (CHO). GC-MS data:retention time 10.050 min; *m/z* (Irel %): 148(20) [M^+], 132 (8) [M-O$^+$], 120 (40) [M-CO]$^+$, 103 (10) [M-CO_2H]$^+$, 91(100), 78(10) [C_6H_5]$^-$.

3-Phenyl- acrylic acid or (3 phenyl-2-propenoic acid) (3), (*trans* cinnamic acid): Yield (60 %) white crystal, m.p. 99.5 °C, $C_9H_8O_2$ (M 148.154). IR spectrum, (KBr, ν_{max}, cm^{-1}): 3426, 3058, 2925, 2735, 1726, 1670, 1614, 1583, 1450, 1100. ^{1}H NMR spectrum, δ, ppm: 6.5 d (1H, 2′- H, *J* = 13Hz) 7.2-7.5 comp.pat. (5H, phenyl protons), 7.9 d (1H, 3′-H, *J* = 13 Hz)), 10.045 (1H, COOH). ^{13}C NMR spectrum, δ ppm: 117 ($C^{2'}$), 127.07 (C^2), 127,4 (C^6), 127.9 (C^3), 128.2 (C^4), 128.8 (C^5), 157.7(C^1), 178 (COOH). GC-MS data:retention time 13.68 min; *m/z* (Irel %): 148(5) [M^+], 120 (4) [M-CO]$^+$, 103 (70) [M-CO_2H]$^+$, 91(50), 78(15) [C_6H_5]$^-$, 46 (100) [HCOOH].

Phenyl-(3-phenyl-allylidene)amine (4): (Yield (85 %) dark yellow crystal, m.p. 105 °C, $C_{15}H_{13}N$ (M 207.264). IR spectrum, (KBr, ν_{max}, cm^{-1}): 3049.3, 1650, 1596, 1311.5, 1153. ^{1}H NMR spectrum, δ, ppm: 7.14 comp. pat. (5H, phenyl protons) 7.21 t (1H, 3-H, *J* = 7 Hz), 7.26 d (1H, 4-H, *J* = 7Hz), 7.4 comp. pat. (5H, phenyl protons in aniline), 7.55 d (1 H, 2-H, *J* = 7 Hz). ^{13}C NMR spectrum, δ ppm: 162 (C^2), 152 (C^4), 144 (C^3), 136 ($C^{1'}$ phenyl of aniline), 129.5 ($C^{1''}$phenyl), 129 ($C^{3'}$,$^{5'}$ phenyl of aniline), 128.5 ($C^{3''}$,$^{5''}$ phenyl), 128 (4″ phenyl), 127 ($C^{4'}$ phenyl), 126 ($C^{2''}$,$^{6''}$ phenyl), 121 ($C^{2'}$,$^{6'}$ phenyl of aniline). Mass spectrum; *m/z* (Irel %): 208(15) [M + 1], 207 (100) [M^+].

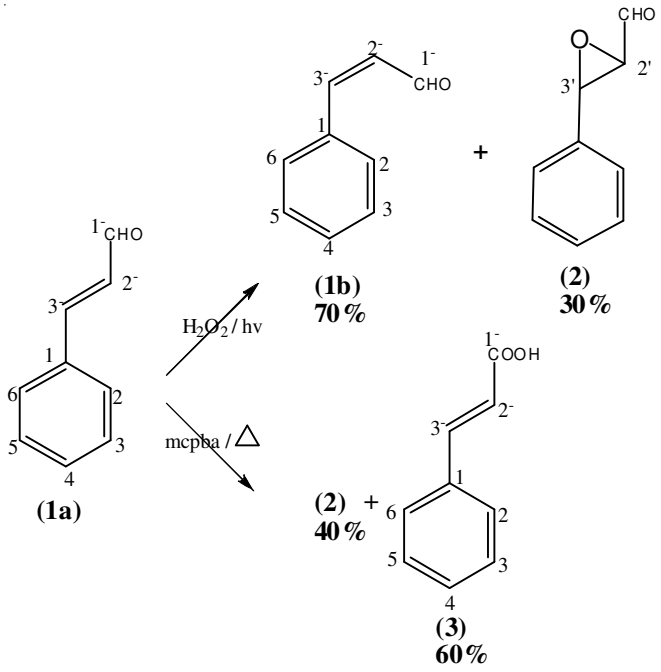
1-Phenyl-3-phenyl-imino-propen-1yl-hydroperoxide) 5: (Yield (25 %) pale yellow oil, $C_{15}H_{13}NO_2$ (M 239.264). IR spectrum, (KBr, ν_{max}, cm^{-1}): 3504, 3056, 2830, 1623, 1456, 1240, 1127. ^{1}H NMR spectrum, δ, ppm: 9.71 S (1H, OOH), 8.28 d (1H, 3-H, *J* = 7 Hz)), 7.71 d (1H, 2-H, *J* = 7Hz), 7.17-7.55 comp. pat. (10 H, 2 phenyl protons). ^{13}C NMR spectrum, δ ppm: 162.7 (C^3), 163 (C^1), 135 ($C^{1'}$), 133 ($C^{1''}$), 130 (C^3, $^{5'}$), 129.2 ($C^{3''}$, $^{5''}$), 128.8 ($C^{4'}$, $^{4''}$), 127.5 ($C^{2''}$, $^{6''}$), 120 ($C^{2'}$, $^{6'}$), 68.2 (C^2).

RESULTS AND DISCUSSION

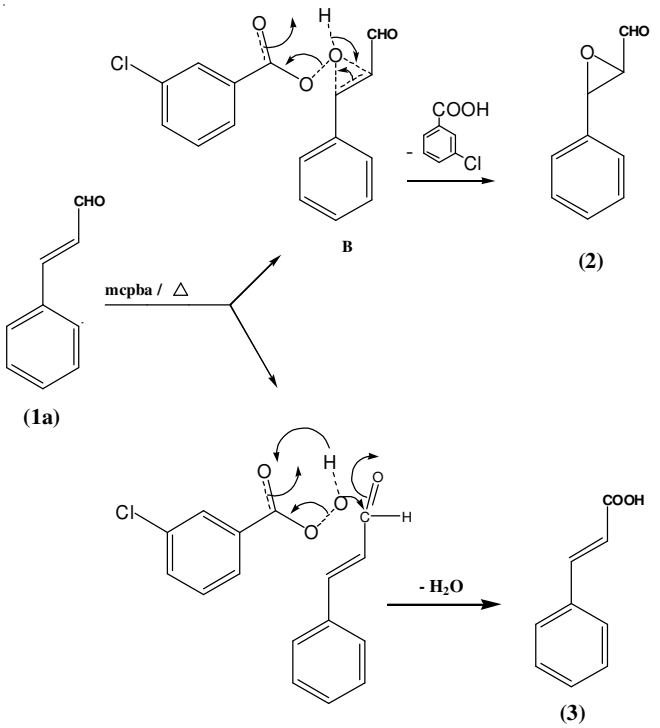
***trans*-Cinnamaldehyde:** [3-phenyl-propenal] (**1**) is the major component of essential oil of cinnamon, which was extracted from *Cinnamomum veru*.

The chemical structure of **1a** was confirmed by spectral measurements. ^{1}H NMR spectrum of **1a** showed doublet at δ 9.68 from proton of aldehyde group, and side-chain olefinic protons on C^2 and C^3 resonated, respectively, as a doublet of doublet at δ 6.69 ppm and a doublet at 7.54 ppm.

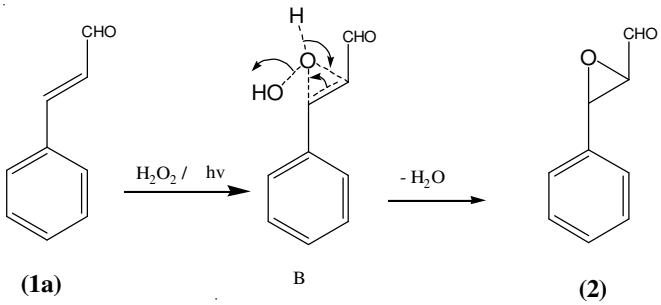
^{13}C NMR spectrum of **1a**, the C^2 and C^3 signals were located at δ_c 134.0 and 152.7 ppm, respectively. signal at δ_c 189.5 ppm for C^1 carbonyl group. Photochemical epoxidation of *trans*-cinnamaldehyde (**1a**) with hydrogen peroxide (H_2O_2, 30 % by volume) in ethanolic medium under irridation with sodium light (irradiation time 15 h) to give 30 % cinnamaldehyde epoxide (**2**) and 70 % of *cis*-cinnamaldehyde (**1b**) (**Scheme-I**). The structures of epoxidation products **1b** and **2** were established by spectral measurements. IR spectrum of **1b** had an absorption band as in the case of **1a**. ^{1}H NMR spectrum of **1b** showed doublet at δ 9.7 from proton of aldehyde group and side-chain olefinic protons on C^2 and C^3 resonated respectively, as a doublet of doublet at δ 6.2 ppm and a doublet at δ 7.57 ppm. The other protons spectra as in the case of **1a**. Compound **2** displayed in ^{1}H NMR two complex patern at δ 3.55 ppm and δ 3.69 ppm for 2′-H and 3-H in oxirane ring respectively. ^{13}C NMR spectrum of **2** showed signals of the oxirane carbon atoms at δ 41 ($C^{2'}$) and 62 ppm ($C^{3'}$). The mass spectrum of **2** contained the molecular ion peak at *m/z* 148. Thermal oxidation of *trans*-cinnamaldehyde (**1a**) with *m*-chloroperoxy benzoic acid in chloroform at room temperature gave 40 % cinnmaldehyde epoxide (**2**) and 60 % of cinnamic acid (**3**) (**Schemes-I** and **II**). The structure of **3** was established by spectral measurements. IR spectrum had two absorption bands at 1726 and 3426 cm^{-1} due to the carbonyl and the hydroxyl groups respectively. On the other hand, the OH proton



Schemes-I: Thermal and Photoepoxidation reactions



Scheme-II: Thermalepoxidation mechanism



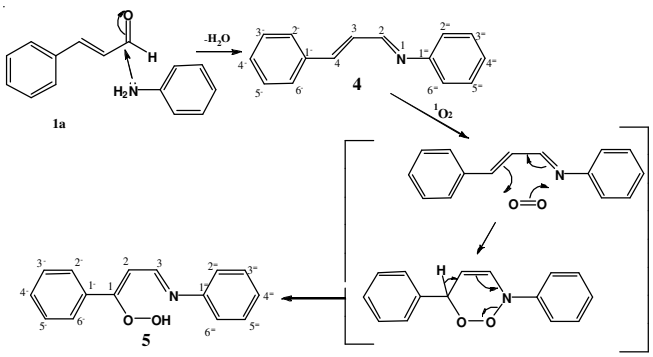
Scheme-III: Photoepoxidation mechanism

signal appeared in ^{1}H NMR spectrum as a singlet at δ_H 10.04 ppm. The carboxylic carbon atom resonated in the ^{13}C NMR spectrum at δ 178 ppm, and the molecular ion peak in the mass spectrum of **3** was at *m/z* 148. Attempts to photooxidation *trans*-cinnamaldehyde (**1a**) failed even when the irradiation time was prolonged.

Cinnamaldehyde derivative phenyl-(3-phenyl-allylidene amine (Schiff base) (**4**) was prepared by means of condensation of the respective carbonyl component in *trans*-cinnamaldehye with aniline[19].

Interestingly, the photo induced oxygenation of compound **4** in the presence of tetraphenylporphin (TPP) as singlet oxygen sensitizer led to the formation of 1-phenyl-3-phenylimino-propen-1-yl hydroperoxide (**5**) as sole photo-products.

The structure of **5** was established by spectral measurements. IR spectrum of **5** showed signal at 3504 cm^{-1} for OOH group and signal at 1127 cm^{-1} for C=N group. ^{1}H NMR spectrum of **5** showed two protons doublet at δ 8.28 ppm and δ 7.71 ppm for 3-H and 2-H, respectively. A complex multiplet at δ 7.17-7.55 ppm for **2** phenyl protons and a singlet at δ 9.71 ppm due to proton in the hydroperoxide group. Signals at δ_C 135.2 and δ_C 162.7 ppm in ^{13}C NMR spectrum of **5** were as



Scheme-IV: Photosensitized oxygenation of Schiff base

signed to C^2 and C^3. The hydroperoxide carbon atom resonated at δ_C 179.7 ppm.

A probable mechanism for the formation of epoxy derivative **2** is believed to involve oxirane intermediate **B**; elimination of water or *m*-chlorobenzoic acid molecule, depending on the oxidant used, gives the final product (**Schemes-II** and **III**).

Scheme-IV illustrates a probable mechanism of the photosensitized oxygenation of phenyl-(3-phenyl-allylidine)amine (**4**) in the presence of tetraphenylporphin (TPP) leading to formation of endoperoxide through [2 + 4] cyclo addition. The endoperoxide undergo further breaking to form hydroperoxide **5**, the endoperoxide intermediate could not be isolated. The hydroperoxide derivative 1-phenyl-3-phenyl-imino-propen-1-yl hydroperoxide (**5**) was primary photo-tested by mixed it with DNA. The resulting solution was irradiated using a sodium lamp. The primary results showed a moderate degree of DNA degradation. It has been concluded that *trans*-cinnamaldehyde and its derivatives can act as antioxidants. They were trapped the reactive oxygen species (ROS) to give the intermediated epoxides and hydroperoxide derivatives, which could be alkylated or damage DNA, proteins and other biological species.

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