Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Solvent-free Sonochemistry as a Route to Pharmaceutical Co-crystals

*David Roy, Stuart L. James and Deborah E. Crawford**

Queen's University Belfast, David Keir Building, 39 – 123 Stranmillis Road, Belfast, BT9 5AG, United Kingdom

All reagents were obtained from leading chemical retailers at a purity level of 98% and above. Sonication was carried out in a VWR ultrasonic cleaning bath, at a power of 120 W. There was some residual heating during the experiments, however replenishing of the sonic bath water allowed the temperature to be contained at *ca.* 24 °C. X-ray diffraction characterization was carried out in a PANanalytical X'Pert Pro X-ray diffractometer. Copper was used as the X-ray source with a wavelength of 1.5405 Å.

Pretreatment of starting materials

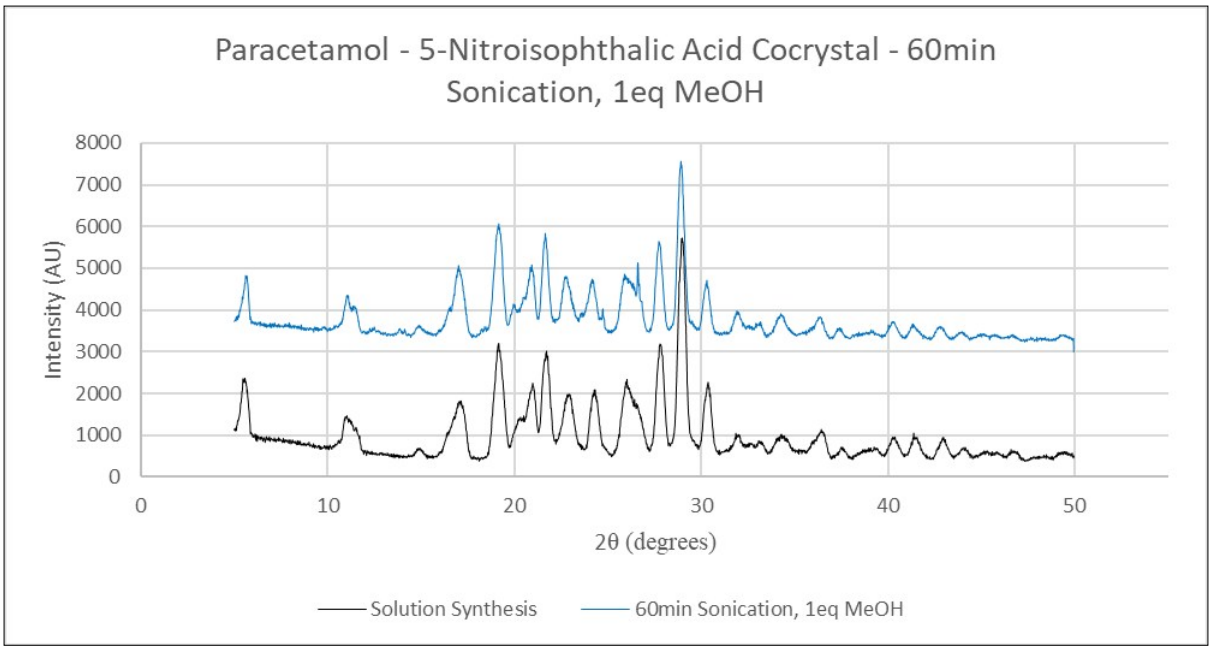
Milling

Milling was carried out by ball milling each reagent individually, in a 25 ml stainless steel ball mill jar, equipped with a 13.6 g (15 mm diameter) ball bearing. A Retsch MM400 ball mill was employed and the reagents were milled individually for 1 minute at 25 Hz. A molecular sieve was then employed to separate the powder into varying particle sizes.

Synthesis of Paracetamol Co-crystals

Paracetamol 5-nitroisophthalic acid cocrystal

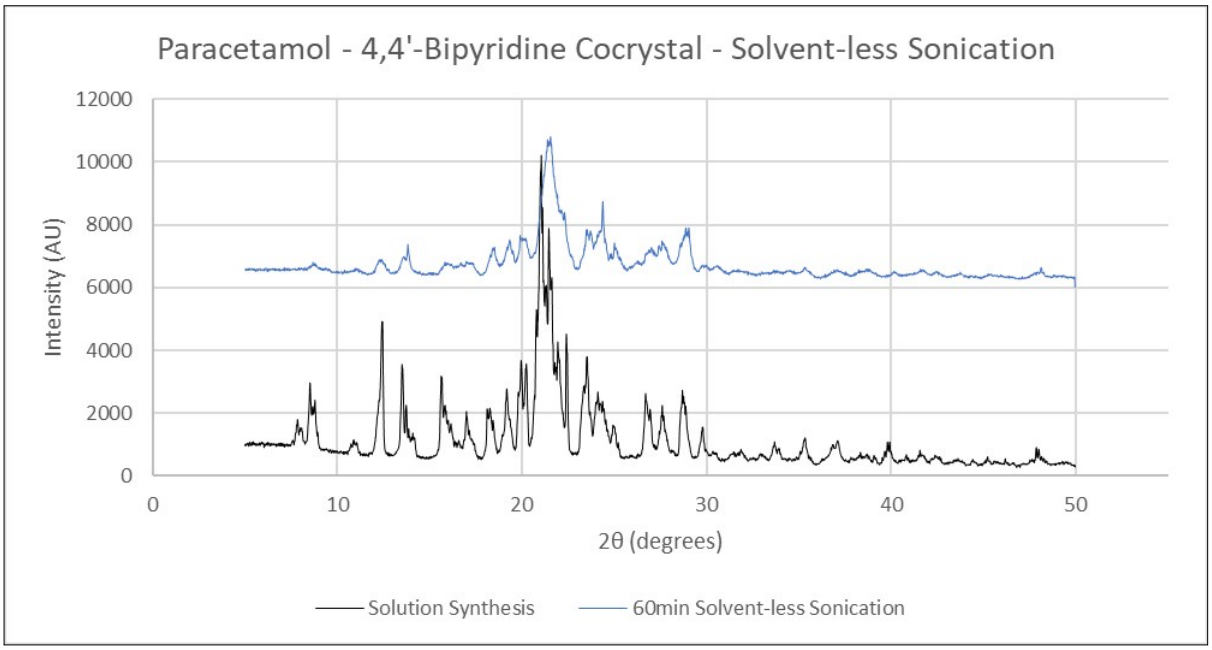
0.07 g of 4-aminophenol (0.66 mmol) and 0.14 g of 5-nitroisophthalic acid (0.66 mmol, 1 equiv.) were placed in a sample vial. 0.06 ml of acetic anhydride (0.66 mmol, 1 equiv.) were added to the mixture and the vial was immersed in the ultrasonic bath for 60 minutes at a power of 120 W. Afterwards, the product was dried by suction filtration, resulting in a yellow solid.



S3: PXRD Pattern of paracetamol 5-nitroisophthalic acid – by sonication and by solution.

Paracetamol 4,4-bipyridine cocrystal

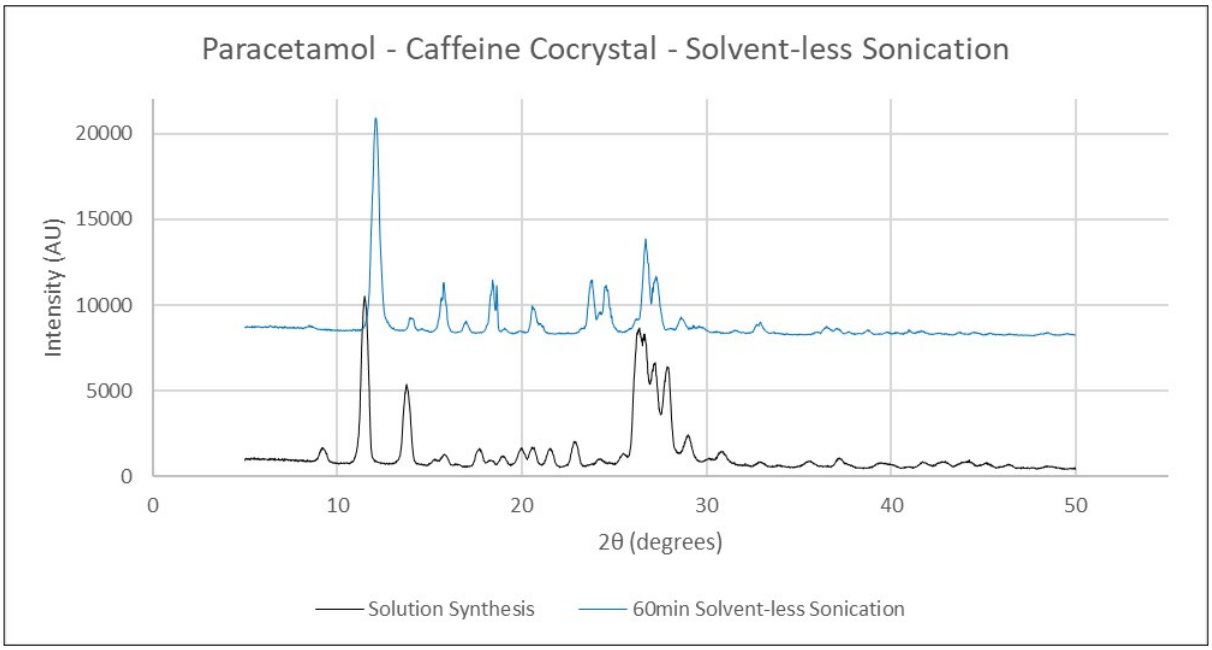
0.1 g of 4-aminophenol (0.92 mmol) and 0.14 g of 4,4'-BPY (0.92 mmol, 1 equiv.) were added to a sample vial. 0.09 ml of acetic anhydride (0.92 mmol, 1 equiv.) were then added to the mixture and the vial was immersed in the ultrasonic bath for 60 minutes at a power of 120 W. After 60 minutes, the product was dried by suction filtration.



S4: PXRD Pattern of paracetamol 4,4-bipyridine – by sonication and by solution.

Paracetamol caffeine cocrystal

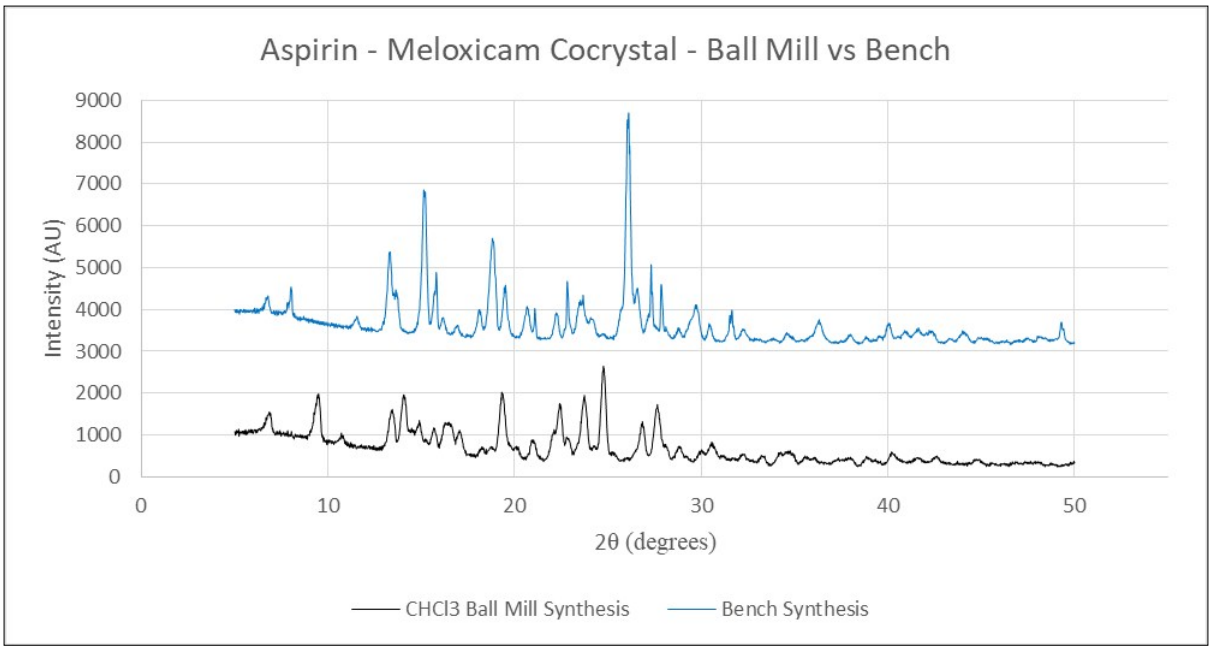
0.07 g of 4-aminophenol (0.66 mmol) and 0.13 g of caffeine (0.66 mmol, 1 equiv.) were placed in a sample vial. 0.06 ml of acetic anhydride (0.66 mmol, 1 equiv.) were then added to the reaction mixture. The vial was then immersed in the ultrasonic bath and sonicated for 60 minutes at a power of 120 W. Next, the product was dried by suction filtration.



S5: PXRD Pattern of paracetamol caffeine – by sonication and by solution.

Meloxicam aspirin cocrystal

0.18 g of aspirin (1 mmol) and 0.35 g of meloxicam (1 mmol, 1 equiv.) were added to a sample vial. 0.16 ml of chloroform (2 mmol, 2 equiv.) were then added to the mixture, and the vial was immersed in the ultrasonic bath for 60 minutes at a power of 120 W. When the time was up, the solvent was removed by suction filtration producing a pale-yellow solid.



S5: PXRD Pattern of aspirin meloxicam – by sonication and by solution.