

# Acid-Base Catalysis in the Mechanochemical Formation of a Reluctant Imine

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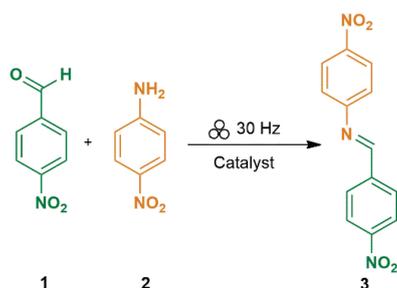
**Abstract:** Understanding the mechanism of action of catalytic amounts of additives on mechanochemical reactions is a growing and increasingly important topic in mechanochemistry, because it allows a significant level of control over the course and selectivity of mechanochemical reactions. Here, we investigate catalysis in the mechanochemical formation of an imine derived from *p*-nitrobenzaldehyde and *p*-nitroaniline, which did not occur by neat grinding at room temperature. Based on *in situ* reaction monitoring and DFT computations, we explain efficient catalysis observed for carboxylic acids, which suitably position the reacting partners and facilitate proton transfer. We also observe the formation of an aminor intermediate and conclude that the final elimination step in imine formation may proceed from either the hemiaminal or the aminor.

**Keywords:** imine, mechanochemistry, acid-base catalysis, mechanism, Raman monitoring.

## INTRODUCTION

THE substituents may determine the reactivity at the functional groups of organic molecules.<sup>[1]</sup> In particular, imine (*i.e.* a Schiff base,<sup>[2]</sup> or an azomethine, or an aldimine if derived from an aldehyde or a benzylideneaniline if the aldehyde and the amine are aromatic) formation benefits from electron-donating substituents on the aniline that increase its nucleophilic character, and from electron-withdrawing substituents on the aldehyde, that increase its

electrophilic character.<sup>[3,4]</sup> Previous work,<sup>[4–11]</sup> as well as our investigation of the mechanochemical imine formation from *p*-nitrobenzaldehyde (**1**) and differently substituted anilines, demonstrated facile preparation of imines by neat grinding.<sup>[12]</sup> However, imine formation from **1** and *p*-nitroaniline (**2**) proved elusive, despite the presence of the favourable nitro group on the benzaldehyde partner, as the product did not form by neat grinding regardless of the milling conditions and the milling time. Surprisingly, a slow solid-state formation of our target imine (**3**) was previously



### Type of catalyst

(l)

1. acetonitrile, CH<sub>3</sub>CN
2. nitromethane, CH<sub>3</sub>NO<sub>2</sub>
3. dimethylformamide, DMF
4. H<sub>2</sub>O
5. methanol, MeOH
6. *n*-heptane
7. isopropanol, 2-PrOH
8. 1,8-Diazabicyclo(5.4.0)undec-7-ene, DBU
9. acetic acid, AcOH
10. diethyl ether, Et<sub>2</sub>O
11. acetone
12. triethylamine, TEA
13. methacrylic acid, META

(s)

1. ammonium acetate, AMC
2. sulfamic acid, SA
3. benzoic acid, BA
4. citric acid, CA

Scheme 1. Imine formation from **1** and **2** with the liquid or solid additives that were tested as catalysts.

reported at room temperature, without milling, and in an open container where the reagents were mixed by stirring and left to age.<sup>[13]</sup> Since the imine **3** was previously also prepared in glacial acetic acid,<sup>[14]</sup> herein we have decided to approach our problem by exploring additives,<sup>[15–17]</sup> that may catalyse the mechanochemical reaction (Scheme 1).

## RESULTS AND DISCUSSION

In our hands, imine formation between **1** and **2** did not occur by neat grinding even after 24 h of milling at 30 Hz on a vibratory ball mill and by using heavy milling media (one WC ball, mass 3.9 g). The *in situ* collected Raman spectra and powder diffractograms, as well as the <sup>1</sup>H NMR and IR spectra of the reaction mixtures after grinding (see Figures S1, S29, S32, S37, S38), for all neat-grinding experiments show only physical mixtures of starting materials. Accordingly, our next goal was to explore the potential for catalysis among a series of solid or liquid, as well as neutral, acidic, or basic additives (Scheme 1).

We were able to achieve the formation of **3**, but, notably, only a few of the additives were catalytic, while the majority were inefficient (Table 1). The most efficient catalyst was acetic acid, which provided the yellow **3** in ca 80 % yield after 1 h of milling, and pure **3** after milling overnight. We could also achieve the formation of **3** by using other carboxylic acids, but the yields after 60 min of milling were lower. Contrary to the previous observations

**Table 1.** Effects of various additives (0.1 equiv., unless stated otherwise) on the mechanochemical synthesis of **3**. The marked fields highlight the entries where imine formation was achieved.

Entry	Additive	NMR Yield / % <sup>(a)</sup>	Entry	Additive	NMR Yield / %
1	CH <sub>3</sub> CN	0.9	11	AcOH	81
2	CH <sub>3</sub> NO <sub>2</sub>	n.d. <sup>(b)</sup>	12	AcOH	97 <sup>(d)</sup>
3	acetone	n.d.	13	AcOH	100 <sup>(c)</sup>
4	<i>n</i> -heptane	n.d.	14	AcOH	98 <sup>(e)</sup>
5	Et <sub>2</sub> O	n.d.	15	DBU	51
6	2-PrOH	n.d.	16	META	32
7	MeOH	n.d.	17	AMC	5
8	H <sub>2</sub> O	n.d.	18	SA	10
9	TEA	n.d.	19	BA	1
10	DMF	13 <sup>(c)</sup>	20	CA	65

<sup>(a)</sup> Yield determined after 60 min of grinding.

<sup>(b)</sup> Not detected.

<sup>(c)</sup> Yield determined after grinding overnight.

<sup>(d)</sup> Yield determined after 3 h of grinding.

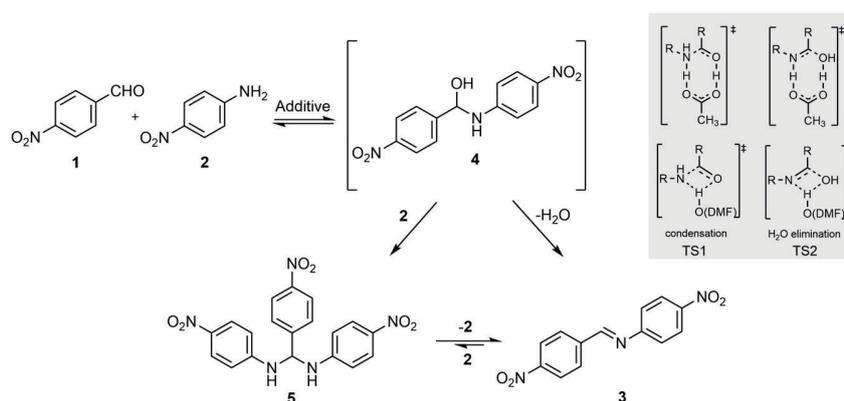
<sup>(e)</sup> 0.44 equiv. (25 μL) was loaded and yield was determined after 2 h of grinding.

of catalysed reactions involving a nucleophilic attack at the carbonyl group,<sup>[18,19]</sup> protic alcohols or strong bases, such as triethylamine, did not facilitate the imine formation, except for DBU, which afforded **3** in 51 % yield and red in colour (Figure S59).<sup>[20]</sup> When the mechanochemical reaction was conducted in the presence of DMF, imine could be observed only after extensively long grinding times (Figure S3, S4). However, the target imine seems to form upon ageing of the DMF-milled mixtures since it was observed in the NMR spectrum of a sample that was collected a few days after being milled (Figure S41, S42).

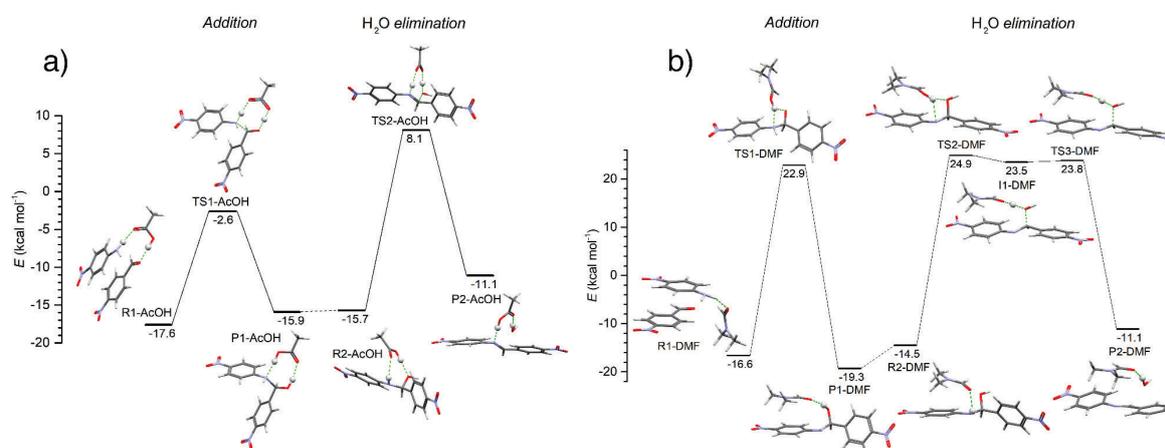
While it is well known that imine formation in solution proceeds under the influence of acid or base catalysis,<sup>[3]</sup> the observed efficiency of carboxylic acids became clear after our *in silico* modelling (Scheme 2). The geometry of the carboxylic group is not only suitable to bring close the aniline and the aldehyde, but also to facilitate proton transfer, which occurs as the nucleophilic attack of the amine on the carbonyl group of the aldehyde is taking place (Figure 1a). A basic additive such as DMF can also act as a catalyst, but clearly as a less efficient one due to higher energy barriers (Figure 1b), which agrees with the experimentally observed slower transformation.

It seems that an efficient catalyst will have both a basic and an acidic fragment that are capable of simultaneous proton abstraction from the amino group, and proton donation to the carbonyl oxygen, respectively. While acetic acid readily serves exactly this role with its carboxylic group, lower efficiency of DMF stems from proton abstraction being its dominant characteristic. We note that calculations also suggest that the condensation of **1** and **2** is not feasible without an additive (Table 2) which again agrees with the experimental data. The energy barrier for the formation of the intermediate hemiaminal (**4**) from **1** and **2** assisted by one molecule of **2** (still present at the beginning of the reaction) is 28.6 kcal mol<sup>-1</sup>. The barrier for an unassisted formation of **4** is even higher, i.e. 43.4 kcal mol<sup>-1</sup>.

Having achieved catalysed imine formation, our next aim was to experimentally track down the reaction pathway, possibly by identifying the hemiaminal **4**. The nitro substituent of **1** should have been favourable for build-up of **4**, given that a number of hemiaminals that have been obtained from solution had the aldehyde bear an electron-withdrawing group.<sup>[21–24]</sup> Potential formation of a hemiaminal intermediate has been discussed during imine formation *via* eutectic melting.<sup>[25]</sup> Also, previous investigations in the solid-state synthesis of imines have highlighted quantitative imine formation and revealed large-scale molecular migrations and regrowth on the crystallite surfaces,<sup>[4]</sup> but without focusing on the reaction pathways at the molecular level.



**Scheme 2.** Reaction pathways in the imine formation. The inset depicts the geometry in the transition states (TS) for the catalysed reactions with acetic acid or DMF.



**Figure 1.** DFT calculated reaction pathways for imine formation using (a) acetic acid and (b) DMF as the catalytic additive.

**Table 2.** Calculated energies (in kcal mol<sup>-1</sup>) relative to the starting **1** and **2** of reactants (R), products (P) and transition states (TS) for (1) condensation of **1** and **2** and (2) water elimination from **4** catalysed by different additives.

Species	Molecules	Additive					
		none	2	4	H <sub>2</sub> O	AcOH	DMF
R1	<b>1</b> + <b>2</b> + additive	-1.2	-5.4	-20.9	-15.1	-17.6	-16.6
TS1	-	43.4	28.6	16.6	14.9	-2.6	22.9
P1	<b>4</b> + additive	-1.9	-6.5	-21.7	-11.0	-15.9	-19.3
R2	<b>4</b> + additive	-	-5.7	-19.0	-11.5	-15.7	-14.5
TS2	-	-	35.9	13.3	27.3	8.1	24.9 <sup>(a)</sup>
P2	<b>3</b> + H <sub>2</sub> O + additive	-	-1.5	-18.1	-4.9	-11.1	-11.1

<sup>(a)</sup> Two-step reaction, see Figure 1b. One-step reaction needs 31.5 kcal mol<sup>-1</sup> (see Figure 4).

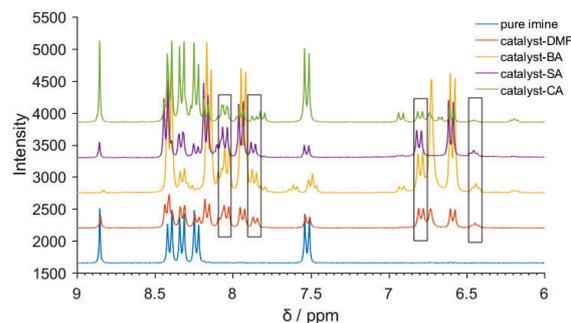
In our case, the NMR spectra of several milling products revealed a set of peaks, which did not belong to the starting materials nor to the product (Figure 2). These additional NMR signals would usually disappear in the samples that were milled for a longer period of time, while ageing

seems to have had no effect on their disappearance. These signals were only detectable if the NMR spectra were collected in DMSO-*d*<sub>6</sub>, while they disappeared from the spectra collected in CDCl<sub>3</sub>. The additional peaks were not observed in the spectrum of the pure product nor in the

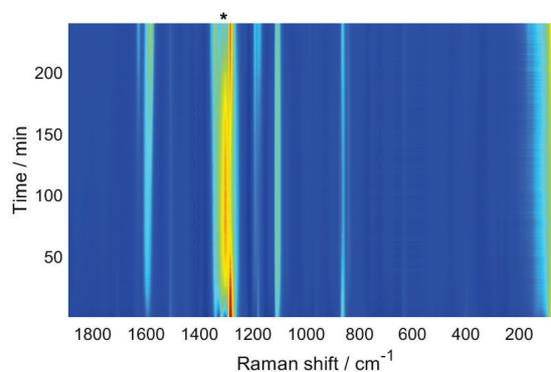
spectrum of the physical mixture of **1** and **2**, indicating that they belong to a reaction intermediate obtained by milling. Attempts to identify the intermediate in the solid-state NMR spectra of the reaction mixtures (Figure S61) were unsuccessful as the spectra did not present any additional signals other than the signals from the reactants and the product, potentially due to a small proportion of the intermediate in the samples. A detailed analysis of COSY and  $^1\text{H}$  NMR spectra (Figure S62) suggested that the transient species could rather be the aminal (**5**), resulting from the condensation of one molecule of **1** and two molecules of **2**, and not the expected hemiaminal **4**.

To prove the formation of **5** as an intermediate, we have performed the reaction between **1** and **2** in the molar ratio 1 : 2 (Figures S63-S66). *In situ* monitoring by Raman spectroscopy revealed the formation of a new and intense band at  $1303\text{ cm}^{-1}$ , which persisted for almost 4 hours, but eventually diminished as the bands of the imine emerged (Figure 3, Figures S20-S23). Appearance of the band at  $1303\text{ cm}^{-1}$  was accompanied by the complete loss of the aniline band indicating that full two equivalents of the aniline were consumed. Eventually, disappearance of the band at  $1303\text{ cm}^{-1}$  was concomitant with the emergence of the imine bands, but also of the aniline bands, strongly suggesting that the additional species was indeed the aminal, since its decomposition into the imine must also release one equivalent of aniline. Additionally, the calculated Raman spectrum of the aminal matches well with the observed spectrum of this intermediate, thus confirming its identity (Figure S25-S28). The data obtained by *ex situ* PXRD monitoring indicate a temporary emergence of an intermediate phase (Figure S31). Noteworthy, the instability of the aminal in  $\text{CDCl}_3$  has been observed before and is in accordance with our observation of the intermediate only in NMR spectra for samples dissolved in  $\text{DMSO-}d_6$ .<sup>[26]</sup>

The formation of the aminal **5** can proceed along two pathways: through the hemiaminal intermediate, or by nucleophilic addition of the aniline to the imine (Scheme 2). Experimental analysis suggests the dominance of the former pathway *via* the hemiaminal. First, *in situ* Raman monitoring and *ex situ* solution NMR for milling **1** with a large excess of **2** (5 equiv.) and with acetic acid (0.1 equiv.) as an additive indicates preferred formation of **5** (Figure S23). As **3** is eventually formed, the aniline band increases in intensity, consistent with the decomposition of **5** to the starting aniline and the product **3**. Second, **5** was not detected in Raman spectra during milling of **3** with an excess of **2** (Figure S24) and the  $^1\text{H}$  NMR spectrum of this mixture indicated less than 5% of the aminal (Figure S67). Therefore, aminal formation from the imine is also possible, but is less preferred. We have also conducted milling of **3** and **2** in the presence of 1 equiv. of water, which is otherwise present as a by-product of imine formation, but this did not facilitate the generation of **5**.



**Figure 2.** Selected sections of the  $^1\text{H}$  NMR spectra (300 MHz,  $\text{DMSO-}d_6$ ) of the reaction mixtures obtained using different additives. Signals in rectangles indicate protons of the aminal **5**.



**Figure 3.** Monitoring of imine synthesis from **1** and **2** performed in the molar ratio of 1:2 and catalysed by acetic acid (0.1 equiv.) during 240 min. Position of the strongest band of the aminal at  $1303\text{ cm}^{-1}$  is designated with an asterisk '\*'.

## CONCLUSION

This study shows that the imine-forming reaction, which did not proceed by neat grinding, can be successfully completed by using a suitable catalyst. The best results were achieved using liquid carboxylic acids, notably acetic acid, leading to the pure imine. The efficiency of carboxylic acids as catalysts stems from their geometry, which suits positioning of the reactant molecules and facilitates the concerted hydrogen-donation and hydrogen-abstraction steps in the reaction mechanism. Additives that can serve only as bases or only as acids are less efficient, if catalytic at all. The hemiaminal intermediate was not directly observed, but is inferred from the formation of the aminal. The resulting imine likely forms in elimination reactions from either the hemiaminal or the aminal.

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**Supplementary Information.** Supporting information to the paper is attached to the electronic version of the article at: <https://doi.org/10.5562/cca3954>.

PDF files with attached documents are best viewed with Adobe Acrobat Reader which is free and can be downloaded from [Adobe's web site](https://www.adobe.com/acrobat/).

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