Determination of composition distributions of multi-particle crystalline samples by sequential dissolution with concomitant particle sizing and solution analysis

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Synthesis of N-(2-nitro-4-trifluoromethylphenyl)pivalamide 4

N-(2-nitro-4-trifluoromethylphenyl)pivalamide 4 was prepared by heating a mixture of 2-nitro-4-trifluoromethylaniline (1.0 g, 4.852 mmol), trimethylacetic anhydride (1.5 mL, 7.390 mmol), and two drops of sulphuric acid to 80 °C for 3 hours. The resulting solution was allowed to cool to room temperature with the formation of yellow plate-like crystals. Water (10 mL) was added to the reaction mixture, and with manual stirring further solid precipitated out of solution. The crude product was isolated by vacuum filtration, washed with two 10 mL portions of water and air dried. The crude product was purified by recrystallization with 20 mL of ethanol, isolated by vacuum filtration, washed with a further 10 mL of ice-cold ethanol and air dried. Yield 0.462 g (33 %) of a yellow crystalline solid. M.p. 92 - 94 °C. $^1$H NMR (300 MHz, CDCl$_3$): δ 10.89 (1H, s, NH), 9.05 (1H, d, $^3$J$_{HH}$ = 9 Hz, H6), 8.52 (1H, d, $^4$J$_{HH}$ = 2 Hz, H3), 7.87 (1H, dd, $^3$J$_{HH}$ = 9, $^4$J$_{HH}$ = 2 Hz, H5), 1.37 (s, 9H, $3 \times$ C(CH$_3$)$_3$) ppm; $^{13}$C{${^1}$H} NMR (DEPTQ-135) (75 MHz, CDCl$_3$): δ 178.17 (s, C=O), 138.37 (s, C1), 135.54 (s, C2), 132.43 (q, $^3$J$_{CF}$ = 3.3 Hz, C5), 124.86 (q, $^3$J$_{CF}$ = 34.6 Hz, C4), 123.77 (q, $^1$J$_{CF}$ = 272.1 Hz, CF$_3$), 123.51 (q, $^3$J$_{CF}$ = 4.1 Hz, C3), 122.67 (s, C6), 40.91 (s, C(CH$_3$)$_3$), 27.43 (s, $3 \times$ CH$_3$) ppm; $^{19}$F{${^1}$H} NMR (282 MHz, CDCl$_3$): δ -62.65 (s, CF$_3$) ppm. ESI-MS (CH$_3$CN): 291.2 positive mode [M + H$^+$, calc. 291.10 for C$_{12}$H$_{14}$N$_2$F$_3$O$_3$]; 292.2 positive mode [M + H$^+$ + 1, calc. 292.10 for C$_{12}$H$_{14}$N$_2$F$_3$O$_3$]; 289.2 negative mode [M - H, calc. 289.08 for C$_{12}$H$_{12}$N$_2$F$_3$O$_3$]; 290.3 negative mode [M - H + 1, calc. 290.09 for C$_{12}$H$_{12}$N$_2$F$_3$O$_3$] R$_f$ (1:7 ethyl acetate:hexane on silica gel) = 0.55.

[$^{1}$H (300 MHz), $^{13}$C{${^1}$H} (75 MHz), and $^{19}$F{${^1}$H} NMR (282 MHz) spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluent; samples were prepared in acetonitrile.]
Figure S1. $^1$H NMR spectrum of 4 in CDCl$_3$.

Figure S2. $^{13}$C NMR {$^1$H} (DEPTQ-135) spectrum of 4 in CDCl$_3$. CH and CH$_3$ signals are positive, all other signals are negative.
Figure S3. $^{19}$F NMR $^{1}$H spectrum of 4 in CDCl$_3$. 
# HPLC Calibration Data

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Correlation: 0.99996
Residual Std. Dev.: 15.54065
Formula: y = mx
m: 34.34116
x: Amount[ng/ul]
y: Area
**Figure S4.** TGA curve overlaid the DSC curve for 1 doped with 8 mol % of 4.

**Figure S5.** Chart comparing particle area versus the ranking of each particle in a partial dissolution series of 1 doped with 0.5 mol % of 2.
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Data from dissolution of single crystal grown from solution containing 3.0 mol % 3.

Figure S37. Plot of percentage by HPLC of added impurity in a single crystal of compound 1, grown from solutions containing 3.0 mol % of additive 3, vs. the dissolution mid-point for the crystal.