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Dry-vortex grinding facilitates a [2 + 2] cycloaddition reaction that triggers a cascade-like reaction that improves the yield under substoichiometric conditions†

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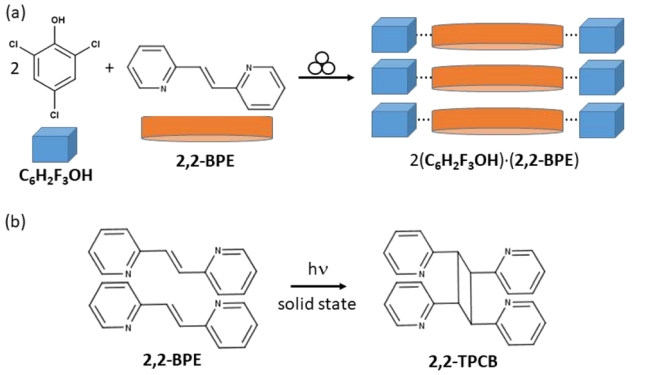
The ability to achieve a series of photoreactive solids using dry-vortex grinding that contains *trans*-1,2-bis(2-pyridyl)ethylene along with 2,4,6-trifluorophenol at different molar ratios is reported. In all cases, mechanochemical grinding generates a three-component hydrogen-bonded co-crystal that undergoes a [2 + 2] cycloaddition reaction. Curiously, the solids formed with a substoichiometric ratio of the template also reached a nearly quantitative yield, since the formation of the photoproduct causes a cascade-like reaction within the solid which shifts the remaining reactant molecules into a suitable position to photoreact.

Mechanochemistry continues to be an important process in the synthesis of organic molecules that are difficult or nearly impossible to form using a traditional solvent-based approach.[1] These solid-state transformations are generally high yielding and require little to no solvent to generate these molecular targets. In addition, mechanochemical grinding has also been shown to be an effective approach in the formation of co-crystals that will ultimately have different physical and chemical properties when compared to their constituent components.[2]

The [2 + 2] cycloaddition reaction remains an important synthetic route in the formation of cyclobutane-based molecules.[3] By definition, this solid-state photoreaction is solvent-free since it only requires proper alignment of a pair of carbon–carbon double bonds (C=C) along with ultraviolet light to initiate this pericyclic reaction. Unfortunately, most olefin-containing reactants are photostable as a single-component solid due to improper crystal packing of the reactive centres.[4] In order to overcome this packing issue, a template-based approach has been employed using non-covalent interactions to align a pair of C=C in a suitable position to photoreact.[5] These photoreactive co-crystals have been based upon various hydrogen- and halogen-bonding interactions between the template and reactant molecule.

A continued focus within our research group has been the formation of photoreactive co-crystals by utilizing various co-crystal formation approaches.[6] Recently, we reported the formation of a photoreactive co-crystal where 2,4,6-trifluorophenol ($C_6H_2F_3OH$) acts as a molecular template to organize *trans*-1,2-bis(2-pyridyl)ethylene (**2,2-BPE**) to undergo a solid-state [2 + 2] cycloaddition reaction.[7] Upon exposure to ultraviolet light, the co-crystal **2($C_6H_2F_3OH$)·(2,2-BPE)** (Scheme 1a) undergoes a quantitative photoreaction to form *rctt*-tetrakis(2-pyridyl)cyclobutane (**2,2-TPCB**) (Scheme 1b).

Another area within mechanochemistry is the formation of co-crystals that undergo the solid-state [2 + 2] cycloaddition reaction.[8] Generally, this solvent-free approach will have lower costs and higher yields associated with it when compared to traditional liquid-based approach. In addition, these high



Scheme 1 Rendering of (a) the dry-vortex grinding formation of the three-component hydrogen-bonded co-crystal **2($C_6H_2F_3OH$)·(2,2-BPE)** and (b) the solid-state [2 + 2] cycloaddition reaction of **2,2-BPE** to yield **2,2-TPCB**.

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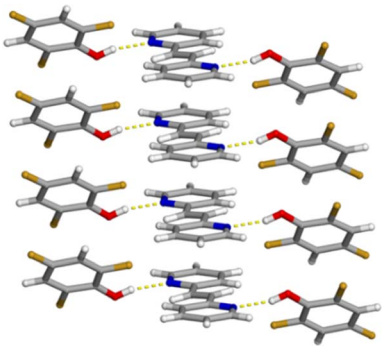

Fig. 1 X-ray structure of **2($C_6H_2F_3OH$)·(2,2-BPE)** illustrating both the hydrogen-bonded three-component assembly and the infinite homogeneous face-to-face π–π stacking pattern.

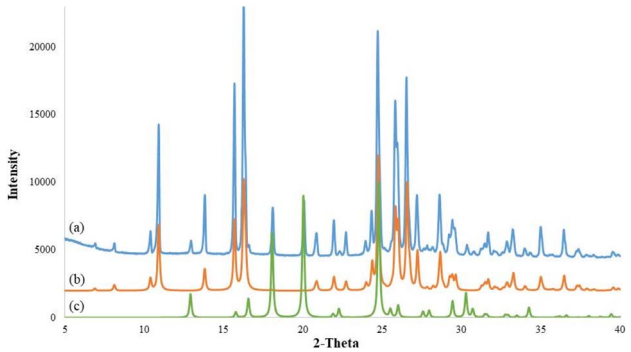

Fig. 2 Powder X-ray diffraction diffractogram of (a) the vortex-ground stoichiometric sample (2 : 1 molar ratio) along with the theoretical pattern for both (b) **2($C_6H_2F_3OH$)·(2,2-BPE)** and (c) **2,2-BPE**.

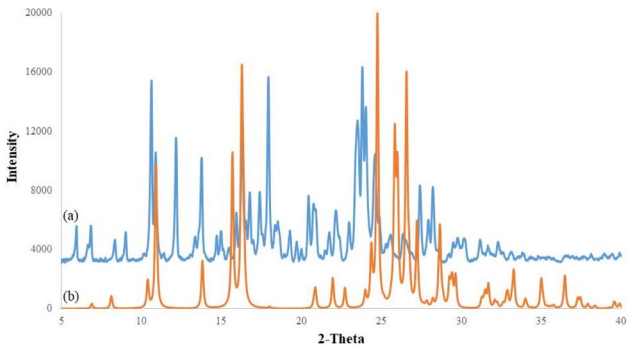

Fig. 3 Powder X-ray diffraction diffractogram of (a) photoreacted stoichiometric sample (2 : 1 molar ratio) along with the theoretical pattern for (b) the co-crystal **2($C_6H_2F_3OH$)·(2,2-BPE)**.

yielding photoreactions have been achieved at sub-stoichiometric ratios for the template where they behave like a solid-state catalysts.[9]

With the goal to form **2($C_6H_2F_3OH$)·(2,2-BPE)** and ultimately **2,2-TPCB**, without the use of solvent, a mechanochemical approach was attempted. As a result, we report, herein, the ability to form **2($C_6H_2F_3OH$)·(2,2-BPE)** *via* dry-vortex grinding at both a stoichiometric (*i.e.* 2 : 1) and a substoichiometric (*i.e.* 1 : 1 and 0.5 : 1) ratio of the components. At all proportions, the resulting solid contains **2($C_6H_2F_3OH$)·(2,2-BPE)** and in the cases of the 1 : 1 and 0.5 : 1 ratio, an excess of crystalline **2,2-BPE** was expected and observed. Interestingly, after photoreaction, all samples reached a nearly quantitative yield for the photoreaction. The high yield for the [2 + 2] cycloaddition reaction in the substoichiometric solids are attributed to a cascade-like reaction caused by the photoreaction.[10] In general, systems that are capable of self-catalysis or a cascade reaction are extremely useful in industrial applications and are more environmentally friendly. To the best of our knowledge, this work represents the first example to report the synthesis of **2,2-TPCB** by using a mechanochemical approach.

The components of the co-crystal were purchased from commercial sources and used as received. The solvent-free formation of **2($C_6H_2F_3OH$)·(2,2-BPE)** was achieved by adding the components to a 30 mL SmartSnap Grinding Jar along with 2 ball bearings (5 mm diameter). The solids were then dry-vortexed using a VWR Vortex Genie 2 for a total of 30 minutes with the solid being scraped from the sides of the vessel at the 10 and 20 minutes marks. In particular, the amount of **2,2-BPE** was 50.0 mg at all ratios while the mass of **$C_6H_2F_3OH$** was either 81.4 mg, 40.7 mg or 20.3 mg for the stoichiometric (2 : 1) and substoichiometric (1 : 1 and 0.5 : 1) ratio, respectively.

Previously, we reported the single-crystal X-ray structure along with the photoreactivity of **2($C_6H_2F_3OH$)·(2,2-BPE)** using a standard solvent technique.[7] In this structure, proper alignment of the reactive centres occurred through a combination of O–H···N hydrogen bonds and homogenous face-to-face π–π stacking interactions (Fig. 1). As a result, the C=C between nearest neighbouring three-component hydrogen-bonded assemblies are aligned parallel and at a distance of 3.81 Å, which satisfies the requirement for a photoreaction within the infinite stack.[11] After exposure to UV light, molecules of **2,2-BPE**, within the co-crystal, undergo a quantitative photoreaction in the solid state to form **2,2-TPCB** (Scheme 1b).

With the goal to prepare **2($C_6H_2F_3OH$)·(2,2-BPE)** *via* a solvent-free approach, the molecular components were ground with a vortex grinder at a 2 : 1 molar ratio for the template and reactant, respectively. Then, the bulk crystallinity of the resulting stoichiometric solid was investigated by powder X-ray diffraction (PXRD). The resulting diffractogram (Fig. 2a and S1†) indicated that the majority of the bulk solid matched the theoretical pattern for **2($C_6H_2F_3OH$)·(2,2-BPE)** based upon the single-crystal structure (Fig. 2b and S1†). Unfortunately, the presence of free **2,2-BPE** was also observed within the sample (Fig. 2c and S1†) with major peaks at 12.9, 18.1 and 20.1° 2θ. These powder diffraction peaks are in agreement with a previously reported orthorhombic polymorph structure of **2,2-BPE**.[12] The resulting diffractogram was then analyzed using a Rietveld refinement (Whole pattern fitting) within Jade Pro (ver. 9.1) to calculate the relative amount of each phase present in the bulk. In the stoichiometric molar sample, the amount of the co-crystal, namely **2($C_6H_2F_3OH$)·(2,2-BPE)**, within the solid returned a value of 96% while **2,2-BPE** was only 4% (Fig. S10†).

To determine if the ground stoichiometric phase would undergo a [2 + 2] cycloaddition reaction, the resulting solid was

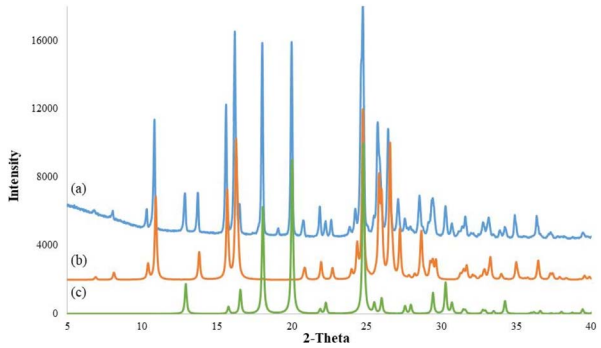

Fig. 4 Powder X-ray diffraction diffractogram of (a) vortex-ground substoichiometric sample (1 : 1 molar ratio) along with the theoretical pattern for both (b) 2($C_6H_2F_3OH$)·(2,2-BPE) and (c) 2,2-BPE.

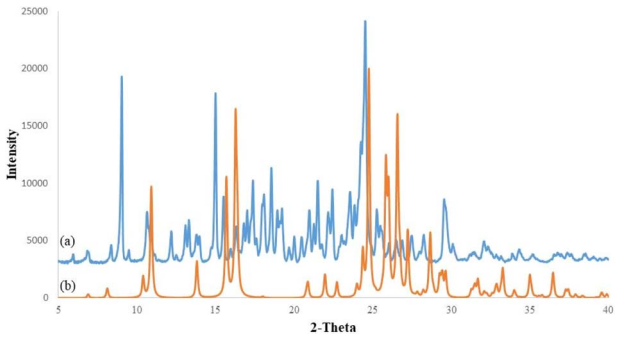

Fig. 5 Powder X-ray diffraction diffractogram of (a) photoreacted substoichiometric sample (1 : 1 molar ratio) along with the theoretical pattern for (b) the co-crystal 2($C_6H_2F_3OH$)·(2,2-BPE).

placed between a pair of glass plates and put into a photocabinet to be exposed to ultraviolet light from a 450 W mercury vapour bulb. As expected, the solid, which mostly contains **2($C_6H_2F_3OH$)·(2,2-BPE)**, underwent a photoreaction as determined by ^{1}H Nuclear Magnetic Resonance Spectroscopy (^{1}H NMR). This was confirmed by taking a small sample of the photoreacted material and studied using ^{1}H NMR. In particular, the formation of **2,2-TPCB** was confirmed by the systematic decrease of the olefin peak on **2,2-BPE** at 7.70 ppm along with the concomitant appearance of the cyclobutane peak for the photoproduct at 4.93 ppm (Fig. S11 and S12†).[7] A solid-state photoreaction was not detected after just grinding of the components, since no peak was observed at 4.93 ppm before exposure to ultraviolet light (Fig. S11†). The integration of these two ^{1}H NMR peaks determined that the overall percent yield for the photoreacted material was 97% after 50 hours. It is important to note, the observed yield for the photoreaction is in good agreement with the calculated amount of co-crystal within the bulk material with a value of 96%.

In order to determine if the three-component hydrogen-bonded assembly is maintained after photoreaction, an additional PXRD experiment was undertaken on the resulting crystalline solid. The diffractogram revealed that after photoreaction (Fig. 3a and S2†) the structure of the solid phase was drastically altered and the starting co-crystal is no longer present in the bulk (Fig. 3b and S2†). In particular, the resulting solid, after photoreaction, had strong diffraction peaks at 10.6, 12.2, and 13.7° 2θ which does not match with the predicted unreacted hydrogen-bonded assembly. The presence of free **2,2-TPCB** was observed in minor amounts based upon phase matching the theoretical pattern from the reported monoclinic single-crystal structure (Fig. S3†).[13]

With the goal to achieve **2($C_6H_2F_3OH$)·(2,2-BPE)** at a substoichiometric ratio of the template, a second dry-vortex grinding experiment was performed. As before, the solids were ground in a similar manner except at a substoichiometric (1 : 1) ratio which is a lower amount of the template. Again, the resulting solid was studied by PXRD to identify the phases present within the sample. As expected, both the co-crystal **2($C_6H_2F_3OH$)·(2,2-BPE)** and crystalline **2,2-BPE** were again observed within solid (Fig. 4 and S4†).

Then, the resulting substoichiometric (1 : 1) solid was plated and placed in a photocabinet to be exposed to ultraviolet light. After 75 hours of exposure, a portion of the photoreacted sample was then investigated by using ^{1}H NMR to determine the overall yield for the [2 + 2] cycloaddition reaction. The resulting solid underwent a photoreaction as indicated by the near complete loss of the olefin peak at 7.70 ppm and the presence of a cyclobutane peak for **2,2-TPCB** at 4.93 ppm (Fig. S13†).[7] Curiously, the overall percent yield for the photoreaction was significantly higher, when compared to the predicted yield based upon the initial amount of template, at a value of 98%. This nearly quantitative percent yield cannot be explained by the initial formation of the three-component hydrogen-bonded assembly due to the lower amount of the template present in the solid; however, a possible explanation is that the photoreaction causes a cascade-like reaction where the unreacted **2,2-BPE** moves in a cooperative manner to reposition itself in a suitable location to photoreact.[14] It should be noted that the air temperature within the photoreactor increases slightly due to heat given off from the mercury vapour bulb.[15] As a result, it is reasonable to conclude that this increase in air temperature has little to no effect on causing the cascade-like reaction, within the plated solid, which only occurs due to the observed photoreaction.

With the goal to confirm if a new phase is achieved, as a possible reason behind this enhanced yield, a PXRD experiment was undertaken after photoreaction on the crystalline solid. Again, the resulting diffractogram for the 1 : 1 molar ratio solid after photoreaction had no peaks associated with the initial co-crystal structure (Fig. 5 and S5†). It is then logical to conclude that the resulting cascade-like reaction, caused by the cycloaddition, must have moved unreacted **2,2-BPE** to a suitable position to photoreact which lead to the nearly quantitative yield even with the lower amount of the template. As before a small amount of free **2,2-TPCB** was observed in the final solid phase (Fig. S6†).[13]

To determine if even a lower amount of **$C_6H_2F_3OH$** would again achieve this cascade-like reaction and reach a high yielding photoreaction a third dry-vortex grinding experiment was undertaken at a 0.5 : 1 molar ratio for the template and reactant, respectively. The components were again ground in

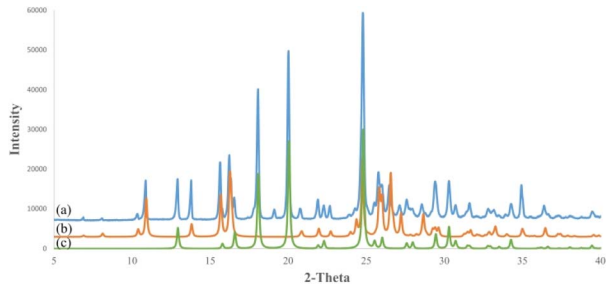

Fig. 6 Powder X-ray diffraction diffractogram of (a) vortex-ground substoichiometric sample (0.5 : 1 molar ratio) along with the theoretical pattern for both (b) **2($C_6H_2F_3OH$)·(2,2-BPE)** and (c) **2,2-BPE**.

a similar approach as before except only 20.3 mg of **$C_6H_2F_3OH$** was added to the vessel. As expected, PXRD identified the presence of both **2($C_6H_2F_3OH$)·(2,2-BPE)** and crystalline **2,2-BPE** within solid (Fig. 6 and S7†).

As before, the resulting 0.5 : 1 molar ratio solid was plated and exposed to ultraviolet light radiation in a photocabinet. Afterwards, a part of the photoreacted sample was then investigated by using ^{1}H NMR to determine the extent for the [2 + 2] cycloaddition reaction reaching a percent yield of 97% after 40 hours (Fig. S14†). The nearly quantitative yield for the cycloaddition reaction, within this 0.5 : 1 molar sample, suggests that the remaining **2,2-BPE** molecules must move in a suitable manner which allows for a photoreaction to occur.

To determine if the cycloaddition caused a similar change in the crystalline phase a PXRD experiment was undertaken on the 0.5 : 1 molar ratio solid after photoreaction. As before, the resulting diffractogram did not have any peaks associated with the original co-crystal structure (Fig. 7 and S8†). A trace amount of free **2,2-TPCB** once again was observed after photoreaction in the PXRD diffractogram (Fig. S9†).[13] Even though this cooperative motion, caused by the photoreaction, is not predictable, but it does allow for the formation of **2,2-TPCB** in a more sustainable fashion due to the lower amount of the template required to achieve this photoreaction in the organic solid state.

The ability to exploit the [2 + 2] cycloaddition reaction as a means to induce structural changes in a crystalline lattice remains a rare and underexplored phenomenon in material science. Even with limited examples, the influence solid-state photoreactions has on the physical, such as the release of included solvent molecules,[16] and chemical properties, namely cascade reactions,[10] of organic co-crystals has been clearly illustrated. It is hoped and expected that additional photo-triggered transformations will be achieved leading to high-order and complexed molecular solids with predictable and tuneable properties.

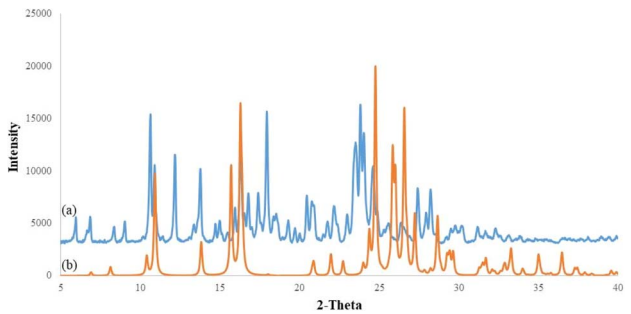

Fig. 7 Powder X-ray diffraction diffractogram of (a) photoreacted substoichiometric sample (05 : 1 molar ratio) along with the theoretical pattern for (b) the co-crystal **2($C_6H_2F_3OH$)·(2,2-BPE)**.

Conclusions

The formation of a photoreactive co-crystal based upon *trans*-1,2-bis(2-pyridyl)ethylene and 2,4,6-trifluorophenol utilizing dry-vortex grinding is reported. The mechanochemical grinding generates a photoreactive three-component hydrogen-bonded co-crystal that undergoes a [2 + 2] cycloaddition reaction at different initial molar ratios. Interestedly, the solids formed at a substoichiometric ratio of the template also reaches a near quantitative yield, since the photoreaction causes a cascade-like reaction within the solid which moves the remaining reactant molecules to a suitable position which allows further photoreaction. Currently, we are investigating similar systems to determine if this cascade-like reaction will also be observed when using other isosteric templates.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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