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Mechanochemical Synthesis of Phthalimides with Crystal Structures of Intermediates and Products.

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A series of phthalimides have been successfully synthesized in the solid state by grinding (or kneading) of substituted phthalic anhydrite and aniline derivatives. Selected products and intermediates were crystallized and characterized by crystallography leading to a potential rationale for the solid-state reactivity that suggests that co-crystals could serve as intermediates.

Introduction

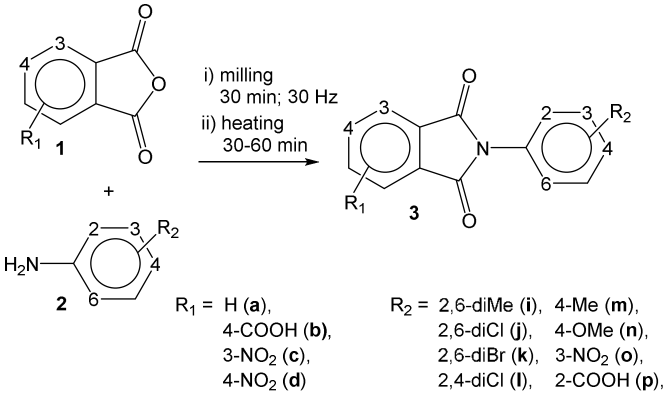
Mechanochemistry is now recognized as a clean and efficient synthesis approach to prepare coordination polymers, metal-organic frameworks or metallodrugs.[1] It plays a major role in the development of solvent-free chemical synthesis approaches and has been successfully applied to a variety of organic transformations including oxidations and reductions, Wittig condensations[2], fullerene dimerization[3], oxime functionalization[4], and coupling reactions[5]. Mechanochemisty, either by neat grinding or liquid-assisted grinding (LAG), also plays a major role in preparation of pharmaceutical co-crystals.[6]
Real-time and *in-situ* monitoring of mechanochemical reactions is now possible and shows the highly dynamic process that leads to reaction rates comparable or greater than those observed in solution.[7]

Molecular-level mechanisms underlying grinding mechanosynthesis still need to be studied. Concerning LAG (also known as solvent-drop grinding or kneading, as coined by Braga et al.[8]) no detailed mechanism underlying the process is known but molecular diffusion enhanced by the added liquid has been proposed to explain the efficiency of the reactions.[9]
Co-crystallization has also been proposed to play a major role during the solid-state process and led Zaworotko to develop the concept of co-crystal controlled solid state synthesis C3S3.[10]
Formation of co-crystals in the same lattice brings functional groups close enough to react.

The reaction between various substituted phthalic anhydrites and aniline derivatives (Scheme 1) has been selected for the present study.

The most important synthesis of phthalimides is the dehydrative condensation of phthalic anhydride at high temperatures with primary amines, when the amine is available. When the amine is not readily accessible, the direct N-alkylation of phthalimides with alcohols under Mitsunobu conditions[11] and of potassium phthalimide with alkyl halides (Gabriel Synthesis)[12] are popular alternative approaches. Among other applications, phthalimides are suitable protective groups in peptide synthesis.

The present work shows that mechanochemistry is an interesting alternative for the synthesis of these compounds. Our study further supports the use of this approach for the solid state reaction of amines and carbonyl compounds.[13]



Scheme 1 Formation of phthalimides (**3**) from corresponding substituted phthalic anhydrites (**1**) and aniline derivatives (**2**).

Experimental

Materials and methods

Reagents were purchased from Sigma-Aldrich, TCI and Santa Cruz BioTechnologies. Solvents were purchased from Acros Organic (Geel, Belgium) and used with no further purification.

General procedure

2,5 mmol of aniline **2**, 1 equivalent of corresponding anhydride **1** and 2-10 balls are added to a 2 mL plastic vial or a zirconium oxide jar. The total mass of all reactants did not exceed 1 g. The mixture is ground using a vibration ball mill Retsch MM400 for 90 minutes at 30 Hz. The melting point or phase transition temperature of the ground mixture was initially determined using a Koffler bench apparatus. The bulk was then heated to 10°C below this temperature in a heating metal block thermostat (MBT 250, Kleinfeld). The temperature was maintained for 60 to 90 minutes to give imide **3**.

Single Crystals

Single crystal X-ray diffraction was performed on a Gemini Ultra R system (4-circle kappa platform, Ruby CCD detector) using Mo (λ = 0.71073 Å) or Cu K_λ radiation (λ = 1.54056 Å). Selected crystals were mounted on the tip of a quartz pin using cyanoacrylate (Commercial glue). Cell parameters were estimated from a pre-experiment run and full data sets collected at room temperature. Structures were solved by direct methods with sir92 (v.3.0)[14] program and then refined on F^2 using SHELXL-97 software[15]. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms (not implicated in H-bonds) in the riding mode with isotropic temperature factors fixed at 1.2 times $U_{(eq)}$ of the parent atoms (1.5 times for methyl groups). Hydrogen atoms implicated in H-bonds were localized by Fourier difference maps (ΔF). CCDC 1021624-1021632 entries contain the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

X-Ray Powder Diffraction (XRPD)

Powder X-Ray Diffraction (PXRD) data were collected on a PANalytical reflexion-geometry diffractometer, using Ni-filtered Cu Kα radiation (λ = 1.54179 Å) at 40 kV and 40 mA with an X'Celerator detector. Each sample was analyzed between 4 and 50°2θ with a step size of ca. 0.0167°2θ and a total scan time of 3 min 48 s.

Nuclear Magnetic Resonance (NMR)

All NMR (^{1}H) were recorded on Jeol spectrometer (JNM EX-400) at 25°C. Chemical shifts are reported in parts per million (ppm) using the solvent residual peak as reference ($CDCl_3$: 7.26 ppm; DMSO-d6: 2.50 ppm; CD_3OD: 3.31 ppm). Coupling constants (J) are reported in Hertz (Hz). The resonance multiplicity is described as s for singlet, bs for broad singlet, d for doublet, t for triplet, q for quadruplet and m for multiplet. Data are provided as supplementary material.

Results and discussion

Solid mixtures of **1** and **2** (Scheme 1) were ground using a Retsch MM400 ball mill operating at 30Hz for 30 min. For 2,6-dimethyl-aniline (**2i**, Scheme 1), which is a liquid at room temperature, the resulting wet paste was ground following the general procedure. The ground products obtained were further heated in a metal block thermostat (MBT 250, Kleinfeld). In each case, the outcome was characterized by calorimetry (melting point), NMR, powder X-ray diffraction (PXRD) and, when possible, by single X-ray crystallography (SCXRD). Highlights of the results are summarized in Table 1.

Grinding of phthalic anhydrite (**1a**) with aniline derivatives led to either an amorphous solid (**2i**) or a physical mixture (**2k** and **2n**) of the starting reactants. Heating of the resulting solids allowed formation of the corresponding phthalimides (**3ai**, **3ak** and **3an**) as white crystalline powders.

In the case of N-phthaloyl-2,6-dimethylaniline (**3ai**, m.p. 204°C), X-ray diffraction data measured on both powders and single crystals (Fig. 1, Fig. S1) confirm unambiguously the formation of the product. NMR data indicate 100% conversion of the reactants.

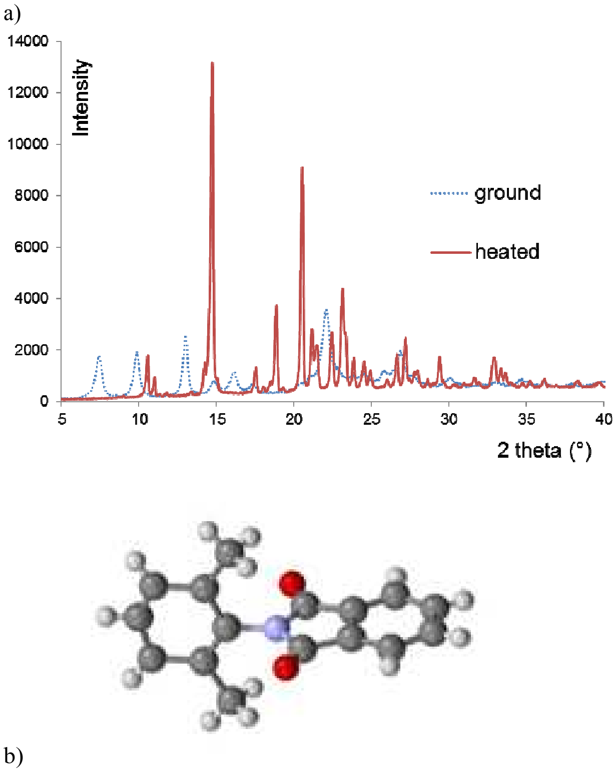


Fig. 1 X-ray diffraction analysis of the solid corresponding to N-phthaloyl-2,6-dimethylaniline (**3ai**), obtained after grinding of **1a** and **2i** and heating to 200°C. a) Powder diffractograms recorded before and after heating of the ground sample and b) single crystal structure

Interestingly, the powder diffractogram of the ground product (2θ = 7, 10, and 13.5°) is not only different from the starting phthalic anhydrite (**1a**, 2θ = 13, 17, and 23°) [*2,6-dimethyl-aniline (**2i**) is a liquid*] (Fig. S1) but also from the final N-phthaloyl-2,6-dimethylaniline (**3ai**, 2θ = 11, 15, 19 and 22°) product obtained after heating (Fig. 1, Fig. S1). This suggests that the unheated solid corresponds to an intermediate state that needs to be heated to form the final phthalimide product.

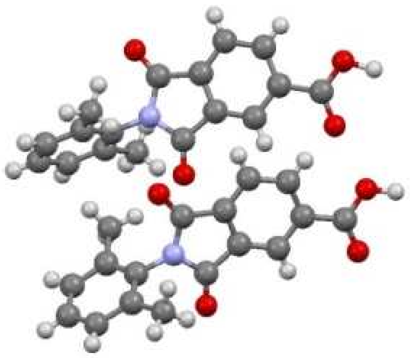


Fig. 2 Single crystal structure of 4-carboxylic-N-phthaloyl-2,6-dimethylaniline (**3bi**) obtained by grinding of **1b** and **2i** and heating to 200°C. Recrystallization from EtOAc.

Table 1. Outcome of grinding (and heating) of phthalic anhydrites (**1a-d**) with different aniline derivatives (**2i-p**)

R_1 = H *(1a)*				R_1 = 4-COOH *(1b)*		
R_2 =	2,6-diMe **(2i)**	2,6-diBr **(2k)**	4-OMe **(2n)**	2,6-diMe **(2i)**	2,6-diBr **(2k)**	4-OMe **(2n)**
Colour	white	white	white	white	yellow	white
m.p.[a] (°C)	226	160	158	220	164	>260
Solid	µcrystalline	µcrystalline	mixture	amorphous	µcrystalline	amorphous
Heated to (°C)	200	150	150	200	140	200
Colour	white	white	brown	white	white	yellow
m.p. (°C)	204	160	160	222	160	>260
Solid	µcrystalline	µcrystalline	µcrystalline	µcrystalline	µcrystalline	µcrystalline
R_1 = 4-COOH						
R_2 =	2,6-diCl **(2j)**	2,4-diCl **(2l)**	4-Me **(2m)**	3-NO_2 **(2o)**	2-COOH **(2l)**	
Colour	yellow	white	white	yellow	yellow	
m.p. (°C)	202	222	>260	>260	230	
Solid	µcrystalline	amorphous	amorphous	amorphous	amorphous	
Heated to (°C)	180	180	200	200	180	
Colour	white	white	yellow	grey	white	
m.p. (°C)	230	>260	>260	>260	230	
Solid	µcrystalline	µcrystalline	µcrystalline	µcrystalline	µcrystalline	
R_1 = 3-NO_2 *(1c)*						
R_2 =	2,6-diMe **(2i)**	2,6-diCl **(2j)**	2,6-diBr **(2k)**	4-OMe **(2n)**	4-Me **(2m)**	3-NO_2 **(2o)**
Colour	white	yellow	white	yellow	yellow	white
m.p. (°C)	206	178	168	200	170	224
Solid	µcrystalline	µcrystalline	mixture	amorphous	amorphous	amorphous
Heated to (°C)	180	150	150	180	150	120
Colour	white	white	white	yellow	yellow	white
m.p. (°C)	206	176	190	202	160	224
Solid	µcrystalline	µcrystalline	µcrystalline	µcrystalline	µcrystalline	µcrystalline
R_1 = 4-NO_2 *(1d)*						
R_2 =	2,6-diMe **(2i)**	2,6-diCl **(2j)**	2,6-diBr **(2k)**	4-OMe **(2n)**	4-Me **(2m)**	3-NO_2 **(2o)**
Colour	brown	yellow	orange	yellow	yellow	yellow
m.p. (°C)	168	168	178	212	178	254
Solid	amorphous	mixture	mixture	amorphous	amorphous	amorphous
Heated to (°C)	120	160	150	180	150	120
Colour	brown	brown	white	yellow	brown	brown
m.p. (°C)	168	168	178	212	160	254
Solid	µcrystalline	µcrystalline	µcrystalline	µcrystalline	µcrystalline	µcrystalline

[a] *Tg for amorphous* s

Grinding of 4-carboxylic acid phthalic anhydrite (**1b**) with aniline derivatives usually resulted in changes in colour of the solids. In most cases, grinding led to amorphous solids which, upon heating, transformed to crystalline material (Table 1). This is well illustrated by the synthesis of 4-carboxylic-N-phthaloyl-2,6-dimethylaniline (**3bi**, m.p. 222°C), obtained by grinding of **1b** and **2i** and heating to 200°C (Fig. 2). The amorphous solid obtained by grinding (kneading) of **1b** and **2i** transforms to a crystalline white powder (Fig. S2a, 2θ = 5, 12, 13, 14, and 17°).

Single crystals of the resulting product could be obtained, either from a saturated solution in Toluene/MeOH or from a solution in EtOAc.

The crystal structure from EtOAc confirms formation of the **3bi** phthalimide product (Fig. 2). The second structure corresponds to a solvate (toluene) (Fig. S2). The X-ray diffraction pattern simulated from the single crystal structure obtained in EtOAc confirmed that the phthalimide product was obtained in the ground solid powder after heating (2θ = 6, 16, 17, 19, and 25°, Fig. 2S).

Similarly, crystals of 4-carboxylic-N-phthaloyl-p-anisole (**3bn**, m.p. >260°C) could be grown from the solid resulting from solid state reaction between **1b** and 4-methoxyaniline (**2n**). This crystal structure experimentally confirmed the formation of the phthalimide product (Fig. 3S).

Mechanochemical reactions of 3- and 4-nitrophthalic anhydrites (**1c** and **1d**) with aniline derivatives have also been studied. Like in the case of phthalic anhydrite (**1a**) and 4-carboxylic acid phthalic anhydrite (**1b**), grinding followed by heating led generally to the corresponding nitro-N-phthaloyl products (Table 1).

Evidence for formation of 3- and 4-nitro-N-phthaloyl-p-anisole (**3cn** and **3dn**) starting from 4-methoxy aniline (**2n**) was obtained by the determination of the corresponding crystal structures (Fig. 3).

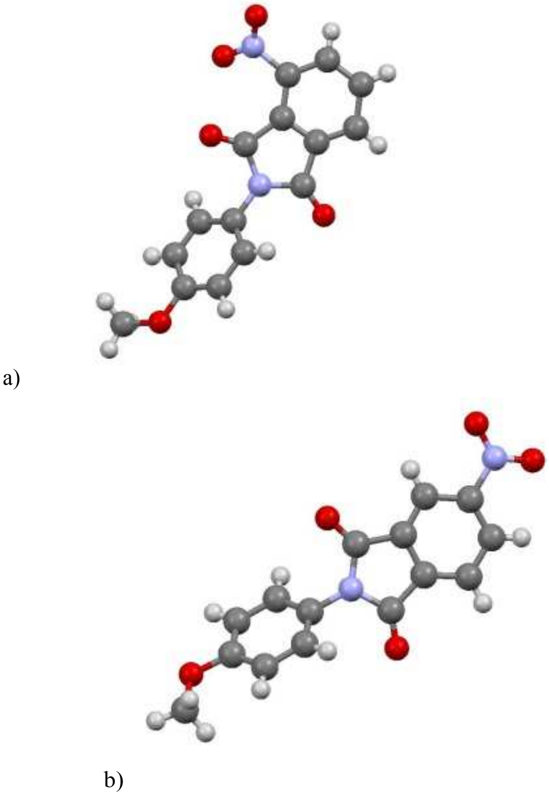


Fig. 3 Solid-state reaction of 3- or 4-nitrophthalic anhydrite (**1c** or **1d**) with p-anisole (**2n**) leads to 3- and 4-nitro-N-phthaloyl-p-anisole (a, b).

In the case of the reaction of 4-nitro-phthalic anhydrite with 2,6-dibromoaniline (**2k**), the corresponding 4-nitro-N-phthaloyl-2,6-dibromoaniline (**3dk**) product is formed as evidenced by determination of its crystal structure (Fig. 4a). Very interestingly, we were also able to trap an open intermediate of the reaction (Fig. 4b), *i.e.* the open amide product of **3dk**. The same open product was observed after reaction of 3-nitrophthalic anhyd anhydrites rates (**1c**) and 2,6-dibromoaniline (**2k**) (Fig. S4). In all cases the single crystals are obtained from the heated sample.

NMR confirmed that there was more of the open form of the product along with the expected nitro-N-phthaloyl-2,6-dibromoanilines (**3ck** or **3dk**) product. This is also consistent with the fact that corresponding single crystals were obtained as a mixture with amorphous powder.

Whether the open products result from partial hydrolysis of the nitro-N-phthaloyl-2,6-dibromoanilines or correspond to the first step of the nucleophilic attack of the aniline nitrogen on the nitro-phthalic anhydrites s is still to be studied. However, the second hypothesis is favoured in the present case.

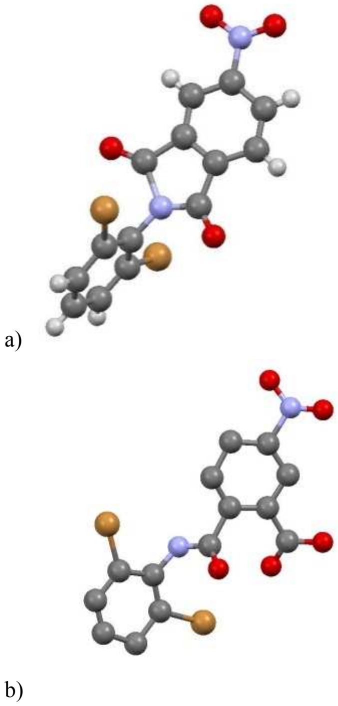


Fig. 4 Solid-state reaction of 4-nitro phthalic anhydrite (**1d**) and 2,6-dibromoaniline (**2k**) leads to nitro-N-phthaloyl-2,6-dibromoaniline (**3dk**) (a) but also to the open intermediate (b).

Indeed, together with the open intermediates described in figures 4b and S4, a new crystal form was trapped in the case of the solid state reaction between 4-nitrophthalic anhydrite (**1d**) and 4-methylaniline (**2m**).

In this case, the intermediate corresponded to the co-crystal of 4-methylaniline (**2m**) and 4-nitro-phthalic acid, the hydrolysed 4-nitro-phthalic anhydrite (**1d**) (Fig. 5). Evidence for a co-crystal instead of a salt comes from the geometry of the two carboxylic acids showing clear alterning single C-OH and double C=O bonds for both COOH groups. In the co-crystal, 4-methylaniline (**2m**) and 4-nitrophthalic acid form a 1:1 **1d·2m** complex stabilized by π–π stacking. Stability of the complex is reinforced by intermolecular H-bonds (Fig. S5, Table S1).

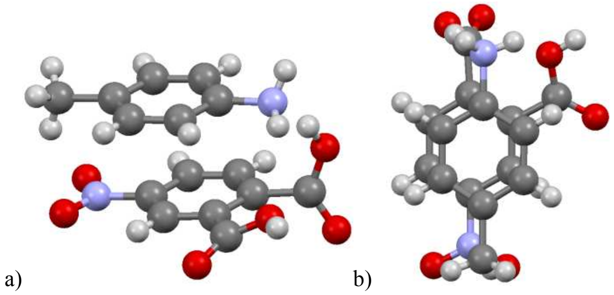


Fig. 5 Two views (a, b) of the π–π stacking 1:1 co-crystal observed during the reaction of 4-nitrophtalic anhydrite (**1d**) and 4-methylaniline (**2m**).

This structure suggests that a co-crystal is a viable intermediate during the solid-state reaction. In addition, the crystal packing supports a mechanism in which molecules are positioned in such a way that the reactive nucleophilic nitrogen of the aniline derivative is optimally placed to react with the electrophilic carbon atom of one of the carboxylic acids (Nu(a) or Nu(b), Fig. 6). Based on the isomer observed in the open intermediate (see Fig. 4b in the case of **3dk**), it is reasonable to favour pathway (b) in Fig 6.

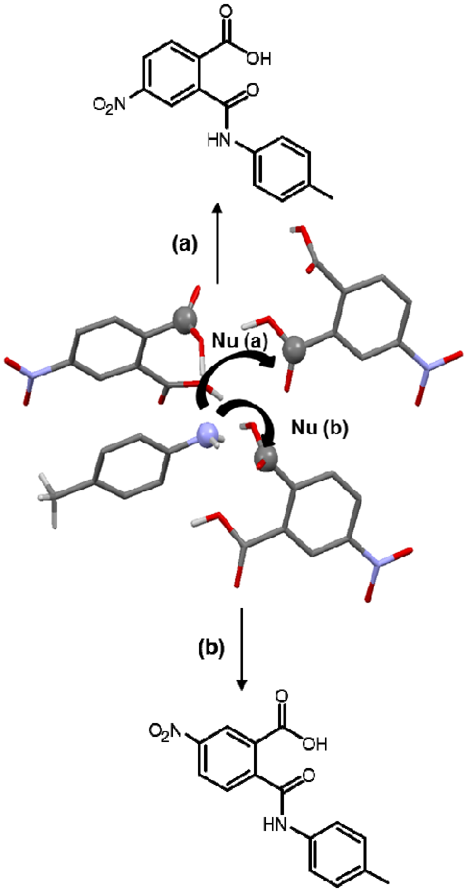
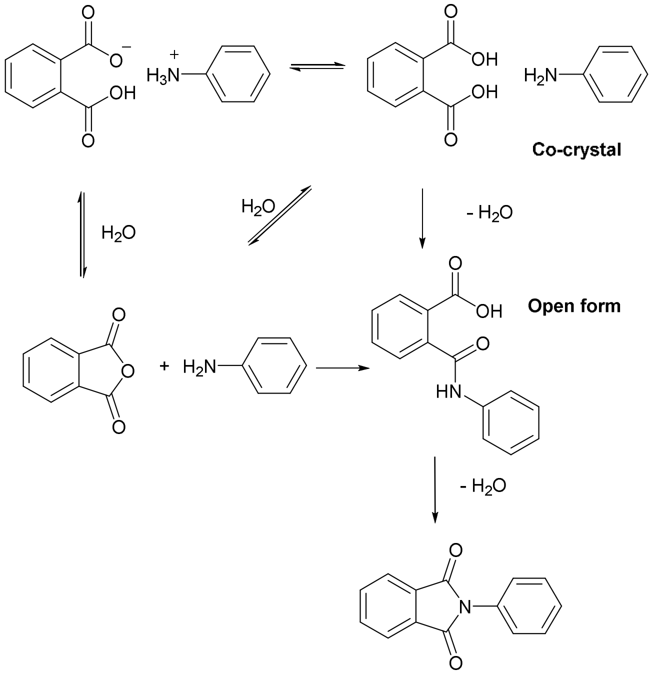


Fig. 6 Possible initial steps in the mechanism of formation of phthalimides leading to the open amide monosubstituted adduct derived from the crystal structure of the 1:1 **1d**·**2m** co-crystal. Nucleophilic attack by the deprotonated nitrogen atom on one of the carboxylic acids (two possible attacks are highlighted Nu(a) and Nu(b) leads to two possible open intermediates (pathway (a) or (b)). *Atoms involved in the mechanism presented as spheres, H_C atoms omitted for clarity.*

Such a nucleophilic attack of the aniline should also be energetically favoured over the reaction with an acid involving a molecule parallely stacked to the aryl-amine, as this would lead to less rearrangement of the solid.
The presence of this co-crystal as a general intermediate in the different reactions that were carried out is suggested by the PXRD data. In most cases, the ground powder obtained before heating (see for example Fig 1a) is characterized by small angle diffraction peaks, corresponding to entities (probably co-crystals) crystallizing in a larger cell.

Conclusions

In the course of our study of the solid state reactions of a series of anilines and phthalic anhydrites, we have shown that grinding of the reactants followed by heating of the resulting solids led to the corresponding phthalimides, in agreement with previous data from the literature.[10,13] Evidence for the formation of these products is provided by the physico-chemical characteristics (m.p., NMR, powder X-ray patterns) of the final samples and by a series of crystal structures. Interestingly, intermediates were also trapped in the solid state. They do pave the way to formation of the final, fully cyclized, phthalimide and suggest a potential mechanism that could involve a co-crystal intermediate and the open amide adduct (Scheme 2). Involvement of co-crystals during the solid state synthetic process is in agreement with evidences provided by Zaworotko et al. [10]



Scheme 2 Possible steps in the pathway leading to formation of phthalimides (**3**) from corresponding substituted phthalic anhydrites (**1**) and aniline derivatives (**2**), involving the intermediates trapped in this study.

Influence of the nature and position of substituents (in particular electronic effects) on the reactivity further needs to be systematically studied. Implication of the hydrolysed, instead of the closed, phthalic anhydrite in the mechanism is another open question that needs to be investigated. Development of recent *in situ* methods now opens new opportunities to directly challenge the mechanism proposed in the present work.

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Notes and references

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Electronic Supplementary Information (ESI) available: [Powder X-ray diffraction data, extra crystal structures, NMR data].
See DOI: 10.1039/b000000x/

Crystal Data for PA-DMA (**3ai**). Prism colourless crystals, orthorhombic, Pbc2$_1$, a = 9.837(2), b = 16.124(4), c = 8.643(3)Å, α =90.00, β = 90.00, γ = 90.00 °, V = 1370.9(6) Å^3, Z = 4, ρ_{calc} = 1.217g cm^{-3}, F_{000} = 528, λ Mo Kα = 0.71073 Å, θ_{max} = 25.0°, 4759 total measured reflections, 1994 independent reflections (R_{int} = 0.031), 1322 observed reflections (I > 2 σ(I)), μ = 0.081 mm^{-1}, 136 parameters, R_1 (observed data) = 0.0880, S = GooF = 1.09, Δ/s.u. = 0.00, residual ρ_{max} = 0.27 e Å^{-3}, ρ_{min} = -0.26 e Å^{-3}.

Crystal Data for BTA-DMA 1st form (**3bi**). Plates colourless crystals, triclinic, P-1, a = 8.3591(3), b = 10.4196(7), c = 19.0455(9)Å, α =88.407(5), β = 88.481(3), γ = 76.340(4)°, V = 1610.95(15) Å^3, Z = 1, ρ_{calc} = 1.311g cm^{-3}, F_{000} = 665, λ Mo Kα = 0.71073 Å, θ_{max} = 25.0°, 11980 total measured reflections, 5663 independent reflections (R_{int} = 0.024), 3983 observed reflections (I > 2 σ(I)), μ = 0.093 mm^{-1}, 438 parameters, R_1 (observed data) = 0.0468, S = GooF = 0.99, Δ/s.u. = 0.02, residual ρ_{max} = 0.16 e Å^{-3}, ρ_{min} = -0.17 e Å^{-3}.

Crystal Data for BTA-DMA 2nd form (**3bi**). Plates colourless crystals, triclinic, P$_{-1}$, a = 8.4040(5), b = 8.4040(5), c = 15.240(1)Å, α =97.881(6), β = 93.354(5), γ = 96.810(6)°, V = 1468.73(18) Å^3, Z = 4, ρ_{calc} = 1.335 g cm^{-3}, F_{000} = 616, λ Mo Kα = 0.71073 Å, θ_{max} = 23.3°, 10179 total measured reflections, 4188 independent reflections (R_{int} = 0.078), 2204 observed reflections (I > 2 σ(I)), μ = 0.096 mm^{-1}, 400 parameters, R_1 (observed data) = 0.0705, S = GooF = 1.01, Δ/s.u. = 0.03, residual ρ_{max} = 0.19 e Å^{-3}, ρ_{min} = -0.21 e Å^{-3}.

Crystal Data for 3NPA-DBA open form (**3ck**). Needle colourless crystals, triclinic, P_{-1}, a = 9.188(5), b = 13.284(7), c = 14.477(8)Å, α = 68.21(5), β = 81.24(4), γ = 75.69(4) °, V = 1586.2(16) Å^3, Z = 2, ρ_{calc} = 1.857 g cm^{-3}, F_{000} = 862, λ Mo Kα = 0.71073 Å, θ_{max} = 25.0 °, 11937 total measured reflections, 5562 independent reflections (R_{int} = 0.052), 3222 observed reflections (I > 2 σ(I)), μ = 5.136 mm^{-1}, 415 parameters, R_1 (observed data) = 0.0655, S = GooF = 1.04, Δ/s.u. = 0.00, residual ρ_{max} = 0.88 e Å^{-3}, ρ_{min} = -0.59 e Å^{-3}.

Crystal Data for 3NPA-pAni (**3cn**). Needle yellow crystals, Monoclinic, P2$_1$, a = 3.8289(1), b = 23.3314(7), c = 7.4554(2)Å, α = 90, β = 98.153(3), γ = 90°, V = 659.3(1) Å^3, Z = 2, ρ_{calc} = 1.502 g cm^{-3}, F_{000} = 308, λ Cu Kα = 1.54184 Å, θ_{max} = 66.6°, 5907 total measured reflections, 2304 independent reflections (R_{int} = 0.0182), 2285 observed reflections (I > 2 σ(I)), μ = 0.977 mm^{-1}, 200 parameters, R_1 (observed data) = 0.0270, S = GooF = 1.08, Δ/s.u. = 0.00, residual ρ_{max} = 0.16 e Å^{-3}, ρ_{min} = -0.14 e Å^{-3}.

Crystal Data for 4NPA-DBA (**3dk**). Plates colourless crystals, monoclinic, $I2/a$, a = 14.8231(9), b = 7.7177(6), c = 25.714(2)Å, α = 90, β = 97.692(7), γ = 90 °, V = 2915.2(4) Å^3, Z = 8, ρ_{calc} = 1.941g cm^{-3}, F_{000} = 1648, λ Mo Kα = 0.71073 Å, θ_{max} = 25.0°, 6774 total measured reflections, 2563 independent reflections (R_{int} = 0.079), 1465 observed reflections (I > 2 σ(I)), μ = 5.580 mm^{-1}, 392 parameters, R_1 (observed data) = 0.0491, S = GooF = 0.96, Δ/s.u. = 0.00, residual ρ_{max} = 0.36 e Å^{-3}, ρ_{min} = -0.40 e Å^{-3}.

Crystal Data for 4NPA-DBA open form (**3dk**). Plates colourless crystals, monoclinic, $P2_1/n$, a = 14.0897(3), b = 4.8183(1), c = 22.6757(3)Å, α = 90, β = 90.555(9), γ = 90 °, V = 1539.3(1) Å^3, Z = 4, ρ_{calc} = 1.916g cm^{-3}, F_{000} = 864, λ Cu Kα = 1.54184 Å, θ_{max} = 66.6°, 8457 total measured reflections, 2710 independent reflections (R_{int} = 0.0344), 2466 observed reflections (I > 2 σ(I)), μ = 6.946 mm^{-1}, 216 parameters, R_1 (observed data) = 0.0465, S = GooF = 1.07, Δ/s.u. = 0.00, residual ρ_{max} = 0.53e Å^{-3}, ρ_{min} = -0.68 e Å^{-3}.

Crystal Data for 4NPA-pAni (**3dn**). Triangular yellow crystals, monoclinic, Pn, a = 6.9750(12), b = 3.876(1), c = 23.998(3)Å, α = 90, β = 91.227(12), γ = 90 °, V = 648.6(2) Å^3, Z = 2, ρ_{calc} = 1.527g cm^{-3}, F_{000} = 308, λ Mo Kα = 0.71073 Å, θ_{max} = 23.3°, 1900 total measured reflections, 1462 independent reflections (R_{int} = 0.045), 1224 observed reflections (I > 2 σ(I)), μ = 0.117 mm^{-1}, 200 parameters, R_1 (observed data) = 0.0724, S = GooF = 1.14, Δ/s.u. = 0.00, residual ρ_{max} = 0.32 e Å^{-3}, ρ_{min} = -0.34 e Å^{-3}.

Crystal Data for 4NPA-pTol co-crystal (**3dm**). Triangular yellow crystals, Orthorhombic, Fdd2 , a = 59.519(2), b = 12.942(5), c = 7.623(2)Å, α = 90, β = 90, γ = 90 °, V = 5872(3) Å^3, Z = 16, ρ_{calc} = 1.440g cm^{-3}, F_{000} = 2656, λ Mo Kα = 0.71073 Å, θ_{max} = 25.0°, 20263 total measured reflections, 2560 independent reflections (R_{int} = 0.052), 2335 observed reflections (I > 2 σ(I)), μ = 0.113 mm^{-1}, 217 parameters, R_1 (observed data) = 0.0433, S = GooF = 1.01, Δ/s.u. = 0.04, residual ρ_{max} = 0.26 e Å^{-3}, ρ_{min} = -0.15 e Å^{-3}.

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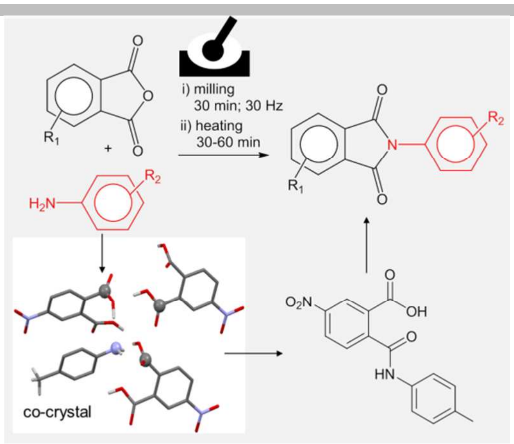
Phthalimides has been successfully synthesized in the solid state by grinding (or kneading) of substituted phthalic anhydrate and aniline derivatives. Selected products and intermediates were crystallized and characterized by crystallography leading to a potential rationale for the solid-state reactivity that involves co-crystals as intermediates.



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