Chapter 2: General Methods

In this chapter the synthesis of *ortho*-ethoxy-*trans*-cinnamic acid (OETCA) and general preparation of its polymorphs are described. General UV irradiation experiment, powder diffraction and single-crystal diffraction methodology are also presented. More specific methodology information can be found in each of the following chapters.

2.1 Synthesis of OETCA

Coumaric acid (2-hydroxy-*trans*-cinnamic acid) (7.2g, 0.0439mol), was dissolved in DMF (100ml). 3 mole equivalents of ethyl bromide (0.1316mol, 14.34g, 9.95ml) and K_2CO_3 (0.1316mol, 18.19g) were added to the stirred solution and the mixture heated under nitrogen at reflux for 24hr. The K_2CO_3 was filtered off and the DMF removed using a rotary evaporator connected to a vacuum pump. The residue was then dissolved in 100ml methanol. Ten equivalents of sodium hydroxide (0.4386mol, 17.54g) in 40ml of methanol was added to the solution together with more methanol to yield a final volume of 150ml. The hydrolysis reaction was allowed to continue for 3 days (followed by spotting on TLC plates). The white precipitate was filtered off and the methanol evaporated. The residue was then applied to a silica column and eluted with 10% ethylacetate in hexane (v/v). The fractions were collected and the eluent evaporated using a rotary evaporator. 6.7g (79.5% yield) of a white solid was afforded as product: mp 407-408 K [lit. 406-407 K (Gupta, 1948)]. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at room temperature using a 200 MHz Bruker NMR spectrometer with tetramethylsilane (TMS) as an internal standard: ^{1}H NMR δ 12.00 (1H, s, -COO$\underline{\text{H}}$), 8.12 (1H, d , *J* 16.15, Ar-CH=C$\underline{\text{H}}$-COOH), 7.53 (1H, m, Ar-$\underline{\text{H}}$), 7.33 (1H, m, Ar-$\underline{\text{H}}$), 6.94 (2H, m, Ar-$\underline{\text{H}}$), 6.57 (1H, d, *J* 16.12, Ar-C$\underline{\text{H}}$=CH-COOH), 4.11 (2H, q, -C$\underline{\text{H}}_2$), 1.49 (3H, t, -C$\underline{\text{H}}_3$); ^{13}C NMR δ 173.24 ($\underline{\text{C}}$OOH), 157.97 (Ar$\underline{\text{C}}$-O), 142.66 (Ar-

CH=<u>C</u>H-COOH), 131.89 (Ar<u>C</u>H), 129.31 (Ar<u>C</u>H), 123.04 (Ar<u>C</u>-CH=CH-COOH), 120.55 (Ar<u>C</u>H), 117.65 (Ar<u>C</u>H), 112.08(Ar-<u>C</u>H=CH-COOH), 64.02 ($\underline{C}H_2$), 14.72 ($\underline{C}H_3$).

2.2 Crystallization of the Three Crystal Polymorphs of OETCA

The crystallization procedures detailed below yield three distinct phases, as shown by powder-XRD (Fig. 2.1). The elemental analyses and NMR data for all three phases also confirm the purity of the samples, and in particular, the nature of the *β*-polymorph which is actually a solvate[1]. As expected, the elemental analyses and NMR data for the *α*- and *γ*-polymorphs are identical to the data given above for the purified white solid. However, the elemental analysis of crystals of the *β*-phase is consistent with the presence of a benzene (or thiophene depending on growing conditions) solvate molecule, confirmed by an additional aromatic peak(s) in the NMR spectrum.

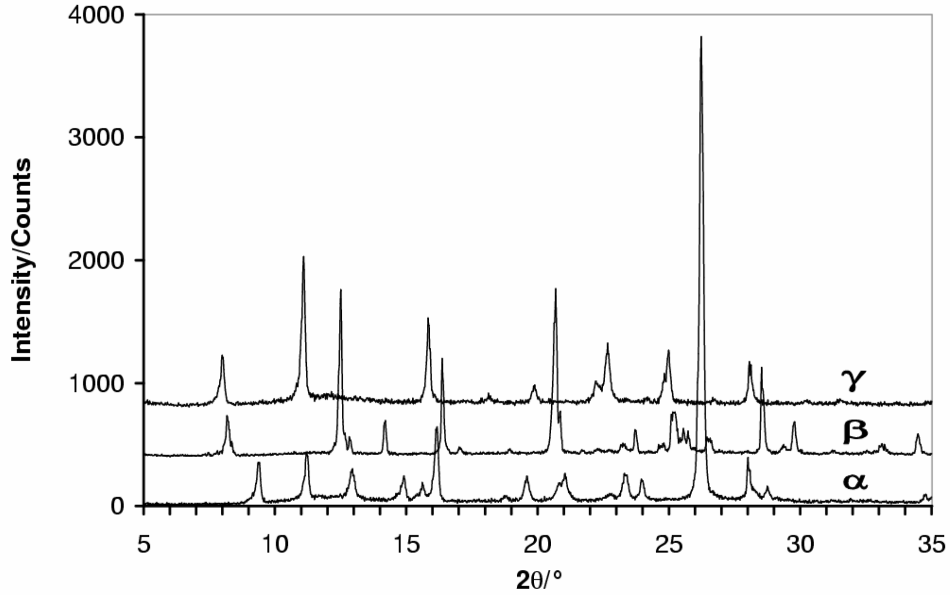


Figure 2.1: Powder XRD of the three phases of OETCA.

---

[1] In this study OETCA was successfully co-crystallized with benzene and thiophene. Co-crystallization with benzene was originally carried out by Schmidt and co-workers and reported as the *β*-polymorph while co-crystallization with thiophene is reported here for the first time.

2.2.1 Crystallization of the *α*-Polymorph of OETCA

The *α*-polymorph was grown by slow evaporation from a saturated solution of OETCA in ethyl acetate at room temperature (298 K) to yield prism-like crystals (Fig. 2.2). The melting point of these crystals, determined by DSC, was 407.9-408.9 K.

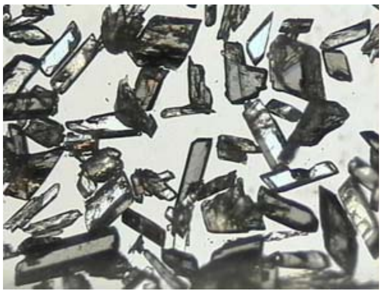


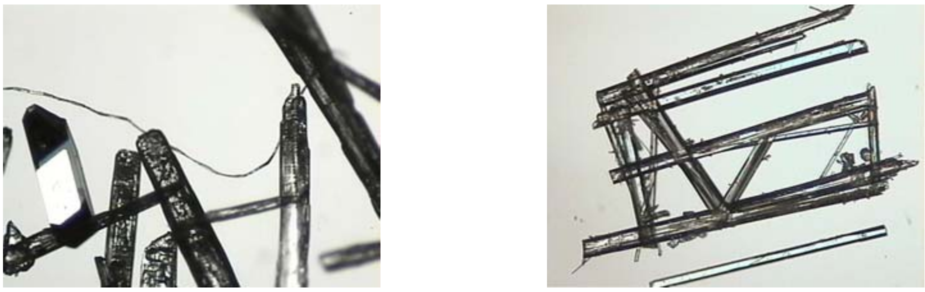
Figure 2.2: *α*-Polymorph crystals.

2.2.2 Crystallization of the *β*-Benzene Form of OETCA

A saturated solution of OETCA in benzene at 290 K was placed in a fume hood in order to evaporate the solvent off quickly. This yielded hexagonal needle-like crystals of the *β*-benzene solvate (Fig. 2.3). The melting point of these crystals as determined by DSC was 407.9-408.9 K. The DSC trace revealed an irreversible endothermic peak at about 366 K. This can be attributed to the benzene guest escaping out of the structure resulting in a phase transformation to the *γ*-polymorph[2], confirmed by X-ray diffraction (see Chapter 5). Elemental analysis for $6(C_{11}H_{12}O_3)$: C_6H_6 calculated: C, 70.23; H, 6.39; O, 23.39. Found: C, 69.95; H, 6.50; O, 23.56. The difference between the calculated and experimental C and H values is attributed to a non-stoichiometric amount of the benzene solvent, $6(C_{11}H_{12}O_3)$: $0.79C_6H_6$. ^{1}H and ^{13}C NMR spectra were recorded for the *β*-benzene solvate in $CDCl_3$ at room temperature using a 200 MHz Bruker NMR spectrometer with tetramethylsilane (TMS) as an internal standard. In addition to the expected OETCA peaks the ^{1}H NMR spectrum revealed a benzene hydrogen peak at δ 7.3591 (1H, s, C$\underline{H}$) and the ^{13}C NMR spectrum a benzene carbon peak at δ 128.31 ($\underline{C}$H), confirming that this is indeed a benzene solvate.

---

[2] Conversion to the *γ*-polymorph happens at temperatures above 328 K (55 °C). At temperatures below this the *α*-polymorph is obtained - as reported by Cohen *et al* (1964).



(a) (b)

Figure 2.3: *β*-benzene-polymorph crystals. Note the presence of a 'non-needle' *α*-polymorph crystal in photograph (a). This usually happens if the crystallization process has taken too long. Slow evaporation as suggested by Cohen *et al*. (1964) does not lead to a crystallographically pure material.

2.2.3 Crystallization of the *β*-Thiophene Form of OETCA

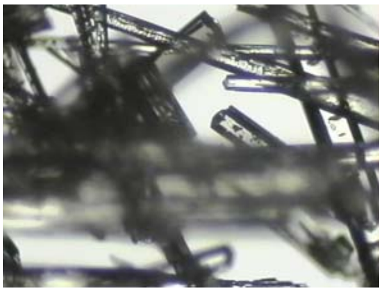
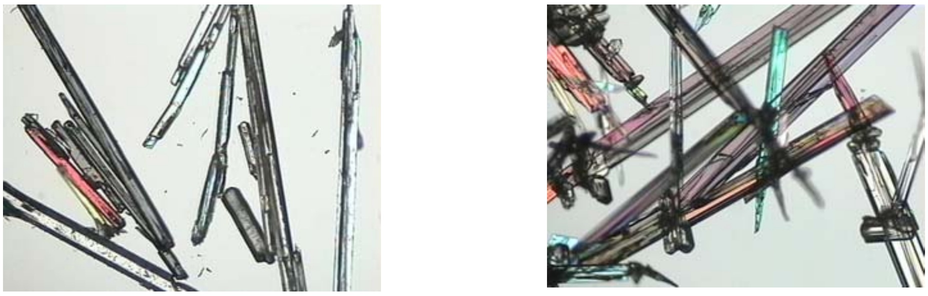


Figure 2.4: *β*-(thiophene) polymorph crystals.

A saturated solution of OETCA in thiophene at 290 K was placed in a fume hood in order to evaporate the solvent off quickly. This yielded hexagonal needle-like crystals of the *β*-(thiophene) solvate (Fig. 2.4).The melting point of these crystals as determined by DSC was 407.9-408.9 K. The DSC trace revealed an irreversible endothermic peak at about 404 K. This can be attributed to the thiophene guest escaping out of the structure resulting in a phase transformation to the *γ*-polymorph, confirmed by powder-XRD. Elemental analysis for $6(C_{11}H_{12}O_3)$: C_4H_4S calculated: C, 67.94; H, 6.19; O, 23.28; S, 2.59. Found: C, 67.96; H, 6.39; O, 23.20; S, 2.45. The difference between the calculated and experimental C and H values was attributed to a non-stoichiometric amount of the thiophene solvent, $6(C_{11}H_{12}O_3)$: $0.94C_4H_4S$. ^{1}H NMR spectra were recorded for the *β*-(thiophene) solvate in C_6D_6 at room temperature using a 200 MHz Bruker NMR spectrometer with tetramethylsilane (TMS) as an internal standard. In addition to the expected OETCA peaks the ^{1}H NMR spectrum revealed signals in the range 6.96 to 6.78 ppm corresponding to an AA'BB' spin system, confirming that this is a thiophene solvate (see Appendix C).

2.2.4 Crystallization of the *γ*-Polymorph of OETCA

The *γ*-crystals were grown from a saturated solution of OETCA in a 1:1 (v/v) mixture of deionised water and ethanol. The solution was filtered to remove any particulate matter and heated to 338 K before slow cooling (0.1 K per hour to 333 K) until crystals started to appear. The solution temperature was then raised to about 338 K to allow the crystals to re-dissolve then cooled to 334 K and kept at this temperature to allow the needle-like crystals to grow (Fig. 2.5). This procedure was thought necessary in order to avoid precipitation of the *α*-polymorph. However, later it was discovered that growing the crystals above 328 K would suffice. The melting point of these crystals as determined by DSC was 407.9-409 K.



(a) (b)

Figure 2.5: *γ*-polymorph crystals obtained *via* (a) ethanol/water and (b) *via* sublimation.

2.3 Elemental Analysis

All elemental analyses were carried out by the Institute Soil, Climate and Water at the CSIR in Pretoria, South Africa.

2.4 Melting Point and DSC Measurements

Melting point measurements were done on a microscope hot-stage and are uncorrected.

DSC measurements were carried out using a Standton Redcroft DSC 700. The measurements were carried out under nitrogen in open aluminium crucibles. The sampling rate was 0.10 points/sec and a heating rate of 5 K/min was used. Typical sample masses were about 5-10 mg.

2.5 Powder XRD Studies of the UV Reaction Processes of all Three Crystal Forms of OETCA

Powder XRD studies were done on a Philips PW1820 powder diffractometer. X-rays were generated from a copper tube set at 40 kV and 20 mA. Samples of the *α*- and *γ*-polymorphs were prepared by lightly grinding the sample in an agate mortar and pestle and sprinkling the powder on silicone grease covered silicon disks [(110) silicon crystal wafers supplied by Philips/PANalytical Part No: PW 1817/32] so that the silicon was thinly and evenly covered by the powder. The *β*-(benzene and thiophene) crystal samples were prepared by finely chopping up the crystals using a razor blade so as to prevent a phase change. Samples were run for about 1 hour over a 2θ range of 5-60° (in 2750 steps) at a scan speed of 0.016° per second (0.016 seconds per step).

2.6 Irradiation of Polymorph Crystals

UV irradiation of powders and single crystals, of the various OETCA polymorphs, was carried out by exposing silicon disks (for powder XRD analysis) and or Petri dishes (for single crystal diffraction, NMR or DSC analysis) containing the appropriate sample. The UV lamps were obtained from Philips and emit in different areas of the UV spectrum (Fig. 2.6).

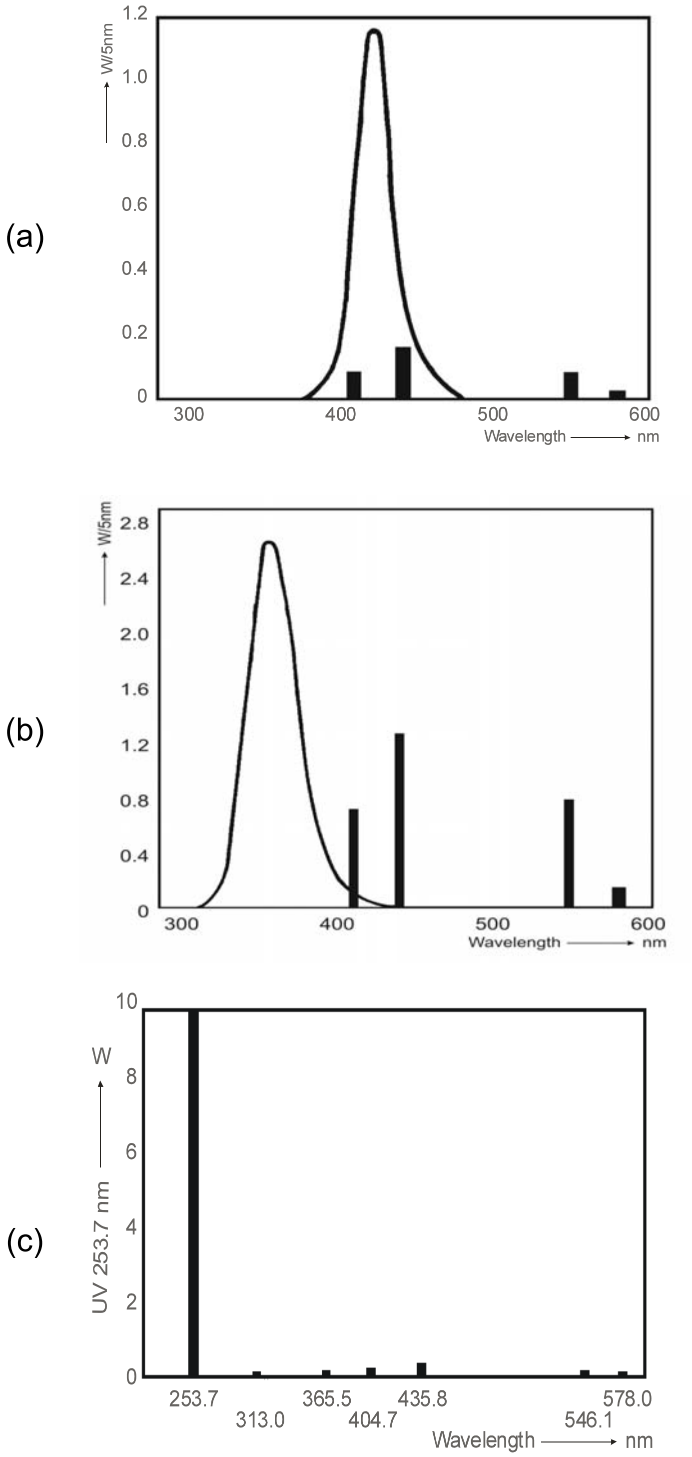


Figure 2.6: Emission spectra of fluorescent UV lamps obtained from Philips. Lamp labels are as follows (a) TL03, (b) TL09N and (c) TUV. The bars in all emission spectra indicate the emission lines of mercury.

The TL03 UV lamp (referred to later as the “TL03 lamp”) has a peak at about 420 nm and was used in photochemical reactions where a slow reaction rate was required. The following reaction setups were used with this lamp:

1) In photochemical reactions, where the possibility of a single crystal to single crystal transformation in the *α*-polymorph was studied, single crystals and powder samples (in Petri dishes and on silicon disks) were exposed to one vertically orientated UV lamp at a distance of 40 cm from the samples. This was to ensure that absorption of the UV was at a minimum so as to maximize the chance of the crystals surviving the reaction process intact. In order to study the reaction kinetics of the *α*-polymorph, powder samples (in Petri dishes and on silicon disks) were exposed to the UV lamps under the same conditions. The results given in Chapter 9 were obtained by the simultaneous irradiation of single crystals for single crystal analysis and powdered samples for PXRD and NMR analysis. *β*-(benzene and thiophene) Solvate and *γ*-polymorph samples were also exposed in an identical manner to test their behavior under the TL03 lamp.
2) In studies of photochemical reactions involving the *α*'-polymorph, single crystals and powder samples on a heating stage set at 343 K were exposed to two vertically orientated UV lamps at a distance of 10 cm from the sample - see Chapters 6, 7 and 8.

The TL09N UV lamp (referred to later as the “TL09N lamp”) has a peak at about 350 nm and was used in photochemical reactions where a fast rate of reaction was required. The following reaction setups were used with this lamp:

1) In photochemical reactions, where the possibility of single crystal to single crystal transformations in the *β*-(benzene and thiophene) solvates were studied, single crystals and powder samples (in Petri dishes) were exposed to one vertically orientated UV lamp at a

distance of 20 cm or 40cm (depending on the experiment). Best results were obtained when the reaction was carried out quickly (3-5 hours), i.e. with the lamp about 20 cm from the sample. The product (2,2'-diethoxy-*β*-truxinic acid) from these reactions was also recrystallized and studied by X-ray single-crystal analysis.

2) In photochemical reactions, where reaction kinetics of the *β*-(benzene and thiophene) solvates was studied, powder samples (in Petri dishes and on silicon disks) were exposed to one horizontally orientated UV lamp at a distance of 20 cm.
3) In photochemical reactions, where the possibility of single-crystal-to-single-crystal transformations in the *α*-polymorph was studied, single-crystals and powder samples (in Petri dishes) were exposed to one vertically orientated UV lamp at a distance of 20 cm or 40cm (depending on the experiment). The product (2,2'-diethoxy-*α*-truxillic acid) from these reactions was also recrystallized and studied by X-ray single crystal analysis.

The TUV lamp was used in the irradiation of the various forms of the *β*-polymorph but found to simply lead to a phase transition to the other forms of OETCA through structure collapse. These results are presented in Chapter 5.

2.7 General Methodology for Single Crystal Analyses

Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50kV, 30mA). The data collection covered a hemisphere of reciprocal space by a combination of three sets of exposures; each set had a different φ angle (0, 90 and 180°) for the crystal and each exposure of 20 s (this being dependent on crystal quality) covered 0.3° in ω. The crystal to detector distance was 4.5 cm and the detector swing angle -28°. Crystal decay was monitored by repeating 50 initial frames at the end of the collection and analyzing the duplicate reflections, and found to be negligible. Data reduction was carried out using the program *SAINT* + [Bruker, 1999a] and instrumental and absorption corrections made using the program *SADABS* [Sheldrick, 1996].

The crystal structures were solved by direct methods using *SHELXTL* [Bruker, 1999b]. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculation based on F^2 using *SHELXTL*. Hydrogen atoms were first located in the difference density map then positioned geometrically (for consistency) and allowed to ride on their respective parent atoms. Publication materials were generated using *SHELXTL*, *PLATON* [Spek, 2003], *SCHAKAL-97* [Keller, 1997] and *ORTEP*3 [Johnson *et al.*, 1997].

More specific details on data collection and structure solutions strategies will be given in Chapters where structures are reported.