Electronic Supplementary Material (ESI) for Green Chemistry.

Supplementary Information

Milligram-scale, Temperature-controlled Ball Milling to Provide an Informed Basis for Scale-up to Reactive Extrusion

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Table of Contents

General

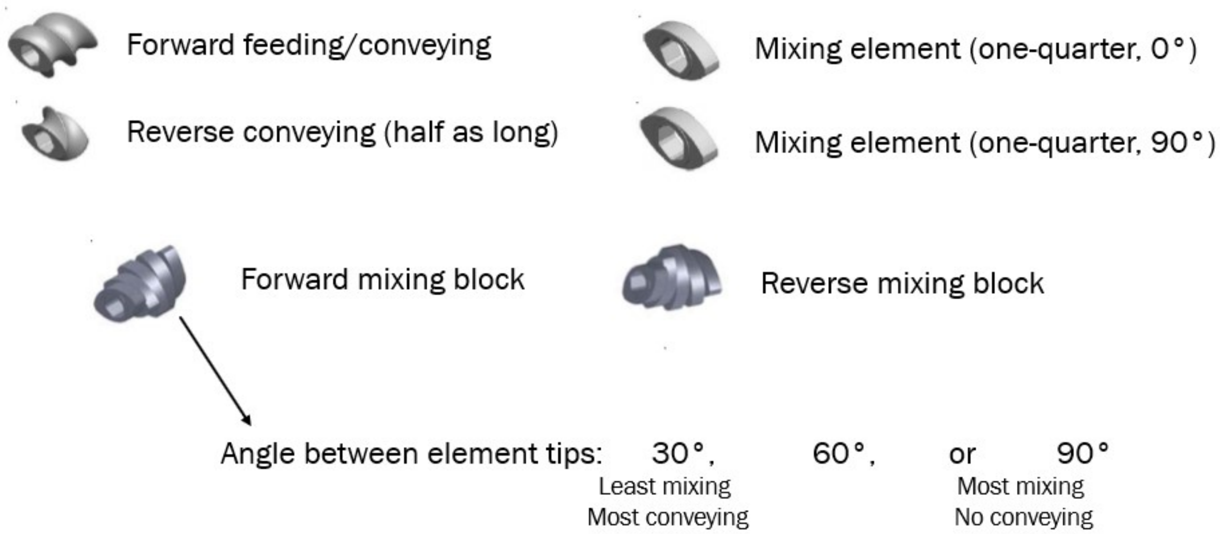
All reagents were purchased from the indicated manufacturer and used without further purification. Thin layer chromatography was performed using TLC Silica gel 60 F_{254} glass plates from Merck. 3-bromo-4-fluoronitrobenzene (98%) was purchased from AmBeed. Barbituric acid (99%), potassium carbonate (anhydrous, free-flowing), benzylamine (99%), vanillin (99%), chloroform-d (99.8% D with 0.03% (v/v) TMS), DMSO-d6 (99.8%), HPLC-grade water, and HPLC-grade acetonitrile were purchased from Sigma-Aldrich.

NMR spectra were obtained on a Bruker Avance spectrometer operating at 400 MHz for 1H and 101 MHz for ^{13}C. Notation for NMR spectra are as follows: s = singlet, d = doublet, m = multiplet, dd = doublet of doublets; br = broad. All GC-MS work was performed on an Agilent Technologies 7890 GC System with a 5977A MSD. HPLC work was performed on an Agilent 1100 Series HPLC. The SPEX 8000M Mixer/mill is manufactured by SPEX Sample Prep. The Process 11 Twin-Screw Extruder is manufactured by ThermoFisher Scientific. Automated flash chromatography was performed on a CombiFlash Rf+ manufactured by Teledyne Isco.

Melting points were determined using a Barnstead Electrothermal IA9100X1 melting point apparatus.

Screw Element Information

Screws are created by combining elements on a hex-shaped rod. Forward feeding/conveying elements result in minimal mixing, and the fastest movement. On the opposite end of the spectrum, reverse conveying elements inhibit travel down the screw, resulting in buildup of material before them. One-quarter mixing elements (0° or 90°) can be used to allow for creation of mixing segments/blocks. Because the rod on which screws are assembled is hexagonal (60° angles), these two blocks can be arranged to be either 30°, 60°, or 90° from one tip to the next. Care must be taken to balance torque overages with the mixing improvements/residence time improvements (e.g., one cannot simply make an entire screw a forward mixing block from end to end).



Experimental Setup

Heated Ball Mill Setup

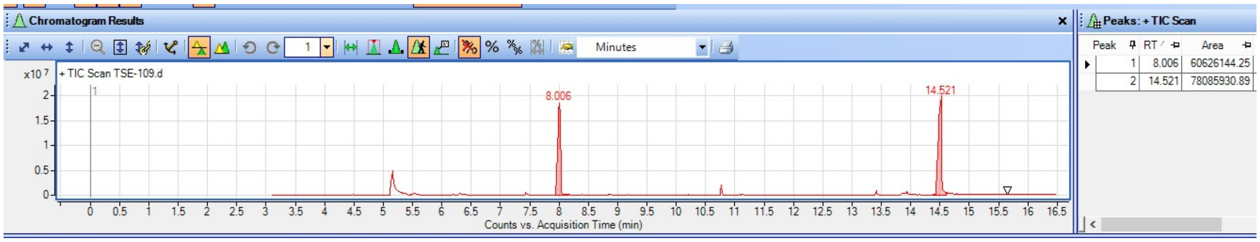
A PID heater-controller is used to heat an aluminum sleeve that surrounds the jar. Extensive details of this—including numerous photographs—are presented in Ref. 25 of the maintext.

TSE Feeder Calibration

Volumetric TSE feeders must be calibrated prior to use. The ThermoScientific software allows integer feed rates from 1%-100% of the maximum feed rate, but the actual mass delivered must be determined by delivering into a tared vessel for several minutes. This determination can be proportionally scaled once it has been made for a given percentage of the maximum feed rate.

S_NAr Ball Mill Reaction

A stainless steel Form-Tech Scientific milling jar containing a single 3/8” stainless steel (316) ball was pre-heated in the reactor’s aluminum sleeve to within 5-10 °C of the target reaction temperature. The jar was removed and potassium carbonate (145.1 mg, 1.050 mmol, 1.05 equiv.), 2-bromo-1-fluoro-4-nitrobenzene (220.0 mg, 1.000 mmol), and benzylamine (115 µL, 1.050 mmol, 1.05 equiv.) were added sequentially. To minimize setup time, solid components were pre-weighed on weigh paper. The mill was operated at 18 Hz and allowed to reaction for 15 minutes. At this time, the reaction was removed hastily using heat-resistant gloves (when necessary) and cooled down quickly by holding under running water with the jar still sealed. The reaction mixture was removed from the jar using ethyl acetate and water. A full liquid-liquid extraction was performed on the combined phases. A portion of this phase was removed for GC-MS analysis. The GC method was as follows: 70 °C for three minutes, ramp increase at 20 °C/min up to 300 °C, and finally hold for two minutes. A sample chromatogram is provided below. This chromatogram was used to obtain the relative response factors for the product compared to the reactant. Based on the integrations, the relative response factor for the product was 1.28.



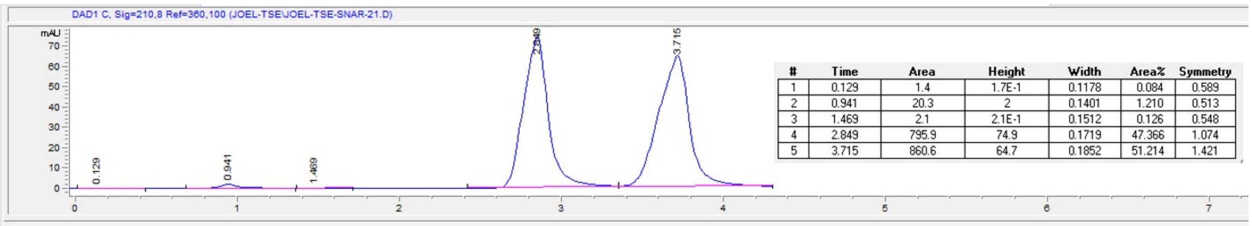
Peak	RT	Area
1	8.006	60626144.25
2	14.521	78085930.89

Note on addition order: Solids were added to the jar prior to the liquid due to their lack of mobility and lack of reaction with one another. In the present set of reactants, benzylamine has the highest mobility and can also act as base in addition to being a nucleophile. Thus, we decided to add that component last. This is especially relevant as the reaction time is relatively short and the jar is pre-heated. It is important to keep in mind the mobility and reactivity of reactants in such cases—solventless chemistry does not necessarily begin at the point of turning on the mill.

S_NAr Twin-screw Extruder Reaction

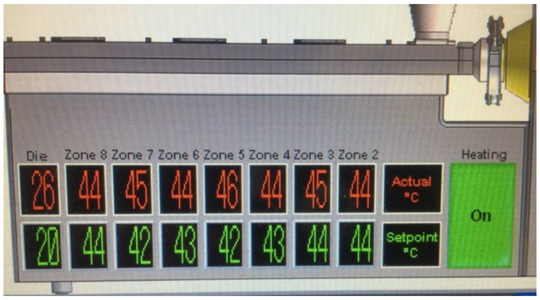
To a plastic container for pre-mixing were added 2-bromo-1-fluoro-4-nitrobenzene and potassium carbonate (1.05 equiv). This was mixed by hand and added to the extruder's feeder. The combined solids were fed at a rate of 1.021 g/min into zone 2 (the first available feeding zone). Benzylamine was added to zone 3 via syringe pump at a rate of 0.322 mL/min (1.05 eq./min). Although temperature can be targeted via software, under some conditions it is mandatory to slightly offset from the targeted temperatures—especially when closer to room temperature—in order to account for the build-up of heat production from the shearing of the screws. Samples were taken periodically by using a microspatula to catch material (approximately 10 mg) at the barrel outlet. This material was dissolved into 3 mL of 70% aqueous acetonitrile and further diluted with the same solution by a factor of 3 to achieve a sample concentration of approximately 1 mg/mL. This sample was analyzed by an Agilent 1100 Series HPLC. Analyses were performed on a 150 mm x 4.6 mm Phenomenex Synergi 4µ Hydro-RP 80A column. The mobile phase was 70% aqueous acetonitrile, the injection volume was 10 µL, and the flow rate was 1.0 mL/min. The product had a retention time of 3.7 minutes and the aromatic starting material had a residence time of 2.8 minutes. At 210 nm, the product was determined to have a response factor of 1.1 relative to the aromatic starting material, and this factor was used to normalize the UV absorbances prior to determining conversion (see below).

An isolated yield was obtained of a sample collected over one minute. The sample mass leaving the extruder was 1.323 g, which is near the 1.343 g/min total mass input rate. The sample was portioned between ethyl acetate and water. The sample was extracted three times with ethyl acetate. Organic layers were combined, and silica gel was added. The ethyl acetate was removed under reduced pressure. The resulting silica gel was loaded into a CombiFlash Rf+ (Teledyne ISCO) for automated chromatography over a RediSepRf Gold column. The following gradient method was used: 0% EtOAc (1 minute), 0->10% EtOAc (1 minute), 10% EtOAc (1 minute), 10%->100% (10 minutes). The sample was confirmed > 99% pure by NMR, resulting in a final isolated yield of 97% (833.6 mg, 2.714 mmol).



#	Time	Area	Height	Width	Area%	Symmetry
1	0.129	1.4	1.7E-1	0.1178	0.084	0.589
2	0.941	20.3	2	0.1401	1.210	0.513
3	1.469	2.1	2.1E-1	0.1512	0.126	0.548
4	2.849	795.9	74.9	0.1719	47.366	1.074
5	3.715	860.6	64.7	0.1852	51.214	1.421

Note on addition order: It is possible to have two feeders separately feeding each solid component into the same feedzone. However, this can present spatial challenges. It is more convenient to pre-mix non-reactive solids so long as this can be done in a sufficiently heterogenous manner to result in dosing the proper stoichiometry. This is also a good solution when dosing many solids, as extruder feeders can each be $20,000 or more depending on features. Combing liquids and solids is undesirable unless they form a non-reactive homogenous mixture that can be easily added via pipette. In this case, benzylamine and the aromatic compound are reactive and benzylamine and potassium carbonate would result in a heterogenous solution that cannot be reliably added via syringe.



Die	Zone 8	Zone 7	Zone 6	Zone 5	Zone 4	Zone 3	Zone 2		Heating
26	44	45	44	46	44	45	44	Actual °C	On
20	44	42	43	42	43	44	44	Setpoint °C	

Knoevenagel Ball Mill Reaction

A stainless steel Form-Tech Scientific milling jar containing a single 3/8” stainless steel (316) ball was pre-heated in the reactor’s aluminum sleeve to within 5-10 °C of the target reaction temperature. The jar was removed and vanillin (152.2 mg, 1.000 mmol) and barbituric acid (128.1 mg, 1.000 mmol, 1.0 equiv.) were added. To this was then added 14.4 µL water (10% w/w, 0.80 equiv.) To minimize setup time, solid components were pre-weighed on weigh paper. The mill was operated at 18 Hz for the allowed time. After the desired reaction time, the jar was removed from the mill. The contents of the jar were mixed with a microspatula, and a portion was removed for direct analysis by ^{1}H-NMR (DMSO-d_6) using the starting material’s proton at δ 9.8 (s, 1H) and the target product’s proton at δ 8.5 (s, 1H). Solubility characteristics prevented the dissolution of the entire sample prior to analysis.

Note on addition order: Water is added last because although the first two components are reactive, they are poorly mobile (solids at our temperatures). Furthermore, water can be measured and added with speed when using an air-displacement micropipette.

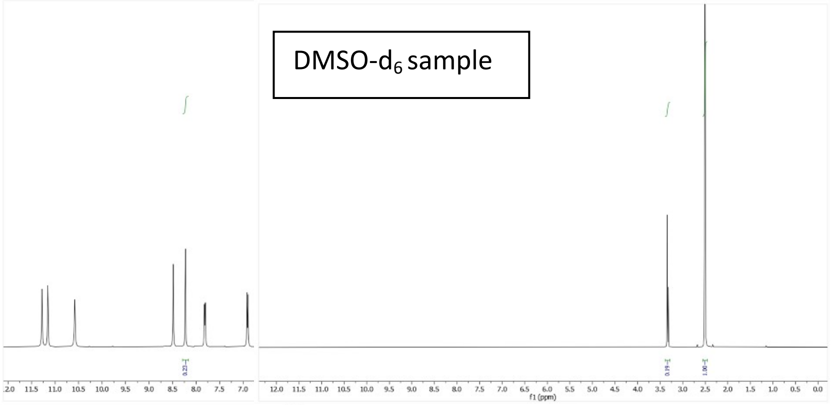
Knoevenagel Extruder Reaction

Vanillin and barbituric acid were combined in a 1:1 molar ratio in a plastic container and pre-mixed by hand. This mixture was then added to the extruder's feeder. Although a color change is observable upon mixing the two, ^{1}H-NMR analysis indicated the conversion of material leaving the feeder (prior to entering the barrel) to be less than 2%, even at the end of the experiment. The combined solids were fed at a rate of 1.2 g/minute, and water was added via syringe pump at 0.12 mL/min into zone 3 (the first zone after the feeding zone). Screw speed was 50 rpm (unless noted). Torque variation with time was used as an indicator of steady-state conditions. Samples were taken periodically by catching material leaving the barrel with a microspatula. This could be directly analyzed for conversion by ^{1}H-NMR (DMSO-*d$_6$*) using the method described in a separate section below.

Note on addition order: With respect to pre-mixing these reactions, one must consider the rate at which they react with one another. Experience with these components in milling experiments and test experiments involving pre-mixing provided sufficient evidence for us to feel comfortable pre-mixing them. Although there may be situations where the 2% conversion mentioned above would need to be avoided, we do not believe that it adds limitations to the conclusions drawn in this work. We did not investigate the possibility of premixing barbituric acid and water to add via syringe. Although it is soluble in water, it is not soluble enough to form a homogeneous mixture with water at the prescribed stoichiometry.

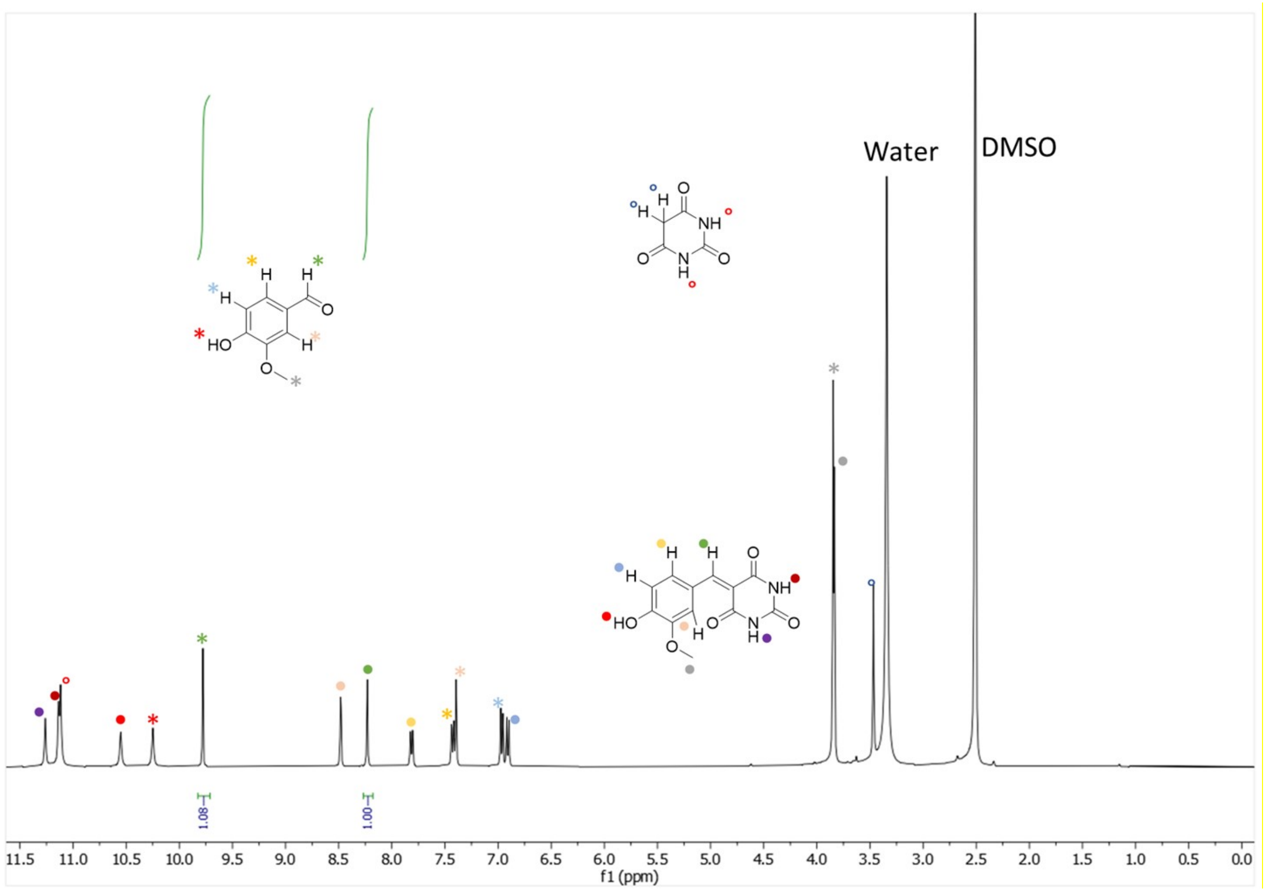
For the optimized extruder conditions (60 °C), a sample of extrudate (1.211 g collected) was worked up as described in Supporting Information Reference 1. In this approach, the sample is washed with boiling water (3 x 15 mL), ethanol (3 x 15 mL), and ether (3 x 15 mL). After this, the collected solids were dried under vacuum for one day. This resulted in the ^{1}H-NMR in the characterization section. The isolated mass was 1.177 g, and by comparing with a standard of our wet DMSO-*d$_6$* (also pictured), it is apparent that there are an extra 0.07 equivalents of water remaining in the sample for each 0.23 equivalence of product (both relative to the DMSO signal). This corresponds to 2% by mass, resulting in a final isolated yield of 95% (1.153 g).

Slightly wet Isolated product



^{1}H-NMR Knoevenagel Analysis

Conversion could be determined by comparing a starting material proton at δ 9.8 (s, 1H) and the target product's proton at δ 8.22 (s, 1H). A sample spectrum is provided below. Note that other than the solvent residual peak and water, there are no other clearly present peaks to indicate side product formation. This analytical approach is consistent with maintext References 31 and 50.



CAUTION: Adding Components to A Hot Jar

As described in the text, this must be done only after proper precautions have been taken. The exothermicity of a reaction should be well understood prior to combining components in a hot jar. Depending on familiarity with the reaction, there may be several ways to explore this. First, a chemist should have the relevant knowledge to develop a safe starting point to investigate the exothermicity. A convenient starting point may be performing an analogous solution reaction at the elevated temperature (or even beginning at room temperature). In these cases, one can use dilute solutions as the safest starting point. Based on observed temperature changes, one can gradually work towards increasingly concentrated conditions. If an acceptable exotherm is observed, one may try combining the reactants in an open, heated jar at progressively higher temperatures. Essential to the safety of this approach is to not work with unnecessarily large quantities and to maintain an open jar. An open jar allows the chemist to make visual observations as well as to avoid unforeseen pressure build-ups from gas release. In many cases, however, the chemist will already be familiar with the reaction from prior experimentation with unheated reactions. However, similar thought processes regarding safety of exotherms should be applied to even those reactions.

SNAr Experiment Without Temperature Control

An experiment was performed to compare a heated and non-heated SNAr reaction. These are conceptually analogous to the Knoevenagel work presented in the maintext. In the present case, one can observe that there is no sigmoidal curve as there was the Knoevenagel reaction. There are several factors that must be considered when deciding if a reaction may have a sigmoidal conversion curve when run in a ball mill that is not temperature controlled.

1) How much does the operating temperature increase above room temperature?

   In this case, it increases from about 21 °C to 38 °C.

2) How long does a reactor take to reach operating temperature?

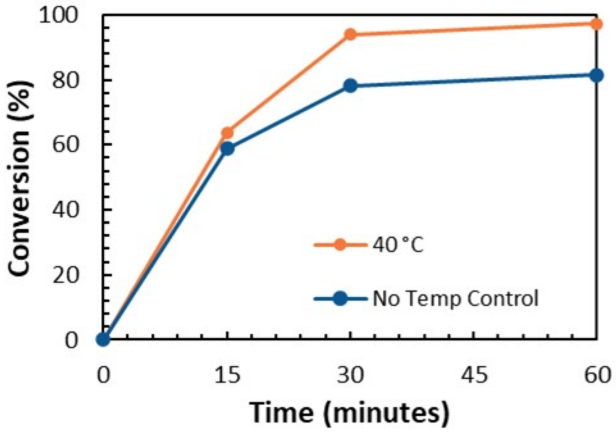
   For this mill, the temperature is within 3 °C of its final temperature within 30 minutes.

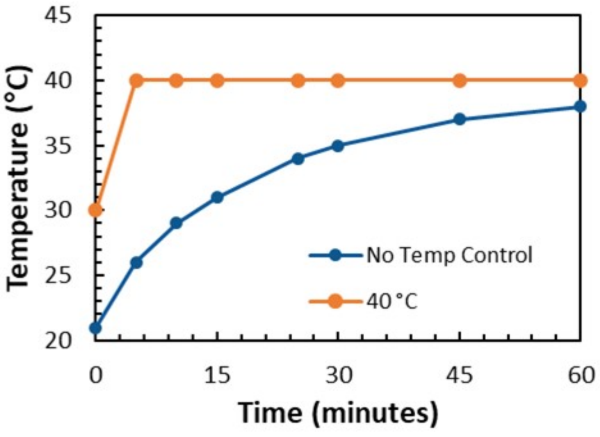
3) How does that number compare with the overall reaction time?

   For this reaction and these temperature profiles, it is about 50% of the overall reaction time.

4) How temperature sensitive is the reaction near the operating temperature?

   Notice that the Knoevenagel is far more temperature sensitive in the region of the operating temperature than the S_NAr reaction. In this case, it seems to be the biggest contributing factor.





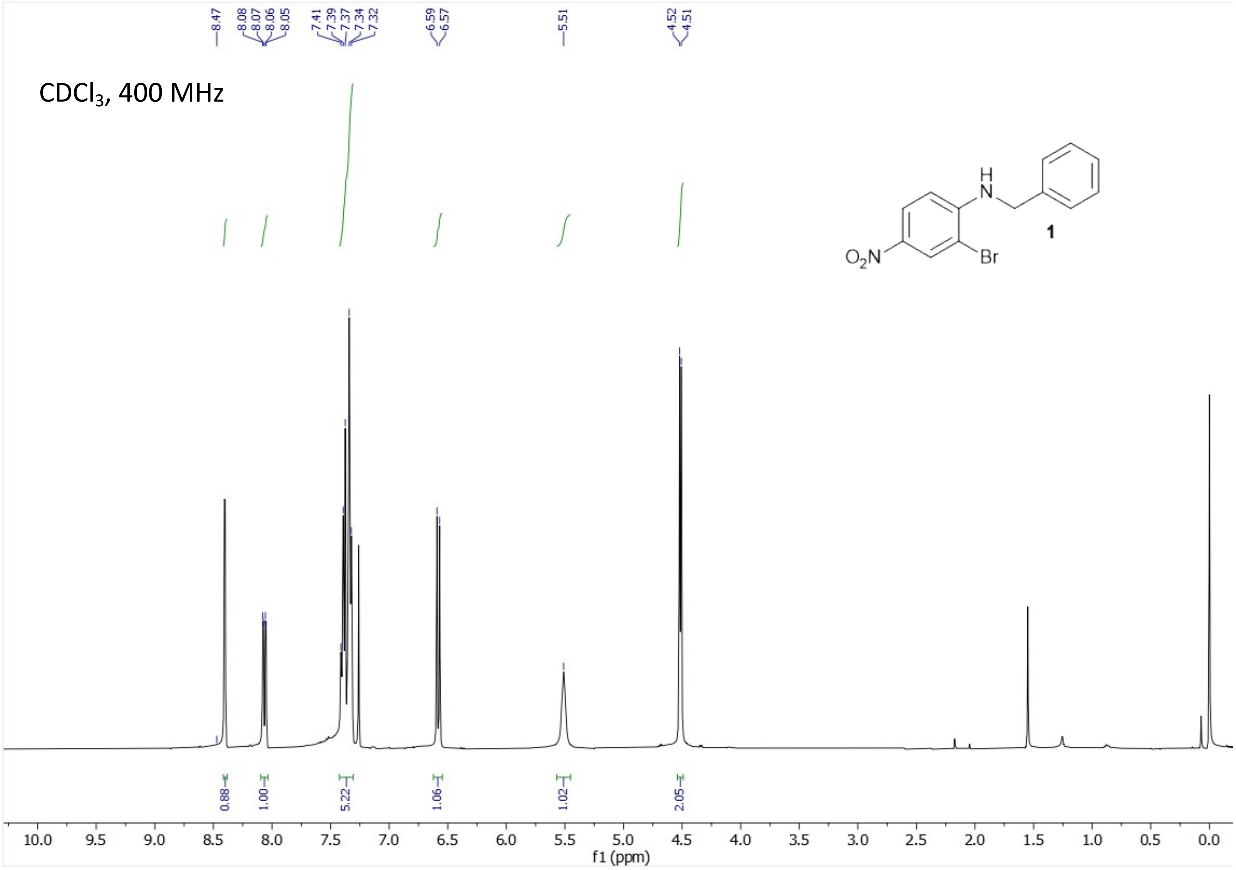
Residence Time Determination ("Spike" Experiment)

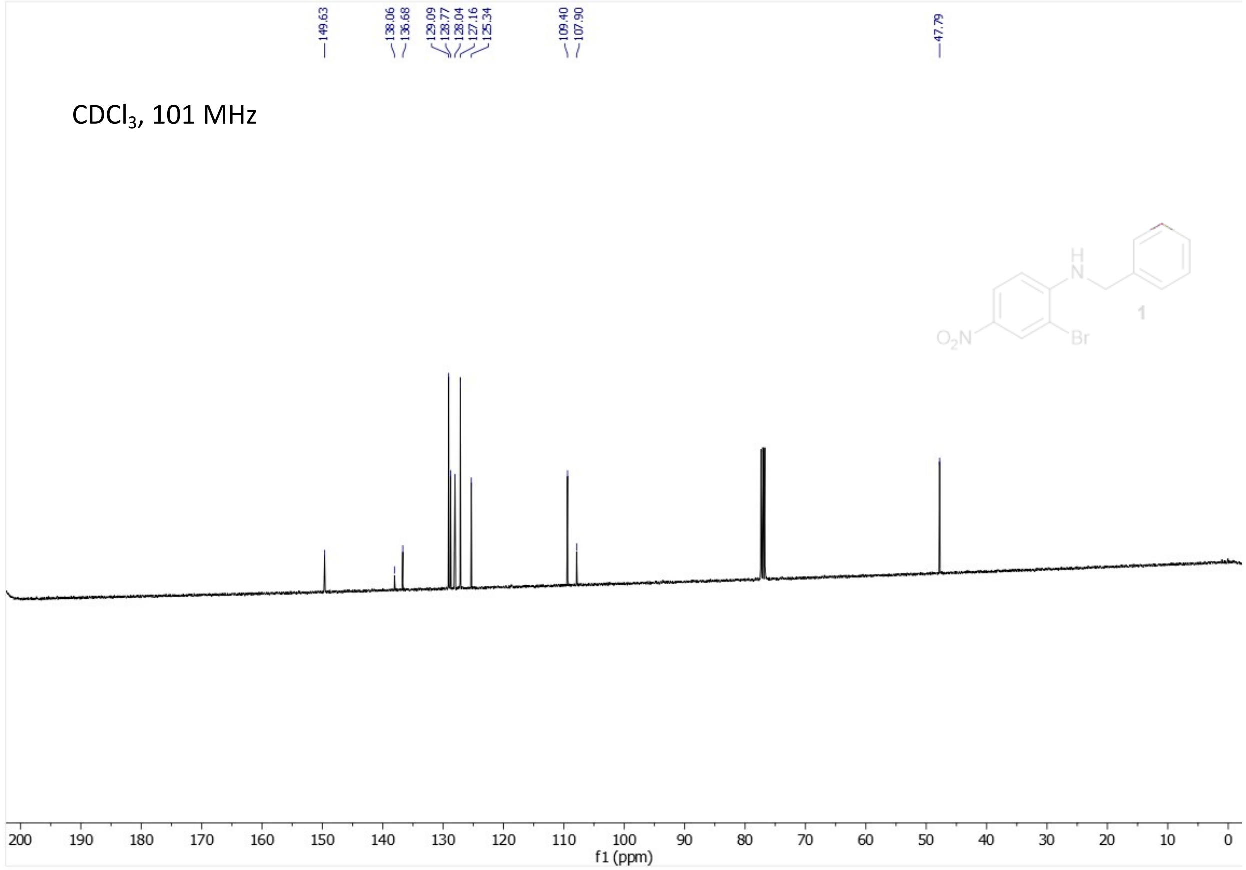
Prior to running the spike experiment, the torque value should become constant. If the torque changes during the determination, it is suggested to re-run the experiment. A change in torque corresponds to a change in the nature of the materials being processed. This means the system is not at steady state and will produce an unreliable value for the residence time distribution.

The color of the food coloring can be selected based on the material color(s). For example, red is not suggested for yellow materials since it can be especially tough to differentiate as it near the endpoint. One must take care during the determination to add a single drop of food coloring. Addition of multiple drops can lead to broadening of the residence time distribution, especially at lower feed settings. Upon addition of one drop of food coloring, a timer can be started. As mentioned in the maintext, we suggest recording the experiment to follow the changes in color and later scrub back-and-forth through the video to most accurately determine the appearance, peak, and disappearance of the material. It is suggested to include the timer in the video (see photo below) to easily determine the relevant times.

Characterization Data

N-benzyl-2-bromo-4-nitroaniline (**1**). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 149.6, 138.1, 136.7, 129.1, 128.8, 128.1, 127.2, 125.3, 109.4, 107.9, 47.8. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.06 (dd, *J* = 9.1 Hz, 2.5 Hz, 1 H), 7.41-7.39 (m, 5 H), 6.58 (d, *J* = 9.1 Hz, 1 H), 5.51 (br s, 1 H), 4.51 (d, *J* = 5.6 Hz, 2 H). For obtaining a highly pure sample for melting point analysis, automated flash column chromatography was performed using ethyl acetate in heptane in the follow proportions: 0% (1 minutes), 0%->10% (1 minute), 10% (2 minutes), 10%->100% (5 minutes). After combining fractions and removing the solvent under reduced pressure, a yellow solid was obtained with a melting point of 107.6 – 108.0 °C.


8.47
8.08
8.07
8.06
8.05
7.41
7.39
7.37
7.34
7.32
6.59
6.57
5.51
4.52
4.51
CDCl3, 400 MHz
H
N
O2N
Br
1
0.88
1.00
5.22
1.06
1.02
2.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


149.63
138.06
136.68
129.09
128.77
128.04
127.16
125.34
109.40
107.90
47.79
CDCl$_3$, 101 MHz
H
N
O_2N
Br
1
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

5-(3-methoxyl-4-hydroxybenzylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (**2**). ^{1}H-NMR was consistent with prior literature.[46] ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.27 (s, 1H), 11.14 (s, 1H), 10.60 (s, 1H), 8.48 (s, 1H), 8.23 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 6.93 (d, *J* = 9.8 Hz, 1H), 3.82 (s, 3H).