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ARTICLE

## Polymorphism control in mechanochemical and solution based synthesis of a thermochromic Schiff base

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

### Introduction

There is a continuous strong interest in understanding the phenomenon of identical molecular specie occupying different crystalline arrangements, i.e. polymorphism.<sup>1</sup> Different surroundings of molecules in the solid state significantly influences the physicochemical properties of the compound (colour, solubility, stability, bioavailability, etc.) although the chemical composition is the same.<sup>2</sup> Thus, for the design of functional materials the ability to control the solid-state assembly of molecules into crystals is of considerable importance.<sup>3</sup> 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 solvent or temperature.<sup>4</sup> However, polymorph screening by solvent-free methods are mainly based on melt crystallization or sublimation.<sup>5</sup> An overview of 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.<sup>6</sup>

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.<sup>7</sup> During the past two decades they have been widely used as ligands in coordination chemistry of transition metals.<sup>8</sup> Besides, the imines (and their coordination compounds) have attracted particular interest due to their biological and pharmacological activities.<sup>9</sup> Solid-state thermochromism and photochromism are another characteristic of these compounds leading to their application in various areas of materials science.<sup>2a-d,10,11</sup> 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.<sup>11-14</sup> Mechanochemical synthesis is actually faster and more convenient than the conventional solvent-based method since it avoids large quantities of solvent and heating.<sup>15</sup> Furthermore, the solid-state condensation of solid amines and aldehydes can occur readily simply by mixing solid reactants and without excessive input of mechanical energy.<sup>11,14</sup> Such reactions have shown great potential as efficient technique for imine synthesis and can be accelerated by gas-phase catalysts, very high humidity or organic solvent vapours.<sup>14</sup>

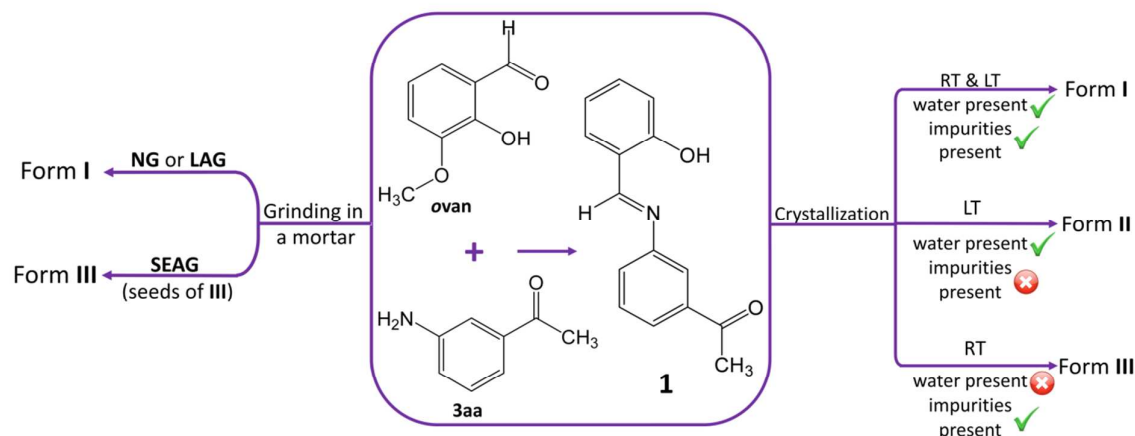
Herein, we report conventional solution-based synthesis of three Schiff base (compound 1) polymorphs and the study of the dependence of the composition of solvent, the crystallization temperature and impurities on the outcome of the polymorph synthesis. As well, we report the synthesis of two polymorphs out of three under solvent-free conditions. We were inspired to pursue mechanochemical experiments in

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† Electronic Supplementary Information (ESI) available: Photographies, FT-IR spectra, DSC and TG thermograms and PXRD patterns for all relevant materials. CCDC No. 1401490-1401493 contain crystallographic data for this paper. These data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; email: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk). See DOI: 10.1039/x0xx00000x

our study by a recent report of our group,<sup>13</sup> where we described mechanochemical



**Scheme 1** Synthetic methods used to obtain compound **1** and its polymorphic forms.

synthesis of a Schiff base and described simultaneous covalent solvent-free synthesis and polymorphism control using neat grinding and seeding-assisted grinding (SEAG), *i.e.* neat grinding in the presence of 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 of 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 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 filtering 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 Figure 1. Form I was obtained both at RT and LT and its formation is not very reliant on the filtration whereas a certain/variable water amount should be present in ethanol. Form II was obtained only by LT crystallization and only if the solution of **3aa** was filtered. 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 single crystal data, thus confirming that all products were obtained as pure single phases (Figure 1, and

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

### Mechanochemical syntheses

Left hand side of Scheme 1 represents the outcomes of 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 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 (Figure 1). LAG

**Table 1** Outcome of the synthesis of three polymorphic forms of **ovan3aa**.

Type of filtering paper <sup>o</sup>	Type of ethanol	Temperature	Obtained polymorph
Filtration not performed	96 %	25 °C	I
	Absolute		
Student grade (21N)	96 %		III
	Absolute		
White ribbon (615)	96 %		I
	Absolute		
Blue ribbon (619)	96 %	I	
	Absolute		
Student grade (21N)	96 %	I + II	
	Absolute		
White ribbon (615)	96 %	II	
	Absolute		
Blue ribbon (619)	96 %	8 °C	I
	Absolute		
	1:1 <sup>‡</sup>		II
	1:2 <sup>‡</sup>		
	2:1 <sup>‡</sup>		I + II

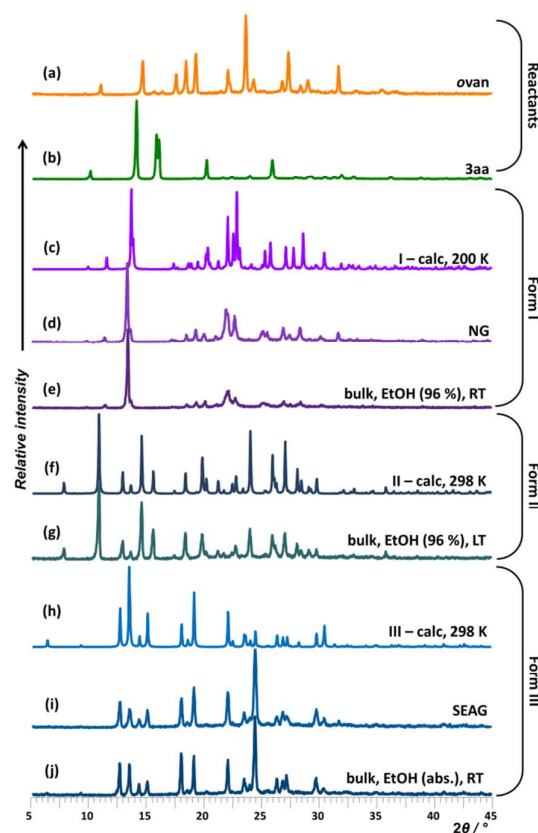
<sup>o</sup> 21/N – weight 80 g/m<sup>2</sup>, thickness 0.28 mm, filtration speed 10 s; 615 – weight 70 g/m<sup>2</sup>, thickness 0.16 mm, filtration speed 22 s; 619 – weight 75 g/m<sup>2</sup>, thickness 0.17 mm, filtration speed 22 s

<sup>‡</sup> Volume ratio of ethanol, 96 % and distilled water.

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 ESI). Encouraged by DSC and polymorph interconversion experiments and the fact that form I and form III are in the monotropic relationship we turned to 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 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. SEAG experiment with form II was expected to result with form I because the fact that form II converts spontaneously into form I if left standing in organic solvent vapour or by kneading with a drop of organic solvent (see ESI). For SEAG experiments with form III the reaction mixture remains as powder for 1 minute as in case of NG, although to some extent moister. The intermediate paste is somewhat denser, stickier and with more solid phase in the liquid and it starts to solidify after 3 min of grinding. When 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 reactants are merely put in close contact and the reaction mixture is left to age.<sup>11</sup> For that reason, we performed similar *in-situ* PXRD monitoring experiments of ageing reaction using (i) reactants as purchased and (ii) pre-ground reactants to assure smaller size of particles and bigger reaction surface to check if the particle size influences the way of product formation. In both cases, polymorph I was obtained (see ESI). The difference in 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 ESI). On the other hand, the diffraction maxima of the pre-ground reactants are present in PXRD patterns for 30 minutes and afterwards cannot be found meaning that they are either overlaid by 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 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



**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 filtering 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 filtering paper) at 25 °C.

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).<sup>11</sup>

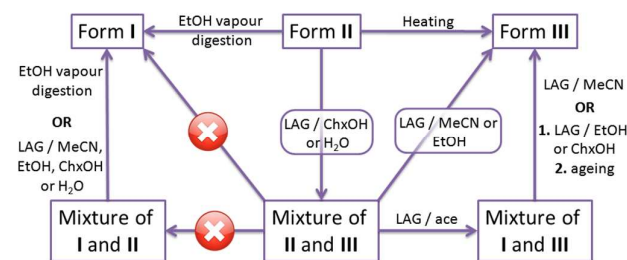
### Polymorph interconversion experiments

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 described below (Scheme 2).

The results of DSC experiments performed on recrystallized material are presented in Figure 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 °C to 82, 101, 106 and 116 °C, keeping samples for 2 minutes at those temperatures and then cooling them back to 25 °C. PXRD measurements were performed on the obtained material (see ESI). Polymorph **II** undergoes a temperature induced polymorphic transition into form **III** already starting from 82 °C. The same DSC experiments were done for form **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 the form in which they are at room temperature. All

three polymorphs undergo exothermic decomposition after approximately 220 °C (see ESI). After performing DSC experiments, we have explored the interconversion of polymorphs from their mixtures. Three combinations of polymorph mixtures in mass ratio of 1:1 were ground in a mortar in the presence of small quantity of organic solvent: acetone (ace), acetonitrile (MeCN), ethanol, cyclohexanol (ChxOH) and water. The results of kneading experiments were monitored *ex-situ* by means of PXRD just after the solvent evaporated and after 3 weeks (see 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 pure form **III** if MeCN or EtOH are used, but if ace is used it converts into form **I** with time. Apparently there is no conversion of form **II** in presence of ChxOH or water. Form **I**, on the other hand, in mixture with **III** rapidly converts to form **III** in MeCN but it takes three weeks for that conversion if EtOH or ChxOH are used to assist grinding. No polymorph conversion in this mixture was observed if water is 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 the 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 ESI).



Scheme 2 Polymorph interconversion experiments and transformation conditions.

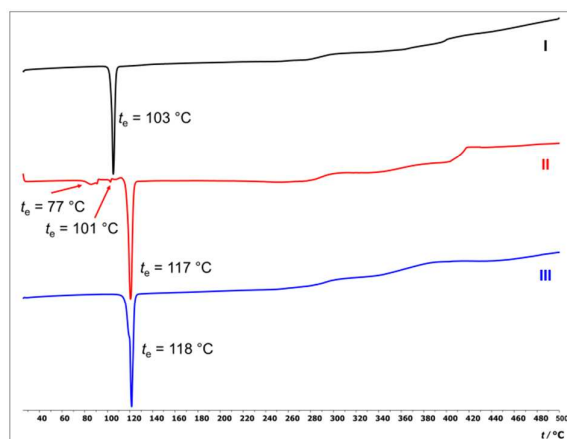
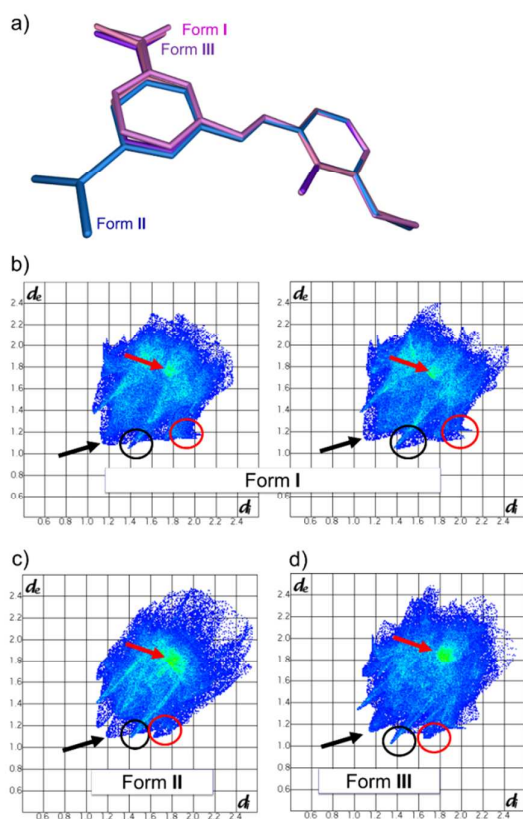


Fig. 2 DSC curves of form **I** (black), **II** (red) and **III** (blue). Onset temperature of a peak is indicated as  $t_0$  value.

### Molecular and crystal structure of polymorphs

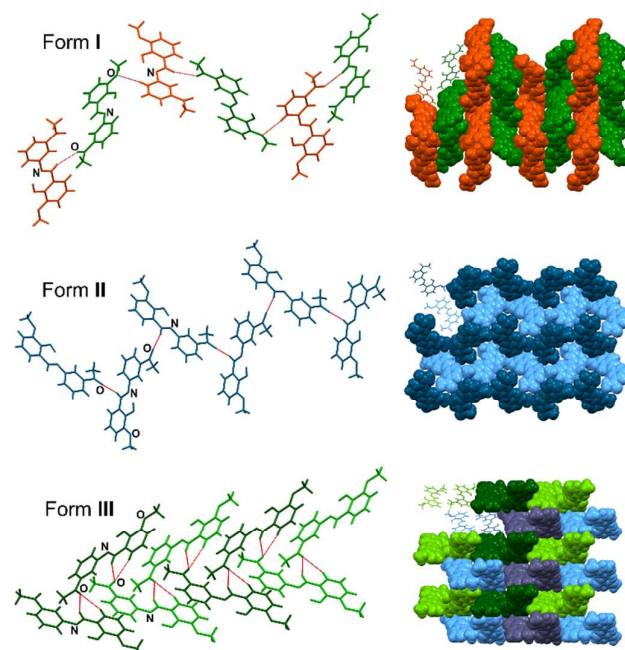
Single crystal X-ray analysis of three crystal forms of **1** revealed conformational differences in molecules. The acetophenone group of the amine moiety and the hydroxy and methoxy groups of the aldehyde moiety are on the opposite side in molecules of forms **I** and **III**. Meanwhile, these groups are on the same side in 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 (Figure 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 analogous values of corresponding Schiff bases (see ESI)<sup>8a,16</sup>, as well as from  $\delta F$  maps calculated in the domain of N1–C7–C1–C2–O1 chelate rings (see ESI). A close analysis of the two-dimensional fingerprint plots derived from the Hirshfield surfaces of the molecule of all polymorphs, revealed weak hydrogen bonds, Figure 3. The polymorphs display interesting and remarkably different molecular packing



**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).

governed by C-H...O interactions (Figure 4) leading to two-dimensional networks in forms I and III, and a three-dimensional network in form II. All three forms crystallize in orthorhombic system, form I in general position of  $Pna_2_1$  space group and forms II and III in  $P2_12_12_1$ . Polymorph I crystallizes with two molecules in the asymmetric unit and with eight molecules per unit cell. The molecules are connected into zig-zag 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 methyl and carbonyl groups of neighbouring molecules with  $C114...O13$  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. The analysis of crystal packing indicated  $C-H...O_{carbonyl}$  interactions between neighbouring molecules. The  $C7...O3$  contacts of 3.571 Å leads to the formation of chains along the [010] direction. The adjacent chains are further connected into 3-D network via C-H...O interactions between methyl and methoxy groups of neighbouring molecules ( $C13...O2$  contacts of 3.411 Å) and via C...C contacts between benzene rings of neighbouring molecules ( $C5...C7$  contacts of 3.341 Å and  $C1...C8$  contacts of

3.371 Å). Polymorph III crystallizes with four molecules per unit cell. The molecules 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  $C7...O3$  contacts of 3.356 Å and 3.417 Å, respectively. The chains thus formed are connected via C-H...O interactions, between 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<sup>2a-d,10,11</sup> i.e. it is derived from an *o*-hydroxy aldehyde so there is a possibility of proton transfer via intramolecular O...N hydrogen bond and the molecules have the ability to change their geometry under crystal packing



**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.

influences. Nevertheless, 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 recrystallized material of all three polymorphs of **1** were put into glass testing tubes which were then submerged into liquid nitrogen. All three samples reversibly change their colour upon cooling from different shades of orange to different shades of yellow as can be seen from Figure 5. Structural and/or other reasons for solid state thermochromism were not thoroughly revised for the purpose of this paper.



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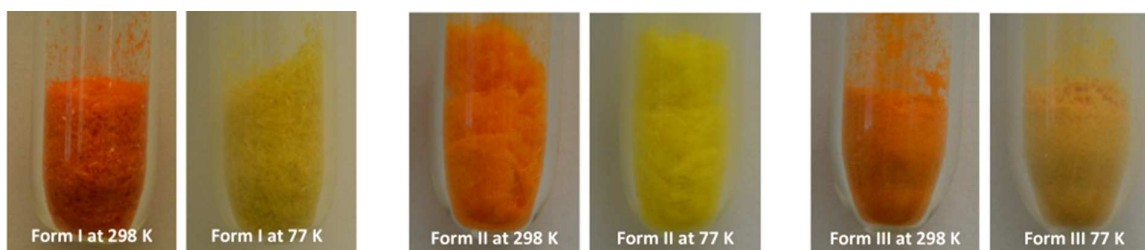


Fig. 5 Pictures of polymorphs of **ovan3aa** at room and liquid nitrogen temperature showing solid state thermochromism.

## Experimental

### Synthesis

All reagents, solvents and filtering 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-aminoacetophenone in 5 mL of corresponding boiling solvent. Single crystals suitable for SCXRD of three different polymorphs were obtained by crystallization from the mother liquor. The details on filtering paper used are in ESI, Table S2.

### Solution-based syntheses of compound 1, form I

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

The same polymorphic form was obtained at 8 °C when **3aa** solution (96 %, absolute EtOH) was filtered using blue ribbon filtering paper and student grade filtering paper for filtration of **3aa** dissolved in absolute ethanol.

### Solution-based syntheses 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 filtering paper, respectively, form II of compound 1 was obtained. Each time the resulting mixture was left semi-closed overnight at 8 °C.

### Solution-based syntheses of compound 1, form III

Reactants were dissolved in boiling absolute EtOH and the **3aa** solution was filtered using student grade filtering paper and then poured into the boiling solution of **ovan**. 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 crystals grown in mother liquor of 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 ones developed by 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 crystals grown by slow evaporation of absolute EtOH at RT when student grade filtering paper was used to eliminate impurities present in the solution of **3aa** used for solution-based synthesis of **1**.

### General procedure for 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 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 LAG experiments where 40 µL of EtOH, 96 %, 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), seed crystals of form III (48 mg, 0.2 mmol) for 2.5 minutes and then 3-aminoacetophenone (0.135 g, 1 mmol) was added. The reaction mixture was ground for another 60 s when an orange

paste forms. 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

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 MoK $\alpha$  ( $\lambda = 0.71073$  Å) radiation (for details see ESI).<sup>17</sup> 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 CuK $\alpha_1$  (1.54056 Å) radiation at 40 mA and 40 kV. Scattered intensities were measured with a scintillation counter. The angular range ( $2\theta$ ) 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 ( $2\theta$ ) was selected according to 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 reactants used as purchased. Measurements were repeated in 40 cycles. In the case of the *in-situ* monitoring of the contact reaction when reactants were separately ground prior to contact, the angular range ( $2\theta$ ) was also selected according to the diffraction maxima of 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. The data collection and analysis were performed using the program package *Philips X'Pert* (for details see ESI).<sup>18</sup>

#### Thermal study

The measurements were performed on a Mettler Toledo TGA/SDTA and DSC823<sup>e</sup> module in sealed aluminium pans (40  $\mu$ L), heated in flowing nitrogen (200 mL min<sup>-1</sup>) at a rate of 10 °C min<sup>-1</sup>. The data collection and analysis was performed using the program package STAR<sup>e</sup> Software V10.00 (for details see ESI).<sup>19</sup>

#### FT-IR spectroscopy

Infrared spectra were recorded on a PerkinElmer Spectrum Two FTIR spectrophotometer using the KBr pellet method. The data collection and analysis was performed using the program package PerkinElmer Spectrum 10.4.2.279.<sup>20</sup> Spectra and the table with characteristic stretching bands are listed in 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 reagents can significantly affect the supramolecular outcome of the synthesis of imine. The

polymorphs are thermochromic and display different molecular packing governed by C–H $\cdots$ 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<sup>13</sup> 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 the solvent-free synthesis and polymorphism control in the solid state.

#### Acknowledgements

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## Polymorphism control in mechanochemical and solution based synthesis of a thermochromic Schiff base

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### Abstract

Three crystal forms of a thermochromic Schiff base derived from *o*-vanillin and 3-aminoacetophenone were obtained by conventional solution-based methods. Two polymorphs out of three were synthesized by mechanochemical syntheses, under solvent-free conditions.

### Graphical abstract

