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Short Report

Synthesis and Stereochemical Assignment of Methyl 3-(3-hydroxyphenoxy)acrylate *via cis-trans* Photoisomerization

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3-(3-Hidroxi-fenoxi)acrilato de metila (**2**), um novo e importante material de partida para inúmeras reações e um precursor potencial do produto natural 3-(3-hidroxi-fenoxi)-2-propenal (**1**), foi sintetizado a partir de resorcinol e propiolato de metila. A configuração *trans* da dupla ligação presente no composto **2** foi confirmada através de uma reação de fotoisomerização.

Methyl 3-(3-hydroxyphenoxy)acrylate (**2**), a new and important starting material for several reactions and a potential precursor of the natural product 3-(3-hydroxyphenoxy)-2-propenal (**1**), was synthesized from resorcinol and methyl propiolate. The *trans* configuration of the double bond present in **2** was confirmed through a photoisomerization reaction.

Keywords: methyl 3-(3-hydroxyphenoxy)acrylate, 3-(3-hydroxyphenoxy)-2-propenal, photoisomerization reaction, synthesis

Introduction

The phytochemistry of *Artemisia* has been extensively investigated in the last few years.[1,2] This medicinal plant produces highly oxygenated sesquiterpenes that can be applied to the treatment of malaria.[1] Examples of such compounds are the potent anti-malarial drug artemisinin and its derivatives, which can be isolated from the aerial parts of *Artemisia annua L.*[2] However, their natural occurrence is very low, which has led to intensive research efforts toward the production of new biotechnological strategies or synthetic ways to enhance their production.[1,2] Apart from highly oxygenated sesquiterpenes, several other aromatic compounds such as coniferaldehyde derivatives and 5-alkyl resorcinols have also been isolated from *Artemisia annua L.*[3] It has also been reported[4] that *Artemisia subdigitata Mattf.* contains flavonoids, coumarins, substituted phenols, and a number of compounds that have not been previously described, like 3-(3-hydroxyphenoxy)-2-propenal (**1**) shown in Figure 1.

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The *cis* to *trans* photoisomerization of organic molecules has found large application in biochemical processes;[5] e.g., the photon signal transduction of rhodopsin in the visual process.[6] The interconversion of *cis*- to *trans*-olefins is a thermodynamically spontaneous process but, in the absence of radical initiators, this conversion usually occurs very slowly at room temperature. Light absorption by olefins leads to a photoisomerization process. Sometimes, the more stable isomer can be transformed into the less stable one upon light irradiation. This process can proceed either *via* the π,π^* singlet (S_1) or triplet (T_1) excited states. Any of the isomers can be formed when the molecule returns to the ground state (S_0), because both the S_1-p state and the T_1-p state have a perpendicular geometry. The barrier of the isomerization process is lowered when there is conjugation of the carbon-carbon double bond with a heteroatomic π-system.[5] The mechanism of acrylate isomerization is dependent on the presence of other compounds in the solution, such as nucleophiles[7] or radicals.[8]

The goal of this paper is to report a short synthetic route for the preparation of methyl 3-(3-hydroxyphenoxy) acrylate (**2**), a new and potential precursor of the natural product 3-(3-hydroxyphenoxy)-2-propenal (**1**) isolated

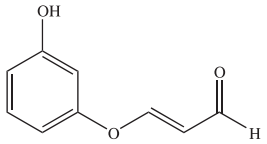

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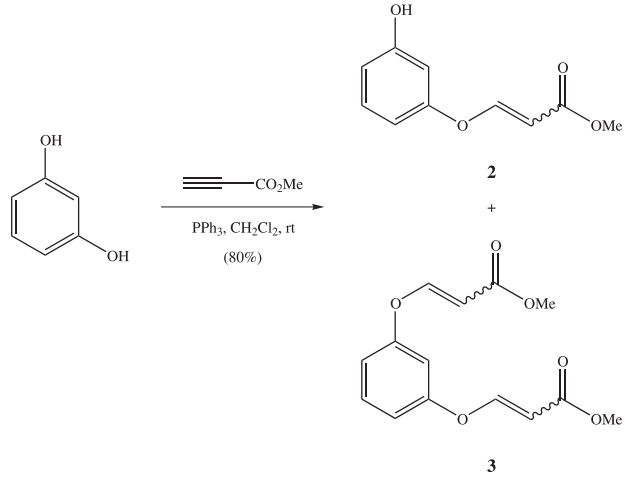
Figure 1. A natural product from *Artemisia subdigitata Mattf.*

from *Artemisia* species. Because it was not possible to obtain the correct configuration of the acrylate double bond in the ester derivative **2** from the magnitude of the vicinal coupling constant of the NMR spectra, a simple *cis-trans* photoisomerization experiment was used to produce the *cis* isomer. The photoisomerization reaction was followed by NMR and UV-Vis spectroscopic measurements from time to time. Determination of the configuration of the initial synthetic natural product and an estimation of the *trans-cis* interconversion rate were obtained from the experimental data.

Results and Discussion

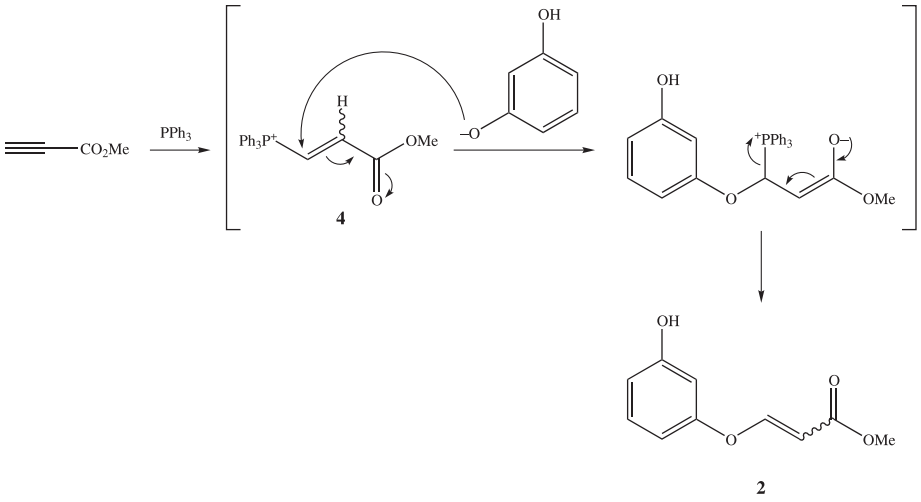
Compound **2** was synthesized from commercial resorcinol (1,3-dihydroxybenzene). Initially, resorcinol and triphenylphosphine were dissolved in dichloromethane. A solution of methyl propiolate in dichloromethane was slowly added to this solution, and the mixture was kept under stirring for 24 h at room temperature.[9] The residue was purified by column chromatography on silica gel. Analysis by ^{1}H and ^{13}C NMR spectroscopy revealed that the product was a mixture of compounds **2** and **3** with yields of 65% and 15%, respectively (Scheme 1).



Scheme 1. Synthesis of compounds **2** and **3**.

Yavari, Hekmat-Shoar and Zonousi[9] performed reactions between substituted phenols and dimethyl acetylenedicarboxylate (DMAD) in the presence of triphenylphosphine under reflux in dichloromethane, and they obtained coumarins in good yields. They assumed that the addition of triphenylphosphine to the acetylenic ester followed by protonation would result in an intermediate vinyltriphenylphosphonium salt. The formation of coumarins should occur by an eletrophilic attack of this vinyltriphenylphosphonium species on the aromatic ring and further intramolecular lactonization.

It has been reported[10] that the coumarin ring could not be produced in a reaction similar to the one described in this work, but it was produced through a process carried out under milder conditions. An unusual *O*-conjugate addition reaction of the phenol to methyl propiolate must have occurred in our case,[11-13] furnishing compounds **2** and **3**. Usually, the *O*-conjugate addition is not very common for most enolate conjugate addition reactions. However, in our work, *O*-addition was especially favored because the



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2

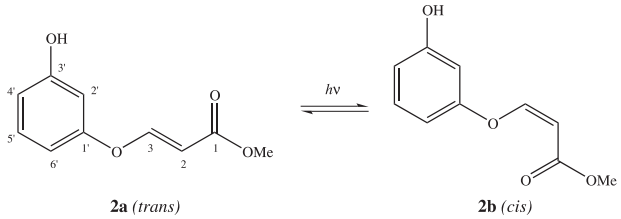
Scheme 2. Proposed reaction mechanism for the preparation of compound **2**.

nucleophile is stabilized and the electrophile has a hard leaving group.

A reasonable mechanism for this addition reaction[9,11-13] is shown in Scheme 2. The first step of the process involves a Michael addition of triphenylphosphine to the propiolate, thus generating an active phosphonium intermediate (**4**). This latter species undergoes a subsequent addition of the phenoxide in a 1,4-fashion, followed by elimination of triphenylphosphine, to afford compound **2**.

Derivative **2** was prepared and its structure was identified spectroscopically. However, the determination of the alkene configuration was not possible. Typically, the stereochemical assignment of the acrylate double bond is based on the magnitude of the vicinal coupling constant (*J*) of the corresponding hydrogens in the ^{1}H NMR spectra. The range for *trans* and *cis* isomers are, respectively, 12 to 18, and 6 to 12 Hz. The value measured for compound **2** was 12.1 Hz, making an unequivocal attribution extremely difficult.[14]

Therefore, in order to correctly assign the stereochemistry of the double bond of compound **2**, we carried out a photoisomerization reaction (Scheme 3). The photoisomerization experiment was carried out in a rotating "merry-go-round" reactor using a 400 W medium pressure mercury lamp.[15] A solution of **2** was prepared in deuterochloroform, and placed into two quartz cuvettes. The first cuvette was a resonance tube and the second one a UV-Vis spectroscopic cell. Both quartz cuvettes were inserted into the photoreactor. At appropriate time intervals, the rotating "merry-go-round" was stopped; the cuvettes were withdrawn from the reactor and allowed to cool down to room temperature. The ^{1}H NMR and UV-Vis spectra were registered. Then both cuvettes were replaced at the same time into the photoreactor and the irradiation process was resumed.



2a *(trans)* **2b** *(cis)*

Scheme 3. Photoisomerization of compound **2**.

The UV absorption spectra of the *trans* and *cis* isomers of compound **2** (Figure 2) are very similar, so very little information could be obtained from the spectrophotometric analysis.

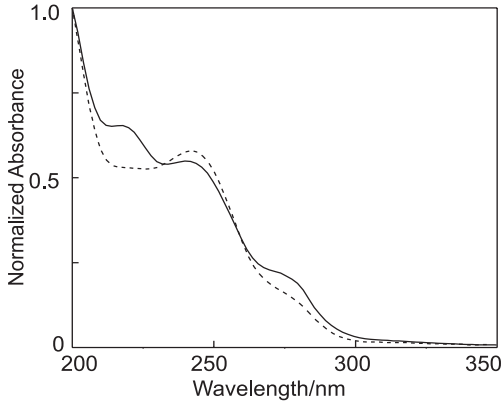


Figure 2. UV spectra of compounds **2** (*trans* dotted line and *cis* full line) in acetonitrile.

However, after 12 h of irradiation, the formation of isomer **2b** was observed in the ^{1}H NMR with 25% yield (Figure 3).

Figure 3A shows the ^{1}H NMR spectrum of compound **2a** before the irradiation, while Figure 3B reveals the appearance of a new set of NMR signals after 12 h of

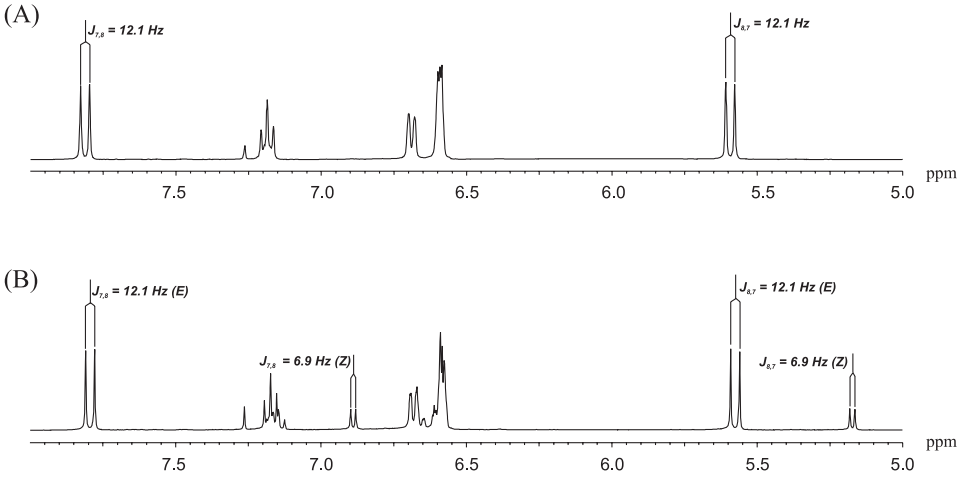


Figure 3. ^{1}H NMR spectra: (A) Isomer **2a**; (B) Mixture of isomers (**2a** + **2b**), after 12 h of irradiation.

irradiation. The *J* values measured between H-2 and H-3 (Scheme 3) show that the double bond of the isomer **2b** formed after irradiation has a *cis* configuration (*J* 6.9 Hz), so the double bond of compound **2a** must have a *trans* configuration (*J* 12.1 Hz). Changes in the chemical shift of hydrogens H-2 and H-3 for each isomer were also noted after the induced isomerization. Analyses of the integration values for H-2 or H-3 showed that formation of the *cis* isomer (Figure 4) is slow under our experimental conditions. A *trans-cis* interconversion rate of 6.7×10^{-5} s^{-1} was estimated.

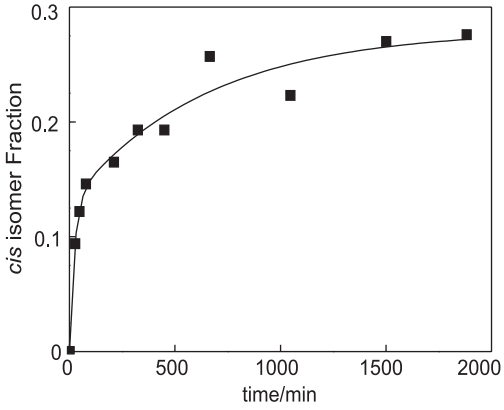


Figure 4. Formation of the *cis* isomer of compound **2** as a function of time.

After the irradiation reaction was completed, the mixture of the two isomers (**2a** and **2b**) was stored at low temperature for several months. The ^{1}H NMR spectrum of this mixture was then registered, showing that the *cis* isomer is highly stable. No interconversion took place during this period.

Conclusions

This work demonstrates the successful synthesis of methyl 3-(3-hydroxyphenoxy)acrylate (**2**), a new compound that is a potential precursor of the natural product 3-(3-hydroxyphenoxy)-2-propenal (**1**). By means of a photoisomerization reaction, we confirmed that the double bond present in **2** is *trans* (isomer **2a**).

Experimental

General experimental procedures

Dichloromethane and the common reagents resorcinol (1,3-dihydroxybenzene), triphenylphosphine and methyl propiolate are commercially available. Column chromatography separation was performed with silica gel 60 (70-230 mesh, Merck). All ^{1}H and ^{13}C NMR spectra were recorded at 400 and 75 MHz, respectively, using a Bruker DPX-400 instrument and chloroform-*d* ($CDCl_3$) or methyl-d_3 alcohol-*d* (CD_3OD) as solvent; chemical shifts are in ppm downfield from a tetramethylsilane internal standard. UV-Vis absorption spectra were measured on a Hitachi U-3000 UV-Vis spectrophotometer. IR (KBr) spectra were measured on a Perkin Elmer Spectrum RX IFTIR System, and the most intense or representative bands are reported (in cm^{-1}). GC-MS analyses were performed by EI ionization at 70 eV on a Shimadzu GC/MS QP-2010 spectrometer. Elemental analyses were performed with a Carlo Erba instrument EA-1110. The rotating "merry-go-round" a pparatus used a Hanovia 400 W medium pressure mercury lamp, together with a cooling immersion well.

*Methyl (2E)-3-(3-hydroxyphenoxy)acrylate (**2a**) and dimethyl (2E, 2'E)-3,3'-[1,3-phenylene-bis(oxy)] diacrylate (**3**)*

A solution of methyl propiolate (0.1651 g, 1.96 mmol) in dichloromethane (5 mL) was slowly added (10 min) to a stirred solution of triphenylphosphine (0.3430 g, 1.31 mmol) and resorcinol (0.1440 g, 1.31 mmol) in dichloromethane (30 mL), cooled to –5 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel, using *n*-hexane and ethyl acetate in a 7:3 ratio as eluent, to afford a mixture of compounds **2a** (0.1651 g, 65%) and **3** (0.0546 g, 15%).

*Analytical data for compound **2**a*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, 1H, *J* 12.1 Hz), 7.18 (t, 1H, *J* 8.3 Hz), 6.69 (ddd, 1H, J_1 1.0 Hz, J_2 2.3 Hz, J_3 8.3 Hz), 6.59 (m, 2H), 5.60 (d, 1H, *J* 12.1 Hz), 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7 (C), 159.5 (CH), 157.5 (C), 156.9 (C), 130.6 (CH), 112.2 (CH), 109.6 (CH), 105.4 (CH), 101.5 (CH), 51.7 (CH_3). IR ν/cm^{-1}: 3394 (O-H), 3056 (C-H, aromatic), 1718 (C=O, ester), 1654 (C=C); 1266 (C-O). MS: *m/z* (relative intensity) 194 (M^+, 98%), 163 (86), 135 (100), 121 (22), 107 (50), 94 (25), 81 (18), 69 (66), 65 (51), 53 (29). Anal. Calc. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19; O, 32.96. Found: C, 61.62; H, 4.98; O, 33.40.

*Analytical data for compound **3***

^{1}H NMR (MeOD, 400 MHz) δ 7.77 (d, 2H, *J* 12.1 Hz), 7.35 (t, 1H, *J* 8.3 Hz), 6.89 (dd, 2H, J_1 2.4 Hz, J_2 8.3 Hz), 6.84 (t, 1H, J_1 2.3 Hz), 5.51 (d, 2H, *J* 12.1 Hz), 3.52 (s, 6H). ^{13}C NMR (MeOD, 75 MHz) δ 168.0 (C), 158.8 (CH), 157.4 (C), 131.5 (CH), 114.1 (CH), 107.8 (CH), 102.4 (CH), 50.9 (CH_3). IR ν/cm^{-1}: 3072 (C-H, aromatic), 1714 (C=O, ester), 1652 (C=C), 1260 (C-O). MS: *m/z* (relative intensity) 278 (M^+, 85%), 247 (49), 219 (78), 215 (31), 205 (15), 187

(100), 163 (39), 147 (16), 131 (18), 118 (31), 108 (47), 92 (18), 77 (17), 69 (18), 64 (26), 59 (47), 53 (15). Anal. Calc. for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07; O, 34.50. Found: C, 60.81; H, 5.12; O, 34.07.

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