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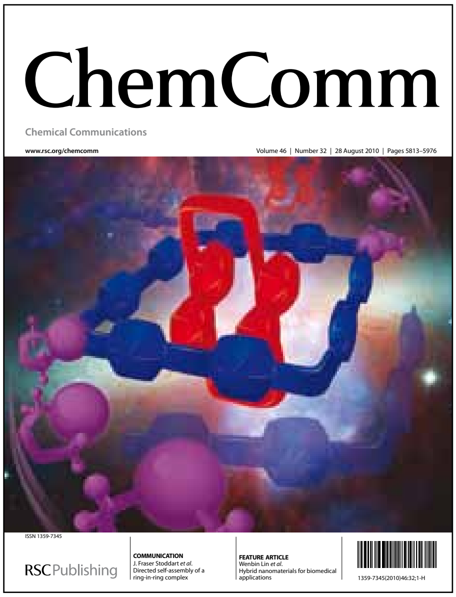

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ARTICLE TYPE

Effect of atmosphere on solid-state amine-aldehyde condensations: gas--phase catalysts for solid-state transformations†‡

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The presence of water or organic solvent vapour accelerates the solid-state condensation of solid aromatic amines and aromatic aldehydes into Schiff bases; we show the important role of catalytic triethylamine in the vapour phase in such vapour digestion synthesis, as well as in the liquid phase in synthesis *via* liquid-assisted grinding.

Mechanochemical methods, such as liquid-assisted grinding (LAG)[1] or ion- and liquid-assisted grinding (ILAG)[2] have shown great potential as efficient methods for supramolecular and covalent synthesis.[3] However, many supramolecular and covalent reactions in the solid state can occur readily simply by mixing solid reactants and without excessive input of mechanical energy.[4] Also, it has been shown that such reactions can proceed efficiently and selectively in the presence of solvent vapour.[5] During the past decade it has been shown that solvent-free synthesis and mechanochemistry are effective for the efficient and rapid synthesis of a wide range of imines.[6] However, the effect of ambient humidity and vapour environment on the reactivity of aromatic amines and aldehydes in the solid state has scarcely been explored.

We now demonstrate a surprising effect of the surrounding atmosphere on the course of solid-state synthesis of Schiff bases.[7] We focused on two different sets of imines: Schiff bases derived from 2-hydroxy-1-naphthaldehyde (**napht**) and compounds derived from 5-aminosalicylic acid (mesalazine; **5asa**)[8]. All solid-state reactions were compared by means of powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and FT-IR spectroscopy.[9] We have previously reported the mechanosynthesis of the Schiff base (**1**) derived from **napht** and 2-aminobenzonitrile (**abn**)[10] (Fig 1a). While ascertaining the reproducibility of synthesis of **1,** by grinding solid reactants in the air, we noticed that the rate of this relatively slow solid-state reaction significantly depends on the ambient relative humidity (RH). We have observed that experiments performed in the different season of the year have different rates of reaction. Tentatively, we associated this to the annual variation in the relative humidity (20%RH-80%RH). Indeed, relative humidity was found to have profound impact on the syntheses of metal-organic frameworks from a metal oxide.[11]

Guided by these observations, we turned to explore reactivity of solid **napht** and **abn** at 0%, 43%, 75% and 98% RH (Fig 1., Fig S3-S6, ESI†). Ageing of a mixture of reactants, obtained by gentle grinding of **napht** and **abn** for 10 min in agate mortar under normal laboratory conditions (temperature *ca* 25 °C, 40%-50% RH) for 3 days at 98% RH quantitatively afforded **1**, according to DSC and PXRD (Fig 1c). In contrast, at 0% RH over the same period the reaction mixture still contained a noticeable amount of reactants (Fig 1b). The observation that humidity accelerates the solid-state reaction of **napht** and **abn** was unexpected since water is a product of the imine condensation. More surprisingly, the reaction appears to be inhibited at 0% RH.

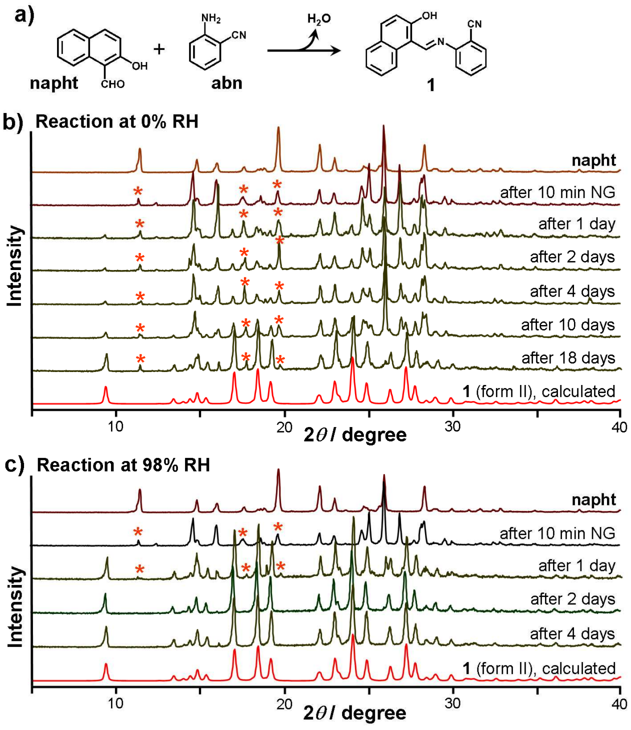

Fig. 1 a) Reaction scheme of preparation of **1** and relevant calculated and experimental PXRD patterns for reaction at 98% RH (b) and 0% RH (c). Characteristic reflections for **napht** are indicated by "*".

4-aminobenzonitrile (**4abn**) and 4-aminobenzoic acid (**4aba**) (Scheme 1) have shown considerably lower reactivity with **napht** in the solid state compared to **abn**. (Table 1). However, these reactions also proceed efficiently in the presence of water vapour. When a reaction of **napht** and **4abn** is carried out at 98% RH, almost quantitative reaction is

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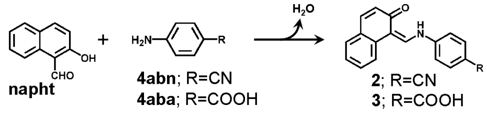


Scheme 1 Reaction scheme of preparation of **2** and **3**.

Table 1 Synthesis of **1-3** in the solid state under different humidity conditions.

Reactants	RH conditions / %	Reaction time	Observed results
napht + **abn**	0	18 days	uncomplete reaction
	43	8 days	complete reaction
	75	18 days	complete reaction
	98	3 days	complete reaction
napht + **4abn**	0	13 weeks	traces of **2**
	98	3 weeks	traces of **2**
	98	13 weeks	complete reaction
napht + **4aba**	0	13 weeks	no reaction
	98	4 weeks	traces of **3**
	98	13 weeks	uncomplete reaction

observed after 13 weeks. Ageing of the ground mixture at 0% RH for the same period afforded small amounts of **2** as evidenced by weak signals in the PXRD pattern of the mixture (Fig S7-S9, ESI†). At 0% RH reaction of **napht** and **4aba** is prevented and even after 13 weeks no traces of **3** are detectable. Ageing of the ground mixture at 98% RH for the same period afforded a mixture of **3** and reactants in traces (Table 1, Fig S10 and S11, ESI†). Overall, ageing at conditions of high humidity favours the condensations (Table 1).

Neat grinding of **5asa** and *o*-vanillin (**ovan**) for 10 min in agate mortar under normal laboratory conditions also provided a mixture of solid reactants (Fig 2a). At 0% RH reaction is prevented and after 28 days only traces of **4** are detectable (Fig 2b). Ageing of the ground mixture at 98% RH for the same period quantitatively affords **4** with a PXRD pattern identical to the one calculated from single crystal data (CCDC code VIKLAD)[12], Fig 2b. We found additional inspiration in the work of Toda *et al.*,[5a] who demonstrated that some organic reactions in the solid state proceed efficiently in the presence of a small amount of solvent vapour. Indeed, after only 1 hour of such vapour digestion[5] of the ground mixture using ethanol vapour the quantitative formation of **4** is observed. Furthermore, LAG of **5asa** and **ovan** in a ball mill for 5 min in the presence of a small amount[14] of ethanol quantitatively afforded **4,** whereas neat grinding yielded a mixture of solid reactants and traces of **4** (Fig 2b).

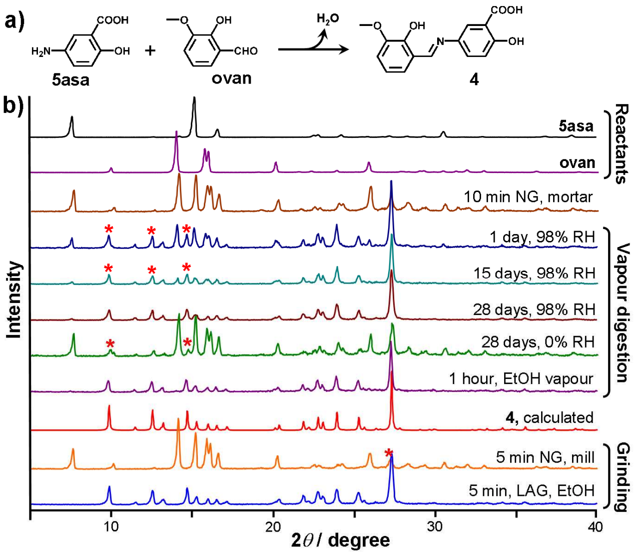


Fig. 2 a) Reaction scheme of preparation of **4**, b) relevant calculated and experimental PXRD patterns. Characteristic reflections for **4** are indicated by "*".

Table 2 Synthesis of **4** and **5** in the solid state in the absence and presence of humidity and solvent vapour**.**

Reactants	Conditions	Reaction time	Observed results
5asa + **ovan**	0% RH	28 days	traces of **4**
	98% RH	1 day	traces of **4**
	98% RH	28 days	complete reaction
	EtOH vapour	1 hour	complete reaction
5asa + **napht**	0% RH	28 days	no reaction
	98% RH	5 days	traces of **5**
	98% RH	28 days	uncomplete reaction
	EtOH vapour	15 days	uncomplete reaction
	EtOH/TEA vapour	1 day	complete reaction

Solid state synthesis of **5** by reaction of **5asa** with **napht** (Fig 3a) proceeds with significantly lower rate than previously described reaction with **ovan** (Table 2). Ageing of the mixture obtained by gentle grinding of **5asa** and **napht** for 10 min in agate mortar for 28 days at 98% RH provided a mixture of solid reactants and **5** in very poor yield, Fig 3b. It was expected that, as with the synthesis of **4**, ethanol vapour digestion would result in a higher rate of reaction than that with water vapour. However, such experiment did not make the reaction quantitative, after 15 days ageing it was obtained the same mixture of reactants and **5** as after 28 days ageing at 98% RH. Instead, we found that the rates of solid-state reaction were significantly improved by ageing of the ground

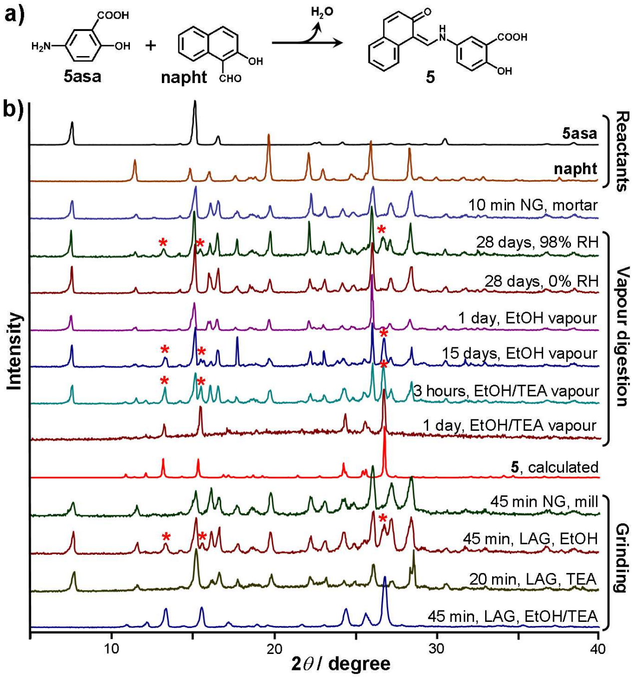
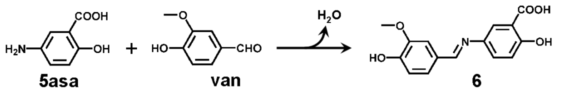


Fig. 3 a) Reaction scheme of preparation of **5**, b) relevant calculated and experimental PXRD patterns. Characteristic reflections for **5** are indicated by "*".

mixture in a vapour mixture of ethanol and an organic base triethylamine (TEA), (5% *v*/*v* of TEA), despite the fact that conventional synthesis of Schiff bases by condensation of primary amines with carbonyl compounds in solution generally requires acid catalysis. Ageing for 3 hours revealed a partial reaction, and complete reaction, yielding **5**, was observed after only 1 day (Fig 3b). Guided by the results of the previously described synthesis of **4**, we explored the mechanosynthesis of **5** in a ball mill (Table 3). Neat grinding of **5asa** and **napht** for 45 min resulted in a mixture of solid reactants. Similarly, LAG for 45 min of **5asa** and **napht** in the presence of a small amount[13] of ethanol gave the same result as vapour digestion: a mixture of solid reactants and **5** in a poor yield. Encouraged by the fact that a catalytic amount of TEA in EtOH vapour can significantly increase the efficiency of the reaction we turned to LAG. Indeed, LAG of **5asa** and **napht** for 45 min in the presence of a small quantity of EtOH/TEA mixture[14] quantitatively afforded **5**, of PXRD pattern identical with one calculated from single crystal data, Fig 3b.



Scheme 2 Reaction scheme of preparation of **6**.

Table 3 Synthesis of **4-6(H_2O)** by NG and LAG in a ball mill.

Reactants	Conditions	Reaction time	Observed results
5asa + ovan	NG	5 min	no reaction
	LAG, EtOH	5 min	complete reaction
5asa + napht	NG	45 min	no reaction
	LAG, EtOH	45 min	traces of **5**
	LAG, EtOH/TEA	45 min	complete reaction
	LAG, TEA	20 min	(solvolysis) no reaction
5asa + van	NG	30 min	no reaction
	LAG, EtOH	30 min	traces of **6(H_2O)**
	LAG, EtOH/TEA	30 min	complete reaction
	LAG, TEA	20 min	(solvolysis) no reaction

To confirm our results we finally turned to milling mechanosynthesis of **6(H_2O)**, a monohydrate of **6** derived from **5asa** and vanillin (**van**) (Scheme 2). Neat grinding of **5asa** and **van** for 30 min and LAG for 30 min in the presence of small amount of ethanol resulted only in a mixture containing solid reactants (Table 3). In contrast, LAG of **5asa** and **van** for 30 min in the presence of a small quantity of EtOH/TEA mixture quantitatively afforded **6(H_2O)** (Fig S20, ESI†).

In conclusion, we demonstrated that ageing reactions of ground mixtures of different solid aromatic amines and aromatic aldehydes are accelerated in the presence of water or organic solvent vapour. We have shown the importance of catalytic amounts of triethylamine in the vapour phase for such vapour digestion synthesis as well as in the liquid phase for Schiff base synthesis *via* liquid-assisted grinding. To the best of our knowledge, this is the first demonstration of ageing reactions catalyzed by a catalytic additive in the gas phase. The described results are important for the understanding of solid state reactivity as well as, we believe, covalent mechanosynthesis in general.

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Notes and references

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‡ Electronic Supplementary Information (ESI) available: experimental details for solution-based synthesis, instrumental experimental details and PXRD, FTIR, and DSC data. CCDC 898504 and 898505 contains the supplementary crystallographic data for this paper. See DOI: 10.1039/b000000x/

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9 To observe solid-state experiments, as well as to facilitate the characterisation of new materials (**5** and **6**) by single-crystal X-ray diffraction, conventional solution-based experiments were performed.

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13 In all LAG experiments no formation of intermediate liquid phase was observed. The amount of liquid used was very small, so as to avoid significant physical role of solvent, acting as lubricant for the reaction. For all LAG experiments the mixture of solid reactants (*ca* 200 mg) was milled in the presence of 30 µL of solvent.

14 LAG in the presence of small amount of pure TEA yielded a slurry material which, according to PXRD, contained a significant amount of reactants. We believe this can be attributed to the fact that milling was hindered because the milling media were fixed with the obtained sticky material due to solvolysis of reactants or formed product.