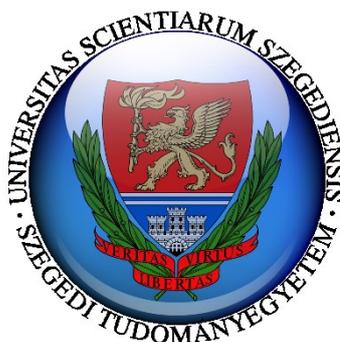


# STEREOSELECTIVE SYNTHESIS AND SELF-ASSEMBLING CAPABILITIES OF HETEROCYCLIC CINNAMIC ACID

PhD Theses

**CSANKÓ KRISZTIÁN**



Supervisors: DR. PÁLINKÓ ISTVÁN

DR. SIPOS PÁL

Doctoral School of Chemistry

Material and Solution Structure Research group

Department of Organic Chemistry

Department of Inorganic and Analytical Chemistry

Faculty of Sciences and Informatics | University of Szeged

Szeged, Hungary

**2015**

## 1. INTRODUCTION

*Cinnamic acid* (*E*-3-phenylpropenoic acid) is a well-known material found in *cinnamon*, which was mentioned for the first time on ancient Egyptian hieroglyphs (2000 B.C). The oil of leafs and the bark of *Cinnamomum Verum* (cinnamon plants are native in *Sri Lanka*) contain *cinnamaldehyde* as a main component (50–80%) and several percent of *esters* and *terpenes*. *Cinnamon* (the bark of the plant and the oil of the leafs) has been widely used as flavor and food preservative for thousands of years, because some of its components, mostly the *cinnamic acid* derivatives, have antimicrobial effect on pathogenic bacteria and on human diseases like upper respiratory tract infection caused by *Pneumococcus*. As it was mentioned, *cinnamic acid* can be found in *cinnamon*, due to the slow oxidation of *cinnamaldehyde* to the more stable *E-cinnamic acid* on contact with air.

*Cinnamic acid* was synthesized first by *W.H. Perkin* in 1868 but, its use and those of its derivatives were delayed until world war II., where the first UV-protective sunscreen was prepared from *cinnamate esters* for the soldiers fighting in the Pacific area. The second “big boom” in the history of *cinnamic acid*, came at the late 80’s, when it gained importance as sample matrix in the MALDI–MS technique due to its high absorbance in the UV range (the average molar extinction coefficient is around  $19556 \text{ M}^{-1}\text{cm}^{-1}$ ).

The substituted derivatives of *cinnamic acids* and some heteroatom-containing derivatives came into the focus of our research group, since they proved to be good models for studying *hydrogen bonding* driven assembling in solutions as well as in the solid state. It was found that they were capable of short- and long-range ordering in solution and the solid state, respectively. The fundamental units were found to be the dimers, kept together by strong *hydrogen bonds*, while the multimers of the dimers interacting with weaker (aromatic)C–H...X (where X = O, N, S) close contacts.

In most of these studies, the combination of spectroscopic methods and molecular modelling was applied for the characterization of the structure-forming interactions.

At the beginning of my doctoral work, several goals have been set out. They are as follows:

1. finding an inexpensive, successful synthetic way to prepare stereochemically pure *E-2 and/or 3-(furyl/thienyl/pyridyl/selenophenyl)cinnamic acids*;
2. finding an expedient and affordable way for the preparation of commercially not accessible *Z-2 and/or 3-(furyl/thienyl/pyridyl/selenophenyl)cinnamic acids*;
3. studying the *self-assembling* features of the above molecules and many of their substituted varieties in solution, the solid state and the adsorbed phase on metal surfaces (*gold* and *silver*), identifying the possible secondary interactions, with the combination of various spectroscopic measurements (<sup>1</sup>H NMR, IR) and surface inspection techniques (SEM, AFM, IRM);
4. complementing the experimental results with computational methods at high theoretical level (geometry and energy calculations for the aggregates, including the computation of precise energies of the secondary bonds and the full conformational analysis of the individual molecules and, occasionally the dimers as well).

## 2. EXPERIMENTAL PART

### Studied materials and their synthesis

The following substances were available at the beginning of my work: *E*- and *Z*-2-phenyl-3-(2-thienyl)propenoic acids, *E*- and *Z*-2,3-di(3-thienyl)propenoic acid, *E*- and *Z*-2-phenyl-3-(3-thienyl)propenoic acid, *E*- and *Z*-2,3-di(2-thienyl)propenoic acid, *E*- and *Z*-2-(2-thienyl)-3-phenylpropenoic acid, *E*- and *Z*-2-(2-thienyl)-3-(3-thienyl)propenoic acid, *E*- and *Z*-2-(3-thienyl)-3-phenylpropenoic acid, *E*- and *Z*-2-(3-thienyl)-3-(2-thienyl)propenoic acid. All of them were prepared via the modified *Perkin* condensation, from the corresponding *aldehyde* and *acetic acid* derivative, in the presence of *acetic anhydride* and *triethylamine* under 1 hour at 100°C. The produced *E* and *Z*-isomers were separated through column chromatography, on *Normasil 60 silica gel*.

The following *heterocyclic cinnamic acid* derivatives: *E*-3-(2 and 3-furyl)propenoic acids, *E*-3-(2 and 3-thienyl)propenoic acids, *E*-3-(2-selenienyl)propenoic acids and *E*-3-(2,3 and 4-pyridyl)propenoic acids were prepared with the modified *Knövenagel-Döbner* condensation of the proper *heterocyclic aldehyde* (which freshly distilled under reduced pressure before usage) and *malonic acid* in *pyridine*, in the presence of a catalytic amount of *piperidine*. The selectivity was 100% for the *E isomer* and the yields were excellent, >95%.

The corresponding *Z isomers* were synthesized in two different ways: with the photoisomerization of the *E isomers* (0.05 M in *ethyl acetate*), using a 1 W UV-source with 254 nm emission maximum, applying 12 hour long irradiation. The other way was a 7 step method, which utilize the *Horner-Wadsworth-Emmons* (HWE) olefination reaction via a *Z-selective* reagent, the *Ando-phosphonate* (*bis-o-cresyl-trimethyl phosphonoacetate*). The starting material was *methyl chloroacetate*, which is converted to *methyl iodo acetate* with *sodium iodide* via  $S_N2$  substitution. The resulting material was reacted with *trimethyl phosphite* in *Arbuzov* reaction to prepare *trimethyl phosphonoacetate*, which is the "traditional" HWE reagent. The *methyl* groups were substituted to trimethylsilyl with *chloro-trimethylsilane* and then the corresponding *methyl-dichloro phosphonoacetate* was synthesized with *oxalyl chloride*. The *Ando* reagent prepared via the esterification with the previous compound and *o-cresol* in *trimethylamine*, in the presence of *4-dimethylaminopyridine* (DMAP). The final

condensation was performed under cryogenic condition ( $-78^{\circ}\text{C}$ ) in *tetrahydrofuran* (THF), with the proper purified *aldehyde* and *t-butoxy potassium*, than the resulting *methyl esters* were cleaved in THF/KOH. The average selectivity was 90:10, *Z:E* and the yield was  $>90\%$ .

For the  $\alpha$ -substituted *pyridylcinnamic acids*, the modified *Perkin* reaction was utilized between *3-pyridineacetic acid* and *benzaldehyde*, to prepare *Z-2-(3-pyridyl)-3-phenylpropenoic acid*, and the *HWE* reaction with *2-phenyl-trimethyl phosphonoacetate* and *3-pyridinecarboxaldehyde* (under the mentioned conditions) to synthesize *E-2-phenyl-3-(3-pyridyl)propenoic acid*.

### Structural characterization and structure-forming properties

The structures of the synthesized materials were checked by  $^1\text{H}$  *nuclear magnetic resonance spectroscopy* (NMR) in each case on a Bruker Avance 500, 500 MHz spectrometer in 99 atom%  $\text{CDCl}_3$ ,  $\text{CD}_3\text{OD}$ ,  $\text{D}_2\text{O}$  or in  $\text{DMSO-d}_6$ .

The structure-forming properties were studied with *infrared spectroscopy* (IR) in the solid and the liquid phase in *chloroform* or in *dimethyl sulfoxide* (DMSO). For the measurements, a Bio-Rad FTS 60-A FT-IR spectrometer was applied. Each spectrum was collected between  $4000\text{--}400\text{ cm}^{-1}$  with  $4\text{ cm}^{-1}$  resolution and 256 accumulations. Numerous techniques was applied including *attenuated total reflection* (ATR) and 1 wt% KBr pellet method for the solid state measurements and NaCl cuvette (0.2 mm liquid film) in transmission mode for the liquid state measurements in the 0.001–0.1 M concentration region.

The weak *hydrogen bonds* were identified with  $^1\text{H}\text{--}^1\text{H}$  *correlation spectroscopy* (COSY) in saturated DMSO solutions, and the conformational space was discovered as well in diluted DMSO solution (0.05 M) with the *nuclear Overhauser effect spectroscopy* (NOESY) method on the same instrument, using 16–64 accumulation for both COSY and NOESY spectra at  $1024\times 512$  resolution.

The possible layered structures were studied by *powder X-ray diffractometry* (XRD). The diffractogram, registered in the  $2\theta = 5\text{--}35^{\circ}$  region on a Rigaku Miniflex II instrument, using  $\text{CuK}\alpha$  ( $\lambda = 1.5418\text{ \AA}$ ) radiation in *Bragg-Brentano* geometry. Reflection positions were determined *via* fitting a *Gaussian* function. They were found to be reproducible within  $0.05^{\circ}$  ( $2\theta$ ).

For the *self-assembling* experiment, 100 nm thick polycrystalline metal layers were created via the *pulsed laser deposition* (PLD) technique. For the measurements, 30×30 mm glass microscope slides were applied as substrates, and 99.99% *gold* and *silver* (Good Fellow) plates as targets. The applied laser was a *krypton fluoride* (KrF) excimer laser ( $\lambda = 248$  nm) focused on the metal target in a 5 mm<sup>2</sup> spot. The pulse length was 18 ns, the repeating frequency was 10 Hz, and the energy of a single impulse was 106 mJ/pulse.

The metal layers were treated with the 0.001M–0.1 M solution in *chloroform* of the studied materials for 48 hours. The resulting plates were studied with *infrared microspectroscopy* (IRM) to determine the success of the adsorption. The measurements were performed on a Bruker Vertex 70 IRM instrument collecting the spectra in total reflection mode from the focused area of the proper surface (1–0.1 mm<sup>2</sup>). A liquid *nitrogen* cooled MCT detector was used to collect observable intensities. Each spectrum was created from 1024 accumulated scans with 2 cm<sup>-1</sup> resolution in the 4000–400 cm<sup>-1</sup> region. The topology of the *self-assembled* layers were observed with *atomic force microscopy* (AFM) utilizing an NT-MDT Solver AFM microscope working in the *tapping* mode (the frequency of the cantilever was 278 kHz). The AFM needle (manufactured by Nanosensors, Inc.) was an SSS-NCH-type 15  $\mu$ m long *silicon* needle with 10° half-cone angle and 2 nm radius of curvature.

Each studied material was modelled, using the *Hyperchem 8* and the *Gaussian 09'* quantum chemical software packages. Conformational analysis was performed for the individual *cinnamic acid* monomers at HF/6-31G(d,p) level and at PM6 level for the  $\alpha$ -*substituted* variants. The resulting monomers were further optimized at higher level (B3LYP/CBSB7). The *hydrogen-bonded* dimers and tetramers were constructed from the optimized monomers as well as the  $\pi$ -*stacked* structures. Precise energy calculation was done for the multimers, using the *basis set superposition error* (BSSE) correction to achieve relevant bonding energies, which can be compared with the experimental results.

### 3. NOVEL SCIENTIFIC RESULTS

**T 1. A general synthetic way was found and optimized for the stereoselective synthesis of *E*-3-heterocyclic cinnamic acids.**

**T 1.1.** It has been found that the modified *Knövenagel-Döbner* condensation can be used as a general and cheap method with great scalability to synthesize heteroaromatic *E*-cinnamic acid derivatives with high yields (>95%) and 100% stereoselectivity, especially for the different *pyridylpropenoic acids*.

**T 2. UV-induced photoisomerization was found to be a powerful way to achieve the corresponding *Z* isomers with acceptable yields.**

**T 2.1.** An inexpensive, automated semi-continuous photoreactor system was designed, to study the photoisomerization process of *E*-heteroaromatic cinnamic acid derivatives.

**T 3. A novel method was developed for the preparation of substituted phosphonoacetates for *Z*-selective Horner-Wadsworth-Emmons olefin synthesis.**

**T 3.1.** With a novel combination of fundamental reactions, leading to *Still-Gennari* and *Ando phosphonates*, the *Z* isomers of the studied *heteroaryl*cinnamic acids were successfully synthesized, with high yield (>90%) and stereoselectivity, (90:10, *Z:E*) applying the prepared, sterically hindered *phosphornoacetates*.

**T 3.2.** The optimized method found to be a powerful tool for the synthesis of several  $\alpha$ -substituted cinnamic acids, especially for the *pyridyl* derivatives.

**T 4. A complex structural analysis method was developed for the identification of the different second-order chemical interactions between the molecules studied.**

**T 4.1.** The general approach of the identification procedure, include solid- and liquid-state *infrared spectroscopy* in aprotic solvent, for the O-H...O=C strong *hydrogen bond* and for the weaker C-H...S=C bond.

**T 4.2.**  $^1\text{H}$ - $^1\text{H}$  *correlation spectroscopy* in dipolar aprotic solvent was used for the determination of weaker (aromatic)C-H...X-(aromatic)C (X=O, N, S, Se) bonding.

**T 4.3.** *Powder X-ray diffractometry* was found to be a possible way to identify  $\pi$ -stacking interactions.

**T 5. A complex method has been devised to prepare and characterize self-assembling heterocinnamic acid derivative layers over polycrystalline metal surfaces.**

**T 5.1.** A simple and inexpensive preparation method was constructed for the preparation of self-assembling layers of *heteroaryl cinnamic acids* and their derivatives over polycrystalline *gold* and *silver* surfaces using *pulsed laser deposition* technique for the synthesis of the metal layers and the dip-coating method to create the *self-assembled* molecular layers.

**T 5.2.** Multiple surface inspection techniques were performed on the layers, including *scanning electron microscopy* to characterize the pristine metal layers, *infrared microspectroscopy* to prove the adsorption of the molecules and *atomic force microscopy* to study the orientation and the thickness of the *self-assembled* molecular layers.

**T 6. An automated standalone conformer generator and a data processing software (Quantum Hyppo v1.0 and Izzy Reader v1.0) were prepared and successfully fitted to the Gaussian 09' package.**

**T 6.1.** With this set a full conformational analysis was performed at acceptably high (HF/6-31G(d,p) for *cinnamic acids* and PM6 for the  *$\alpha$ -substituted variants*) theoretical level and the potential energy surfaces were explored as well.

**T 6.2.** Furthermore, precise energies and geometric parameters of the various secondary chemical bonds; including strong and weak *hydrogen bonds* and  $\pi$ -*stacking* interactions were also calculated.

#### 4. PRACTICAL USE OF THE RESULTS

The results presented here is of fundamental nature. Nevertheless, *cinnamic* and  $\alpha$ -*substituted cinnamic acid* derivatives offer many uses. In this work, a variety of *self-assembling* capabilities are demonstrated, especially the one over metal surfaces, which takes place at ambient circumstances. These phenomena can be useful in corrosion protection or for sensitizing the substrate in printed circuit board production. Their possible pharmacological effect is also highlighted.

## 5. PUBLICATIONS

### 5.1 Papers related to the Theses published in refereed journals

[1] **Csankó, K.**, Darányi, M., Kozma, G., Kukovecz, Á., Kónya, Z., Sipos, P. Pálinkó, I.:  
Self-assembling of Z- $\alpha$ -pyridylcinnamic acid dimers over polycrystalline Ag and Au surfaces followed by FT-IR and atomic force microscopies,  
*J. Mol. Struct.* 993, 67–72 (2011).

IF: 1.551<sub>2011</sub>

IH: –

[2] **Csankó, K.**, Illés, L., Felföldi, K., Kiss, J.T., Sipos, P., Pálinkó, I.:  
C-H...S hydrogen bonds as the organising force in 2,3-thienyl- and phenyl- or 2,3-dithienyl-substituted propenoic acid aggregates studied by the combination of FT-IR spectroscopy and computations,  
*J. Mol. Struct.* 993, 259–263 (2011).

IF: 1.551<sub>2011</sub>

IH: 5

[3] **Csankó, K.**, Forgo P, Boros, K., Hohmann, J., Sipos, P., Pálinkó I.,:  
Conformational properties of a pyridyl-substituted cinnamic acid studied by NMR measurements and computations,  
*J. Mol. Struct.*, 1044, 286–289 (2013).

IF: 1.599<sub>2013</sub>

IH: –

[4] **Csankó, K.**, Kozma, G., Valkai, L., Kukovecz, Á., Kónya, Z., Sipos, P., Pálinkó, I.:  
Self-assembling of 2,3-phenyl/thienyl-substituted acrylic acids over polycrystalline gold,  
*J. Mol. Struct.*, 1044, 32–38 (2013).

IF: 1.599<sub>2013</sub>

IH: –

[5] **Csankó, K.**, Ruusuvuori, K.I., Tolnai, B., Sipos, P., Berkesi, O., Pálinkó, I.:

Structural features of pyridylcinnamic acid dimers and their extended hydrogen-bonded aggregations

*J. Mol. Struct.*, in press, doi:10.1016/j.molstruc.2014.11.041, (2014)

IF: 1.599<sub>2013</sub>

IH: –

## 5.2 Papers related to the Theses published as full papers in conference proceedings

[1] **Csankó, K.**, Kozma, G., Kukovecz, Á., Kónya, Z., Sipos, P., Pálinkó, I.:

Kéntartalmú fahéjsav-analógok önszerveződése arany és ezüstfelületeken (Self-assembly of S-containing cinnamic acid analogues over gold and silver surfaces), *Kémiai Előadói Napok (Chemistry Lectures), (Book of abstracts)*, ISBN 978-96-331-5062-7, pp. 190-194 (2011).

IF: –

IH: –

## 5.3 Conference presentations related to the theses

[1] **Csankó, K.**, Darányi, M., Kozma, G., Kukovecz, Á., Kónya, Z., Pálinkó, I.: Self-assembly of Z- $\alpha$ -pyridylcinnamic acid dimers over polycrystalline Ag and Au surfaces followed by FT-IR and atomic force microscopies, *30th European Congress on Molecular Spectroscopy (EUCMOS 30)*, Florence (Italy), 2010, OR-3-A-B-1, (Book of Abstracts), p. 158. (Oral presentation)

[2] **Csankó, K.**, Kozma, G., Kukovecz, Á., Kónya, Z., Sipos, P., Pálinkó, I.: Tioféntartalmú fahéjsavanalógok önszerveződése ezüstfelületen, (Self-assembly of thiophene containing cinnamic acid analogues over silver surface) *OTDK Pécs*, 2011 (Oral presentation).

[3] **Csankó, K.**, Kozma, G., Kukovecz, Á., Kónya, Z., Sipos, P., Pálinkó, I.: Kéntartalmú fahéjsav-analógok önszerveződése arany és ezüstfelületeken (Selfassembling of S-containing cinnamic acid analogues over gold and silver surfaces), *Kémiai Előadói Napok (Chemistry Lectures), Program és előadásösszefoglalók (Book of abstracts)*, Szeged (Hungary), 2011, p. 190. (Oral presentation)

[4] **Csankó, K.**, Kozma, G., Valkai L., Kukovecz, Á., Kónya, Z., Sipos, P., Pálinkó, I., Self-assembling of 2,3-phenyl/thienyl-substituted acrylic acids over polycrystalline gold, *31<sup>st</sup> European Congress on Molecular Spectroscopy (EUCMOS 31)*, Cluj-Napoca (Romania), 2012, (Book of abstracts) p. 69., O-05 (Oral presentation)

[5] **Csankó K.**, Kukovecz Á., Kónya Z., Sipos P., Pálinkó I., Self-assembling capabilities of S- and N-containing cinnamic acid derivatives in solution and over polycrystalline metal surfaces, *19<sup>th</sup> International conference on chemistry (ICC 19)*, Baia Mare (Romania), 2013, (Book of abstracts) p. 22. (Oral presentation)

[6] **Csankó K.** Pálinkó I., Sipos P. Berkesi O., Self-assembling capabilities of heterocyclic cinnamic acid *1<sup>st</sup> Innovation in Science – Doctoral Student Conference*, Szeged, (Hungary), 2013, (Book of abstracts), p. 38. (Oral presentation)

[7] **Csankó K.**, Sipos P., Pálinkó I. Structural features of pyridylcinnamic acids and their extended hydrogen-bonded aggregations *32<sup>nd</sup> European Congress on Molecular Spectroscopy (EUCMOS 32)*, Düsseldorf (Germany), 2014, HB12.6 (Oral presentation)

[8] **Csankó, K.**, Kozma, G., Valkai, L., Kukovecz, Á., Kónya, Z., Sipos, P., Pálinkó, I.: Supramolecular organisation of 2,3-phenyl/thienyl-substituted acrylic acids over polycrystalline Au surface, *7<sup>th</sup> International. Symposium on Macrocyclic and Supramolecular Chemistry (ISMSC-7)*, Dunedin (New Zealand), 2012, (Book of abstracts) p. 177., P88 (Poster)

[9] **Csankó, K.**, Forgo, P., Boros, K., Hohman, J., Sipos, P., Pálincó, I.: Conformational properties of a pyridyl-substituted cinnamic acid studied by NMR measurements and computations *31<sup>st</sup> European Congress on Molecular Spectroscopy (EUCMOS 31)*, Cluj-Napoca, (Romania), 2012, (Book of abstracts) p. 322., PS2-67 (Poster)

[10] **Csankó K.**, Tolnai B., Sipos P., Berkesi O., Pálincó I. Structural features of heteroatom-containing cinnamic acid dimers and their extended, hydrogen-bonded aggregates *9<sup>th</sup> European Conference on Computational Chemistry (EUCCO-CC9)*, Sopron, (Hungary), 2013, (Book of abstracts) p. P-48 (Poster)

[11] **Csankó K.**, Kozma G., Kónya Z., Kukovecz Á., Sipos P., Pálincó I., Self-assembling capabilities of furyl-, thienyl-, and pyridyl-substituted cinnamic acid derivatives over polycrystalline gold and silver surfaces *4<sup>th</sup> International Colloids Conference (Colloids 2014)*, Madrid (Spain), 2014, P3.46 (Poster)

[12] **Csankó K.**, Sipos P., Pálincó I., Stereoselective synthesis of heterocyclic cinnamic acids *12<sup>th</sup>.International Conference of Young Chemists (Youngchem 12)*, Szczecin, (Poland), 2014, (Book of abstracts) p. 80., P09 (Poster)

#### 5.4 Other papers published in referred journals

[1] **Csankó, K.**, Sipos, P., Pálincó, I.: Monometallic supported gold catalysts in organic transformations: Ring making and ring breaking, *Catalysts* **2**, 101-120 (2012).

IF: –

IH: 1

Full journal papers, total: **6**

Related to the topic of the Theses: **5**

Cumulative impact factor, total: **7.779**

Related to the topic of the Theses: **7.779**

Independent citations, total: **6**

Related to the topic of the Theses: **5**