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Polymorphism control in the mechanochemical and solution-based synthesis of a thermochromic Schiff base†

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Three crystal forms of a thermochromic Schiff base, namely 1-{3-[(2-hydroxy-3-methoxy-benzylidene)-amino]-phenyl}-ethanone, derived from *o*-vanillin and 3-aminoacetophenone, were obtained by conventional solution-based methods. Two out of the three polymorphs were synthesized by mechanochemical syntheses, under solvent-free conditions. Herein, we report a study of the dependence of the composition of solvent, the crystallization temperature and impurities on the outcome of the synthesis of Schiff base polymorphs. We report the important role of seed crystals in directing the supramolecular organization of the product of a covalent solvent-free reaction towards the intended polymorphic outcome as well. All obtained polymorphs were investigated by means of thermal analysis, single crystal X-ray diffraction, *ex situ* and *in situ* powder X-ray diffraction and IR spectroscopy. The polymorphs display interesting and remarkably different molecular packing arrangements governed by C–H⋯O interactions leading to two-dimensional networks in forms I and III, and a three-dimensional networks in form II.

Introduction

There is a continuous strong interest in understanding the phenomenon of identical molecular species occupying different crystalline arrangements, *i.e.* polymorphism.[1] Different surroundings of molecules in the solid state significantly influence the physicochemical properties of the compound (colour, solubility, stability, bioavailability, *etc.*) although the chemical composition is the same.[2] Thus, for the design of functional materials, the ability to control the solid-state assembly of molecules into crystals is of considerable importance.[3] The conventional methods to control polymorphism, as well as the screening of different crystal forms of a compound, are based on a systematic exploration of all possible crystallization conditions, such as by varying the solvent or temperature.[4] However, polymorph screening using solvent-free methods is mainly based on melt crystallization or sublimation.[5] An overview of the literature on polymorphic transformations and their control under solvent-free conditions reveals that many studies were based on compression, grinding or grinding in the presence of seed crystals.[6]

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† Electronic supplementary information (ESI) available: Photographs, FT-IR spectra, DSC and TG thermograms and PXRD patterns for all relevant materials. CCDC 1401490–1401493 contain crystallographic data for this paper. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ce01445j

The compound we were interested in is an imine derived from *o*-vanillin (**ovan**) and 3-aminoacetophenone (**3aa**). *N*-substituted imines, also known as Schiff bases, can be effortlessly obtained by the condensation reaction of primary amines with carbonyl compounds.[7] During the past two decades, they have been widely used as ligands in the coordination chemistry of transition metals.[8] Besides, the imines (and their coordination compounds) have attracted particular interest due to their biological and pharmacological activities.[9] Solid-state thermochromism and photochromism are another characteristic of these compounds leading to their application in various areas of materials science.[2a–d,10,11] Schiff bases are usually obtained by either condensation from a solution, or, more recently, by neat grinding (NG), liquid-assisted grinding (LAG) or accelerated ageing.[11–14] Mechanochemical synthesis is actually faster and more convenient than the conventional solvent-based method since it avoids large quantities of solvent and heating.[15] Furthermore, the solid-state condensation of solid amines and aldehydes can occur readily, simply by mixing solid reactants and without an excessive input of mechanical energy.[11,14] Such reactions have shown great potential as an efficient technique for imine synthesis and can be accelerated by gas-phase catalysts, very high humidity or organic solvent vapours.[14]

Herein, we report a conventional solution-based synthesis of three Schiff base (compound **1**) polymorphs and a study of the dependence of the composition of the solvent, the crystallization temperature and impurities on the outcome of the polymorph synthesis. We report the synthesis of two out of

the three polymorphs under solvent-free conditions as well. We were inspired to pursue the mechanochemical experiments in our study by a recent report of our group,[13] where we described the mechanochemical synthesis of a Schiff base and described its simultaneous covalent solvent-free synthesis and polymorphism control using neat grinding and seeding-assisted grinding (SEAG), *i.e.* neat grinding in the presence of the seed crystals of the desired product. All reactants and polymorphs obtained by crystallization from solution, NG, LAG and SEAG were characterised by means of powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR). *In situ* PXRD experiments on monitoring the ageing reaction of the aldehyde and amine used as purchased and ground before the contact were performed as well.

Results and discussion

Solution-based syntheses

We first attempted the solution-based synthesis of compound **1** by the condensation reaction of equimolar quantities of **ovan** and **3aa** (Scheme 1) in boiling ethanol (EtOH). The **3aa** ethanolic solution is blurry and was, in some cases, filtered using three different filter papers and then added to the **ovan** solution. The resulting mixture was left at 25 °C (RT) or 8 °C (LT). The results of the solution-based syntheses are presented in Table 1 and Fig. 1. Form **I** was obtained both at RT and LT and its formation is not very reliant on the filtration but a certain/variable amount of water was present in ethanol. Form **II** was obtained only by LT crystallization and only if the solution of **3aa** was filtered. The crystallization experiment at RT, when the concentration of water in ethanol is very low, leads to the formation of form **III**. In two different crystallization experiments, forms **I** and **II** appear as concomitant polymorphs. The measured PXRD patterns of all polymorphs are in good agreement with those calculated from the single-crystal data, thus confirming that all products were obtained as pure single phases (Fig. 1, and see the ESI†). The

orange single crystals used for single-crystal X-ray diffraction experiments were obtained by slow evaporation of the mother liquor in cases where only one polymorphic form was obtained (see the Experimental section and ESI†).

Mechanochemical syntheses

The left hand side of Scheme 1 represents the outcomes of the grinding experiments. Equimolar quantities of **ovan** and **3aa** were ground in an agate mortar under normal laboratory conditions (at RT, 40–50% relative humidity). The required grinding time in the agate mortar was determined empirically when the colour of the reaction mixture stopped changing (see the ESI†). After 40 s of NG, the reaction mixture starts to change its colour, and after 60 s, an orange paste appears. The paste starts to solidify after 2 min of grinding. After 3.5 min, an orange powder was obtained. As revealed by PXRD, the reaction resulted in the formation of **1** as form **I** (Fig. 1). The LAG experiments were performed in two ways: (i) by adding a small amount of ethanol (96%) in the reactants before grinding and (ii) by adding a small amount of ethanol (96%) in the paste. In both experiments, the synthesis quantitatively afforded form **I** (see the ESI†). Encouraged by the DSC and polymorph interconversion experiments and the fact that forms **I** and **III** are in a monotropic relationship, we pursued the SEAG experiments. We expected that, by adding a small amount of seed crystals of polymorph **III**, we can direct the polymorphic outcome of a mechanochemical covalent synthesis towards that same form. Indeed, SEAG of **3aa** and **ovan** for 6 min in the presence of a small quantity of seed crystals of form **III** led to the formation of compound **1** as form **III**. The attempt to prepare form **II** by the SEAG experiment was unsuccessful. As revealed by PXRD, grinding of **3aa** and **ovan** in the presence of a small amount of seed crystals of form **II** provided compound **1** but as form **I**. The SEAG experiment with form **II** was expected to result in form **I** because of the fact that form **II** converts spontaneously into form **I** if left standing in an organic solvent vapour or by
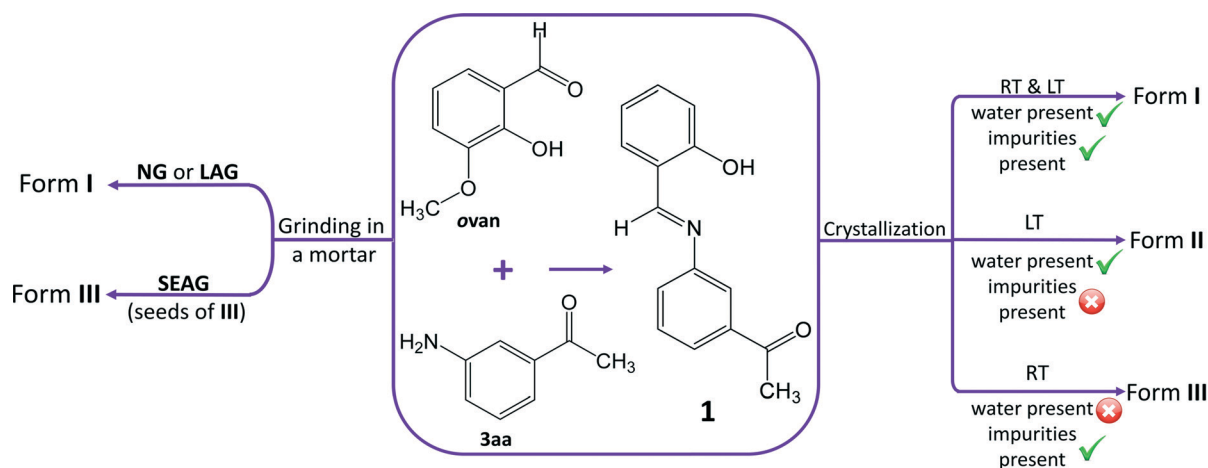
Scheme 1 Synthetic methods used to obtain compound **1** and its polymorphic forms.

Table 1 Outcome of the synthesis of the three polymorphic forms of *o*van3aa

Type of filter paper[a]	Type of ethanol	Temperature	Obtained polymorph
Filtration not performed	96%	25 °C	I
	Absolute	25 °C	I
Student grade (21N)	96%	25 °C	I
	Absolute	25 °C	III
White ribbon (615)	96%	25 °C	I
	Absolute	25 °C	I
Blue ribbon (619)	96%	25 °C	I
	Absolute	25 °C	I
Student grade (21N)	96%	8 °C	I + II
	Absolute	8 °C	I
White ribbon (615)	96%	8 °C	II
	Absolute	8 °C	II
Blue ribbon (619)	96%	8 °C	I
	Absolute	8 °C	I
	1 : 1[b]	8 °C	II
	1 : 2[b]	8 °C	I + II
	2 : 1[b]	8 °C	I + II

[a] 21/N – weight 80 g m^{-2}, thickness 0.28 mm, filtration speed 10 s; 615 – weight 70 g m^{-2}, thickness 0.16 mm, filtration speed 22 s; 619 – weight 75 g m^{-2}, thickness 0.17 mm, filtration speed 22 s.
[b] Volume ratio of ethanol, 96% and distilled water.

kneading with a drop of organic solvent (see the ESI†). For the SEAG experiments with form **III**, the reaction mixture remains as powder for 1 minute as in the case of NG, although to some extent moister. The intermediate paste is somewhat denser, stickier and with a more solid phase in the liquid and it starts to solidify after 3 min of grinding. When the seeds of polymorph **II** are used, a paste forms in 20 s after the addition and it starts to solidify after 2 min of grinding. In both experiments, the orange powder product is obtained after 6 min.

Synthesis by ageing of the reaction mixture – *in situ* PXRD monitoring

A paste is present as an intermediate phase in all performed mechanochemical syntheses of compound **1**. A recent study of our group showed that the reaction pathway does not have to be the same when grinding and when the reactants are merely put in close contact and the reaction mixture is left to age.[11] For that reason, we performed similar *in situ* PXRD monitoring experiments of the ageing reaction using (i) reactants as purchased and (ii) pre-ground reactants to assure a smaller size of the particles and a bigger reaction surface to check if the particle size influences the way of product formation. In both cases, polymorph **I** was obtained (see the ESI†). The difference between using (i) and (ii) is in the reaction rate. When the reactants are used as purchased *i.e.* the particle size is bigger, the intensities of the maxima of the reactants deteriorate severely in the first 10 minutes after they were put into close contact but remain present even after 3 hours (see the ESI†). On the other hand, the diffraction maxima of the pre-ground reactants are present in the PXRD
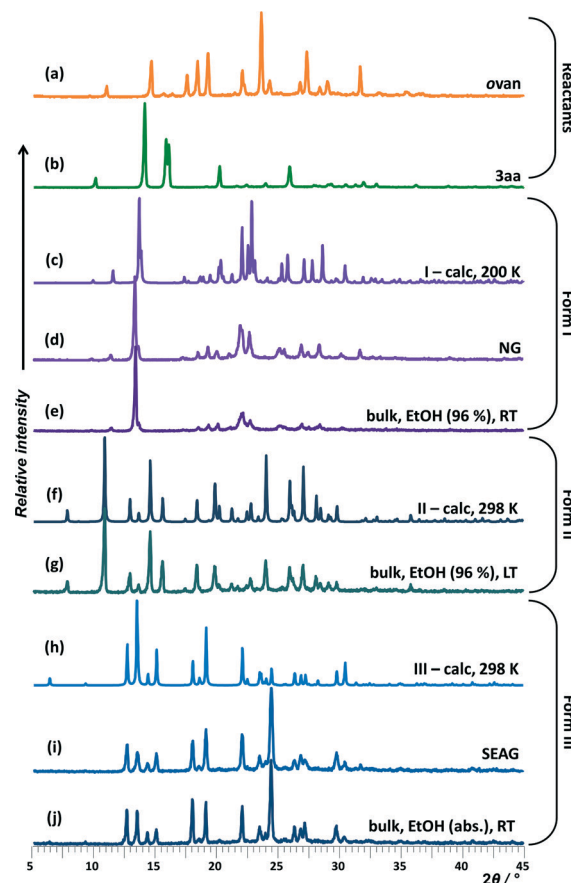

Fig. 1 PXRD patterns of (a) *o*-vanillin, (b) 3-aminoacetophenone, (c) calculated pattern of form I, (d) I prepared by neat grinding, (e) I obtained from ethanol (96%, filtration not performed) at 25 °C, (f) calculated pattern of form II, (g) II obtained from ethanol (96%, white ribbon filter paper used for filtration of **3aa** solution) at 8 °C, (h) calculated pattern of form III, (i) III obtained by means of seeding-assisted grinding and (j) III obtained from ethanol (absolute, filtration performed using student grade filter paper) at 25 °C.

patterns for 30 minutes and afterwards cannot be found, meaning that they are either overlaid by the maxima of the product or all maxima can be attributed only to the product (polymorph **I**). The severe deterioration in the intensity of the diffraction after 30 min is present for 10 minutes and points to the amorphization of the reaction mixture. Afterwards, solid particles of polymorph **I** start to grow and diffract in a liquid (paste-like) intermediate phase. This is in good agreement with the formation of the paste-like intermediate phase in the grinding experiment and with the proposed route (*via* an intermediate liquid or paste-like phase).[11]

Polymorph interconversion experiments

In quest for the information on the transformation conditions of polymorphs and routes to convert one form to the other to be able to control their interconversion, we performed three different methods as described below (Scheme 2).

Scheme 2 Polymorph interconversion experiments and transformation conditions.
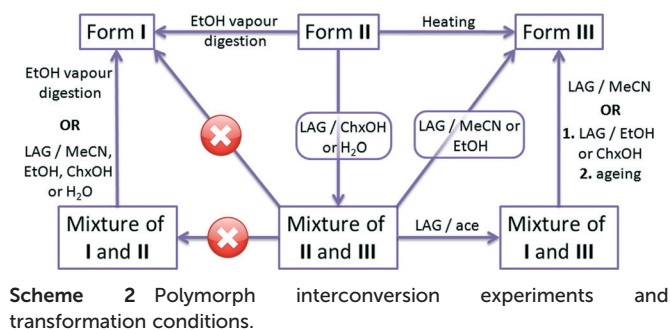
The results of the DSC experiments performed on the recrystallized material are presented in Fig. 2. Polymorph **I** starts to melt at 103 °C while polymorph **III** has a melting onset of 118 °C. The DSC curve of polymorph **II** has three significant peaks. For that reason, samples of form **II** were heated from 25 to 82 to 101 to 106 and to 116 °C, keeping the samples for 2 minutes at those temperatures and then cooling them back to 25 °C. PXRD measurements were performed on the obtained material (see the ESI†). Polymorph **II** undergoes a temperature-induced polymorphic transition into form **III** starting from 82 °C. The same DSC experiments were done for forms **I** and **III**. Samples of form **I** were heated up to 98 and 100 °C while samples of form **III** up to 80, 95 and 108 °C. PXRD measurements were performed on the obtained material and both polymorphs stay in their forms at room temperature. All three polymorphs undergo exothermic decomposition after approximately 220 °C (see the ESI†). After performing DSC experiments, we have explored the interconversion of polymorphs from their mixtures. Three combinations of polymorph mixtures in a mass ratio of 1 : 1 were ground in a mortar in the presence of a small quantity of organic solvent: acetone (ace), acetonitrile (MeCN), ethanol, cyclohexanol (Ch*x*OH) and water. The results of the kneading experiments were monitored *ex situ* by means of PXRD just after the solvent evaporated and after 3 weeks (see the ESI†). Form **II** converts into
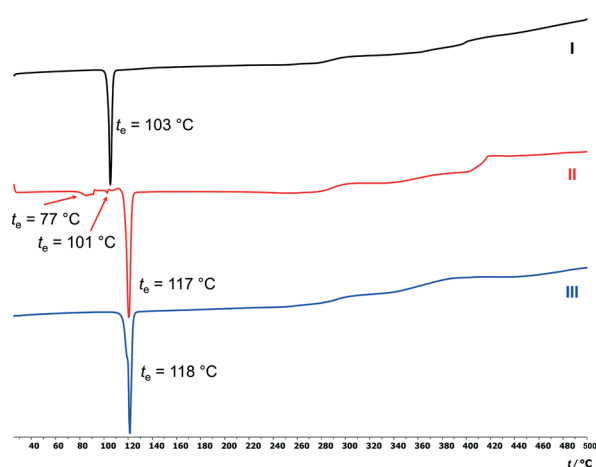
form **I** from a mixture of **I** and **II** in all cases except when ace was used, probably because acetone evaporates fast. When form **II** is in a mixture with form **III**, it converts rapidly into the pure form **III** if MeCN or EtOH is used, but if ace is used, it converts into form **I** with time. Apparently, there is no conversion of form **II** in the presence of Ch*x*OH or water. Form **I**, on the other hand, if in a mixture with **III**, rapidly converts to form **III** in MeCN, but it takes three weeks for that conversion if EtOH or Ch*x*OH is used to assist grinding. No polymorph conversion in this mixture was observed when water was used.

Finally, we have performed vapour digestion experiments. Samples of all three polymorphs were put in open test tubes which were then put in glass vials containing ethanol (96% or absolute), closed and left at RT. As revealed by PXRD, crystals of form **II** convert spontaneously into form **I** in a period of three hours. On the other hand, there is no influence of ethanol vapour to neither form **I** nor form **III** in the same period of vapour digestion (see the ESI†).

Molecular and crystal structures of the polymorphs

Single crystal X-ray analysis of the three crystal forms of **1** revealed conformational differences in their molecules. The acetophenone group of the amine moiety and the hydroxy and methoxy groups of the aldehyde moiety are on the opposite side in the molecules of forms **I** and **III**. Meanwhile, these groups are on the same side in the molecules of form **II**. All four molecules (form **I** has two independent molecules in the asymmetric unit) of these three forms are almost planar. The angles between the aromatic subunits of the molecules are approx. 5°, 4° and 2° in forms **I**, **II** and **III**, respectively. The view of the molecular overlap shows the mentioned similarities and differences (Fig. 3a). The enol–imine tautomer was detected for all three crystal forms from the molecular geometry consideration, where the N1–C7 and C2–O1 bond lengths are in good agreement with the analogous values of the corresponding Schiff bases (see the ESI†),[8a,16] as well as from δF maps calculated in the domain of N1–C7–C1–C2–O1 chelate rings (see the ESI†). A close analysis of the two-dimensional fingerprint plots derived from the Hirshfeld surfaces of the molecule of all polymorphs, revealed weak hydrogen bonds, Fig. 3. The polymorphs display interesting and remarkably different molecular packing arrangements governed by C–H···O interactions (Fig. 4), leading to two-dimensional networks in forms **I** and **III**, and a three-dimensional network in form **II**. All three forms crystallize in the orthorhombic system, form **I** in a general position of the *Pna*2₁ space group and forms **II** and **III** in *P*2₁2₁2₁. Polymorph **I** crystallizes with two molecules in the asymmetric unit and with eight molecules per unit cell. The molecules are connected into zigzag chains along the [001] direction *via* C$_{ar}$–H···O$_{methoxy}$ and C–H···O$_{carbonyl}$ interactions (C213···O12 of 3.469 Å and C27···O13 of 3.487 Å). The chains thus formed interact by C–H···O interactions between the methyl and carbonyl groups of neighbouring molecules with C114···O13

Fig. 2 DSC curves of form **I** (black), **II** (red) and **III** (blue). The onset temperature of a peak is indicated as the t_e value.
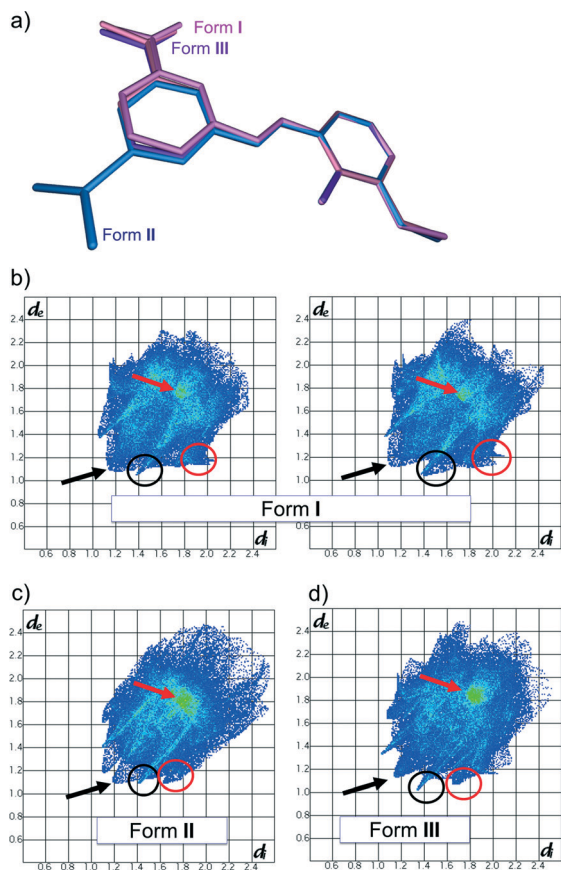
Fig. 3 Compound 1: a) overlapped molecular structures (both molecules of form I – pink, form II – blue, form III – violet); two-dimensional fingerprint plots of form I (b), form II (c) and form III (d) (marked corresponding regions: red arrows for C⋯C contacts, black arrows for H⋯H contacts, red circle for C–H⋯C contacts and black circle for C–H⋯O contacts).

Fig. 4 The crystal structure of polymorphic forms I–III of 1: chains of hydrogen-bonded molecules via C–H⋯O interactions, and assemblies of hydrogen-bonded chains into layers.

and C214⋯O23 contacts of 3.564 Å and 3.578 Å, respectively. The sheets thus formed are further stacked along the *b* axis. Polymorph **II** crystallizes with four molecules per unit cell. Analysis of the crystal packing indicated C–H⋯O$_{carbonyl}$ inter-actions between neighbouring molecules. The C7⋯O3 con-tacts of 3.571 Å lead to the formation of chains along the [010] direction. The adjacent chains are further connected into a 3D network via C–H⋯O interactions between the methyl and methoxy groups of neighbouring molecules (C13⋯O2 contacts of 3.411 Å) and via C⋯C contacts between the benzene rings of neighbouring molecules (C5⋯C7 con-tacts of 3.341 Å and C1⋯C8 contacts of 3.371 Å). Polymorph **III** crystallizes with four molecules per unit cell. The mole-cules are connected into chains along the [100] direction via C–H⋯O interactions between neighbouring molecules. In each molecule, carbonyl oxygen acts as a bifurcated acceptor of C–H⋯O hydrogen bonds with C6⋯O3 and C7⋯O3 con-tacts of 3.356 A and 3.417 A, respectively. The chains thus formed are connected via C–H⋯O interactions, between the benzene rings and hydroxy groups of neighbouring molecules (C13⋯O1 contacts of 3.441 Å), into sheets which are stacked along the *b* axis. Compound **1** fulfils the requirements of the
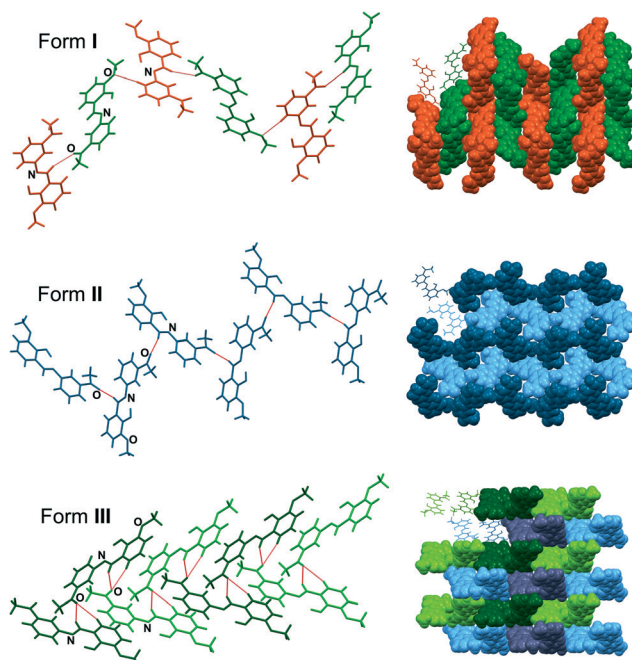
molecule to be able to show reversible thermochromism[2a–d,10,11] *i.e.* it is derived from an *o*-hydroxy aldehyde so there is a possibility of proton transfer *via* an intramolecular O⋯N hydrogen bond and the molecules have the ability to change their geometry under crystal packing influences. Neverthe-less, all molecules of all three polymorphic forms of **1** are almost planar (2–5°) and are present as enol–imines in the solid state at room temperature. Still, small amounts of the recrystallized material of all three polymorphs of **1** were put into glass testing tubes which were then submerged into liq-uid nitrogen. All three samples reversibly change their col-our upon cooling from different shades of orange to differ-ent shades of yellow as can be seen from Fig. 5. Structural and/or other reasons for solid state thermochromism were not thoroughly revised for the purpose of this paper.

Experimental

Synthesis

All reagents, solvents and filter papers were purchased from commercial sources and used as received.

General procedure for solution-based syntheses

All solution-based syntheses were performed using equimolar quantities of reactants *i.e.* 0.153 g (1 mmol) of *o*-vanillin dissolved in 2 mL and 0.135 g (1 mmol) of 3-amino-acetophenone in 5 mL of corresponding boiling solvent.

Single crystals suitable for SCXRD of three different poly-morphs were obtained by crystallization from the mother liquor. The details on the filter paper used are in the ESI,† Table S2.
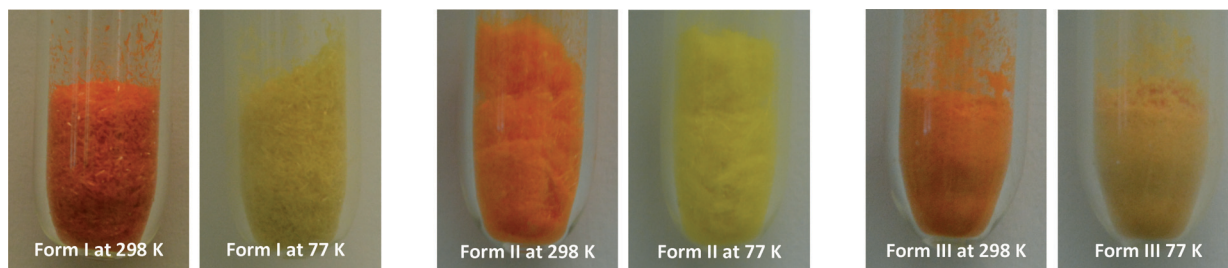
Fig. 5 Pictures of polymorphs of **ovan3aa** at room and liquid nitrogen temperature showing solid state thermochromism.

Solution-based synthesis of compound 1, form I

Form **I** was obtained from a boiling ethanol (96% or absolute) mixture of *o*-vanillin and 3-aminoacetophenone solutions, which was left semi-closed overnight at 25 °C, when the **3aa** solution was not filtered or was filtered using a student grade, white and blue ribbon filter paper prior to its addition to the **o**van solution.

The same polymorphic form was obtained at 8 °C when the **3aa** solution (96%, absolute EtOH) was filtered using blue ribbon filter paper and student grade filter paper.

Solution-based synthesis of compound 1, form II

When the reactants were dissolved in boiling 96% or absolute EtOH and 1 : 1 volume ratio of 96% EtOH and distilled water, and the **3aa** solution was filtered using white ribbon and blue ribbon filter paper, respectively, form **II** of compound **1** was obtained. Each time the resulting mixture was left semi-closed overnight at 8 °C.

Solution-based synthesis of compound 1, form III

The reactants were dissolved in boiling absolute EtOH and the **3aa** solution was filtered using student grade filter paper and then poured into the boiling solution of **o**van. The resulting mixture was left semi-closed overnight at 25 °C.

A rod-like single crystal of form **I** used for SCXRD was harvested from the crystals grown in the mother liquor of the solution-based synthesis of **1** when filtration wasn't performed, 96% ethanol was used as solvent and crystallization was performed at RT. A needle-like crystal used for SCXRD analysis of form **II** was taken from the ones developed by the solution-based synthesis of **1** when filtration of 96% ethanol solution of **3aa** was done using white ribbon and crystallization was performed at LT. A brick-like single crystal of form **III** was collected from the crystals grown by slow evaporation of absolute EtOH at RT when student grade filter paper was used to eliminate impurities present in the solution of **3aa** used for the solution-based synthesis of **1**.

General procedure for the mechanochemical syntheses

All manual grinding experiments were performed in an agate mortar at room temperature and 40–50% relative humidity. Equimolar quantities of *o*-vanillin (0.153 g, 1 mmol) and

3-aminoacetophenone (0.135 g, 1 mmol) were ground for 40 s and when the reaction mixture started to change its colour and after 60 s, an orange paste appeared. The paste started to solidify after 2 min of grinding. After 3.5 min, an orange powder containing form **I** was obtained. The same quantities of reactants were used for the LAG experiments where 40 µL of 96% EtOH was added at the beginning and in another case in the paste-like intermediate phase. Form **I** of compound **1** was again obtained; however, it takes 2.5 min and 3.5 min, respectively, for the reaction mixture to start to solidify and 8 min and 9 min, respectively, for the grinding process to finish. Form **III** was obtained by grinding *o*-vanillin (0.153 g, 1 mmol) and the seed crystals of form **III** (48 mg, 0.2 mmol) for 2.5 minutes, and then by adding 3-aminoacetophenone (0.135 g, 1 mmol) after. The reaction mixture was ground for another 60 s when an orange paste formed. By further grinding, the paste gradually solidifies. After 5.5 min from **3aa** addition, an orange dry powder of form **III** was obtained.

X-Ray diffraction measurements

The crystal and molecular structures were determined at 298 K for polymorphs **II** and **III** and at 200 and 110 K for polymorph **I** using SCXRD on an Oxford Diffraction Xcalibur Kappa CCD X-ray diffractometer with graphite-monochromated Mo K$_\alpha$ (λ = 0.71073 Å) radiation (for details see the ESI†).[17] The data concerning the results of the crystallographic experiments are listed in Tables S4 to S7.† In order to monitor the efficacy of the synthetic method used and to qualitatively identify the products, powder X-ray diffraction (PXRD) experiments were performed on a PHILIPS PW 1840 X-ray diffractometer with Cu K$_{\alpha 1}$ (1.54056 Å) radiation at 40 mA and 40 kV. Scattered intensities were measured with a scintillation counter. The angular range (2θ) was from 5 to 45° with steps of 0.02° and the measuring time was 0.5 s per step in the case of the *ex situ* experiments. In the case of the *in situ* monitoring of the contact reaction, the angular range (2θ) was selected according to the diffraction maxima of the reactants from 10.0 to 20.0° with steps of 0.02°, and the measuring time was 0.5 s per step for the reactants used as purchased. Measurements were repeated in 40 cycles. In the case of the *in situ* monitoring of the contact reaction when the reactants were separately ground prior to contact, the angular range (2θ) was also selected according to the diffraction

maxima of the reactants from 11.5 to 15.0° with steps of 0.02°, and the measuring time was 0.5 s per step. Measurements were repeated in 110 cycles. Data collection and analysis were performed using the program package Philips X'Pert (for details see the ESI†).[18]

Thermal study

The measurements were performed on a Mettler Toledo TGA/SDTA and DSC823[e] module in sealed aluminium pans (40 μL), heated under flowing nitrogen (200 mL min^{-1}) at a rate of 10 °C min^{-1}. Data collection and analysis was performed using the program package STAR[e] Software V10.00 (for details see the ESI†).[19]

FT-IR spectroscopy

The infrared spectra were recorded on a PerkinElmer Spectrum Two FTIR spectrophotometer using the KBr pellet method. Data collection and analysis was performed using the program package PerkinElmer Spectrum 10.4.2.279.[20] The spectra and the table with characteristic stretching bands are listed in the ESI.†

Conclusions

In summary, we have obtained three crystal forms of a Schiff base derived from o-vanillin and 3-aminoacetophenone by conventional solution-based methods. We demonstrated that the composition of solvent, the crystallization temperature and impurities present in the reagents can significantly affect the supramolecular outcome of the synthesis of imine. The polymorphs are thermochromic and display different molecular packing arrangements governed by C–H⋯O interactions leading to two-dimensional networks in forms **I** and **III**, and three-dimensional networks in form **II**. The molecules of all three polymorphic forms are almost planar (2–5°) and are present as enol–imines in the solid state at room temperature.

The present study also highlights the efficiency of mechanochemistry in the polymorphism control in the solid state. Two out of the three polymorphs were synthesized by mechanochemical syntheses, under solvent-free conditions. A paste is present as an intermediate phase in all performed mechanochemical syntheses of compound **1**. We have shown and confirmed our previously reported study[13] which states that seeding-assisted grinding can be used as an efficient approach for simultaneous covalent solvent-free synthesis and polymorphism control. We have shown the important role of seed crystals in directing the supramolecular organization of the product towards the intended polymorphic outcome. The described results are important in the context of solid-state synthesis, as well as supramolecular and materials chemistry, and could have a significant implication for the future aspects of solvent-free syntheses and polymorphism control in the solid state.

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