Stepwise dissolution and composition determination of samples of multiple crystals using a dissolution medium containing aqueous alcohol and fluorocarbon phases.

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Synthetic Procedures

Synthesis of 2-nitro-4-<i>tert</i>-butylacetanilide (3)

![Fig. S1](image)

2-Nitro-4-<i>tert</i>-butylaniline (3.825 g, 19.693 mmol, 1 eq.), acetic anhydride (3.03 g, 2.8 mL, 29.676 mmol, 1.5 eq.) and two drops of sulphuric acid were stirred together at room temperature to form an orange suspension. The mixture was heated, at approximately 55 °C the mixture solidified but eventually formed an orange coloured solution on continued heating towards 90 °C, at which point it was heated at 90 °C for two hours. After two hours, the reaction was allowed to cool to room temperature and then 30 mL of water was added to precipitate the product. The precipitate was isolated by filtration and washed with two 50 mL portions of water and air dried. The crude product was then recrystallized from 45 mL of hot ethanol, isolated by filtration and washed with two 20 mL portions of ice-cold ethanol. Yield: 2.913 g, 63.14 %. M.P. (DSC) 107.68 °C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.18 (s, 1H, NH), 8.63 (d, $^3$J$_{HH}$ = 8.9 Hz, 1H, H-6), 8.17 (d, $^4$J$_{HH}$ = 2.4 Hz, 1H, 3-H), 7.67 (dd, $^3$J$_{HH}$ = 8.9 Hz, $^4$J$_{HH}$ = 2.4 Hz, 1H, 5-H), 2.27 (s, 3H, H$_3$CC(O)), 1.33 (s, 9H, C(CH$_3$)$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.07 (s, C(O)), 147.09 (s, 2-C), 136.40 (s, 4-C), 133.52 (s, 5-C), 132.43 (s, 1-C), 122.26 (s, 6-C), 122.13 (s, 3-C), 34.70 (s, C(CH$_3$)$_3$), 31.09 (s, C(CH$_3$)$_3$), 25.63 (s, (O)CCH$_3$).

Elemental analysis: found (calculated) for C$_{12}$H$_{16}$N$_2$O$_3$ (236.12 g mol$^{-1}$): C, 60.99 (61.00); H, 6.73 (6.83); N, 10.83 (11.86).
NMR Spectra

Fig. S2 ¹H NMR spectrum of 3 in CDCl₃.

Fig. S3 ¹³C NMR {¹H} (DEPTQ-135) spectrum of 3 in CDCl₃.
Fig. S4  $^1$H NMR spectrum of 4 in CDCl$_3$.

Fig. S5  $^{13}$C($^1$H) NMR spectrum of 4 in CDCl$_3$. 
Fig. S6  (Top)(cyan) $^{19}$F-$^1$H NMR spectrum of 4 in CDCl$_3$. (Bottom)(maroon) $^{19}$F NMR spectrum of 4 in CDCl$_3$. 
HPLC Calibration Data
HPLC calibration data for method analysing mixtures of compounds 1 and 3

General Calibration Setting

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Abs. Non-ref. Window : 0.000 min
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Correct All Ret. Times: No, only for identified peaks
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Calibration Curves

HPLC calibration data for method analysing mixtures of compounds 1 and 2

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### Signal Details

**Signal 1: DAD1 A, Sig=234,4 Ref=360,100**

### Overview Table

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Formula: \( y = mx \)
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   \( x: \text{Amount[ng/ul]} \)
   \( y: \text{Area} \)
Particle Sizing

Fig. S7  Image displaying an isolated crystal of compound 1 from a solution doped with 4.0 mol % of compound 2. This image displays how size measurements were taken; the area in µm² was recorded from the area within the external perimeter (highlighted as a red line with white circles); the length in µm was recorded from the longest dimension of the particle (highlighted as a red line bisecting the particle).
**Fig. S8** Graph displaying incorporation level versus solution impurity level of 4-methyl-2-nitroacetanilide (2) in “host” 4-trifluoromethyl-2-nitroacetanilide.

**Table S1.** Overall incorporation (% composition by HPLC) of 4-methyl-2-nitroacetanilide (2) and 4-tert-butyl-2-nitroacetanilide (3) in crystals of 4-chloro-2-nitroacetanilide (1) obtained by crystallisation from solutions in toluene containing various quantities of 2 and 3 at a σ value of 1.5. Data is shown for two crystallisation batches.

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### PXRD

Fig. S9 shows the PXRD pattern for 1 grown in toluene at $\sigma = 1.5$ against the PXRD patterns for 1 grown in toluene at $\sigma = 1.5$ with 5 mol % additions 2. The PXRD pattern for 2 grown under the same conditions is also added for reference. PXRD patterns were obtained for crystals of 1 with additive concentrations as low as 0.5% grown under the aforementioned conditions, however, for none of the samples, as can be seen at the highest additive concentration of 2, there is no discernible formation of additional diffraction peaks. All obtained patterns displayed peaks corresponding to that of 1 with only minor differences in the intensities of some of the peaks peaks.

A similar image comparing the PXRD patterns based around compound 3 can be seen in Fig. S10. This figure compares the PXRD patterns for crystals related to pure 1, 4.5 mol % 3-doped 1, and pure 3, all grown in toluene at $\sigma = 1.5$. Again, the sample doped with impurity displays no diffraction peaks other than from the pure 1 sample with minor differences in intensity.

![Fig. S9](image)

**Fig. S9**  Powder X-ray diffraction patterns obtained for crystals of 1 grown from toluene (red), 1 grown from toluene with concentrations of 5 mol% 2 (blue), and 2 grown from toluene (green).
Fig. S10 Powder X-ray diffraction patterns obtained for crystals of 1 grown from toluene (red), 1 grown from toluene with concentrations of 4.5 mol % 3 (blue), and 3 grown from toluene (green).
Differential Scanning Calorimetry

The DSC curves for pure compounds 1 and 2, and 5 mol % 2-doped 1 are displayed in Fig. S11. The inclusion of additive at the highest level in this study did not alter the melting point of the crystals in any significant way, as the melting of 99.51 °C is for the impurity-doped sample is marginally higher than the melting point of 99.44 °C for pure compound 1.

Fig. S12 shows the DSC curves for pure compounds 1 and 3, and 4.5 mol % 3-doped 1. Again the impurity-doped sample shows a minimal difference in melting point, rising to 100.11 °C from 99.44 °C for pure compound 1.

None of the samples displayed in Fig. S11 and Fig. S12 showed any secondary events such as minor melting points or polymorph changes under the tested conditions.
Partial Dissolution Graphs

Fig. S13 Chart comparing particle area versus the ranking of each particle in a partial dissolution series of 1 doped with 1.5 mol % of 2.

Fig. S14 Chart comparing particle length versus the ranking of each particle in a partial dissolution series of 1 doped with 1.5 mol % of 2.
**Fig. S15** Plot of percentage by HPLC of added impurity in crystals of compound 1 vs. the dissolution mid-point for the sample of crystals grown from solutions containing 1.5 mol % of additive 2.

**Fig. S16** Chart comparing particle area versus the ranking of each particle in a partial dissolution series of 1 doped with 2.0 mol % of 2.
**Fig. S17** Chart comparing particle length versus the ranking of each particle in a partial dissolution series of 1 doped with 2.0 mol % of 2.

**Fig. S18** Plot of percentage by HPLC of added impurity in crystals of compound 1 vs. the dissolution mid-point for the sample of crystals grown from solutions containing 2.0 mol % of additive 2.
Fig. S19 Chart comparing particle area versus the ranking of each particle in a partial dissolution series of 1 doped with 2.5 mol % of 2.

Fig. S20 Chart comparing particle length versus the ranking of each particle in a partial dissolution series of 1 doped with 2.5 mol % of 2.
**Fig. S21** Plot of percentage by HPLC of added impurity in crystals of compound 1 vs. the dissolution mid-point for the sample of crystals grown from solutions containing 2.5 mol % of additive 2.

**Fig. S22** Chart comparing particle area versus the ranking of each particle in a partial dissolution series of 1 doped with 3.0 mol % of 2.
**Fig. S23** Chart comparing particle length versus the ranking of each particle in a partial dissolution series of 1 doped with 3.0 mol % of 2.

**Fig. S24** Plot of percentage by HPLC of added impurity in crystals of compound 1 vs. the dissolution mid-point for the sample of crystals grown from solutions containing 3.0 mol % of additive 2.
**Fig. S25** Chart comparing particle area versus the ranking of each particle in a partial dissolution series of 1 doped with 3.5 mol % of 2.

**Fig. S26** Chart comparing particle length versus the ranking of each particle in a partial dissolution series of 1 doped with 3.5 mol % of 2.
**Fig. S27** Plot of percentage by HPLC of added impurity in crystals of compound 1 vs. the dissolution mid-point for the sample of crystals grown from solutions containing 3.5 mol % of additive 2.

**Fig. S28** Chart comparing particle area versus the ranking of each particle in a partial dissolution series of 1 doped with 4.0 mol % of 2.
Fig. S29  Chart comparing particle length versus the ranking of each particle in a partial dissolution series of 1 doped with 4.0 mol % of 2.

Fig. S30  Plot of percentage by HPLC of added impurity in crystals of compound 1 vs. the dissolution mid-point for the sample of crystals grown from solutions containing 4.0 mol % of additive 2.
Fig. S31 Chart comparing particle area versus the ranking of each particle in a partial dissolution series of 1 doped with 4.5 mol % of 2.

Fig. S32 Chart comparing particle length versus the ranking of each particle in a partial dissolution series of 1 doped with 4.5 mol % of 2.
**Fig. S33**  Plot of percentage by HPLC of added impurity in crystals of compound 1 vs. the dissolution mid-point for the sample of crystals grown from solutions containing 4.5 mol % of additive 2.

**Fig. S34**  Chart comparing particle area versus the ranking of each particle in a partial dissolution series of 1 doped with 5.0 mol % of 2.
**Fig. S35** Chart comparing particle length versus the ranking of each particle in a partial dissolution series of 1 doped with 5.0 mol % of 2.

**Fig. S36** Plot of percentage by HPLC of added impurity in crystals of compound 1 vs. the dissolution mid-point for the sample of crystals grown from solutions containing 5.0 mol % of additive 2.
Table S2. Comparisons of parent batch average and weighted averages from stepwise dissolutions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>%additive in soln.</th>
<th>%additive in parent sample</th>
<th>Weighted% additive in dissolution sample*</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>1.5</td>
<td>0.340 (0.06)</td>
<td>0.1664 (0.0014)</td>
<td>+0.18 (0.06)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2.0</td>
<td>0.442 (0.003)</td>
<td>0.3573 (0.0005)</td>
<td>+0.085 (0.003)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2.5</td>
<td>0.497 (0.017)</td>
<td>0.4054 (0.0011)</td>
<td>+0.091 (0.017)</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>3.0</td>
<td>0.630 (0.05)</td>
<td>0.4961 (0.0015)</td>
<td>+0.13 (0.05)</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>3.5</td>
<td>0.690 (0.015)</td>
<td>0.665 (0.005)</td>
<td>+0.025 (0.016)</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>4.0</td>
<td>0.838 (0.011)</td>
<td>0.7866 (0.0018)</td>
<td>+0.051 (0.011)</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>4.5</td>
<td>0.917 (0.012)</td>
<td>1.014 (0.012)</td>
<td>-0.097 (0.017)</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>5.0</td>
<td>0.980 (0.03)</td>
<td>0.739 (0.003)</td>
<td>+0.24 (0.03)</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>4.5</td>
<td>0.1867 (0.0005)</td>
<td>0.03995 (0.00015)</td>
<td>+0.1468 (0.0005)</td>
</tr>
</tbody>
</table>

*The weighted average was determined from the HPLC data using the following formula:

\[
\sum_{i=1}^{n} \frac{D_i}{\sum_{i=1}^{n} D_i} \cdot R_i
\]

where \( n \) is the number of partial dissolutions in a dissolution series, \( D_i \) is the number of moles of analytes dissolved in a partial dissolution step \( i \), and \( R_i \) is the percentage of additive in the solution obtained from partial dissolution step \( i \).

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**Fig. S37** Comparisons of parent batch average and weighted averages from stepwise dissolutions.
Table S3. Dissolution mid-points calculated for analysed 4.0 mol % 2-doped 1 crystals from both observed measurements and ‘theoretical’ values.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>5.0 (3.9)</td>
<td>3.4</td>
<td>1.6 (3.9)</td>
<td>2.71 (1.08)</td>
<td>1.73</td>
<td>0.98 (1.08)</td>
</tr>
<tr>
<td>PD1</td>
<td>12.5 (8.4)</td>
<td>10.3</td>
<td>2.2 (8.4)</td>
<td>6.8 (2.2)</td>
<td>5.3</td>
<td>1.5 (2.2)</td>
</tr>
<tr>
<td>PD2</td>
<td>18.9 (3.5)</td>
<td>17.5</td>
<td>1.4 (3.5)</td>
<td>10.3 (2.6)</td>
<td>9.2</td>
<td>1.1 (2.6)</td>
</tr>
<tr>
<td>PD3</td>
<td>26.84 (5.08)</td>
<td>25.01</td>
<td>1.83 (5.08)</td>
<td>15.05 (3.92)</td>
<td>13.43</td>
<td>1.62 (3.92)</td>
</tr>
<tr>
<td>PD4</td>
<td>34.6 (5.9)</td>
<td>32.9</td>
<td>1.7 (5.9)</td>
<td>20.2 (4.0)</td>
<td>18.1</td>
<td>2.1 (4.0)</td>
</tr>
<tr>
<td>PD5</td>
<td>46.7 (8.4)</td>
<td>41.4</td>
<td>5.3 (8.4)</td>
<td>26.7 (7.5)</td>
<td>23.5</td>
<td>3.2 (7.5)</td>
</tr>
<tr>
<td>PD6</td>
<td>77.4 (17.7)</td>
<td>72.9</td>
<td>4.5 (17.7)</td>
<td>65.3 (13.9)</td>
<td>63.2</td>
<td>2.1 (13.9)</td>
</tr>
</tbody>
</table>

References