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Scaling-Out Pharmaceutical Reactions in an Automated Stop-Flow Microwave Reactor

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Abstract:

Six pharmaceutically relevant reactions were assessed for scale-out in an automated stop-flow microwave reactor. Daily throughputs of between 50 and 250 g were achieved at typical reaction concentrations; for more concentrated reactions, or with 24 h processing, productivity of 0.5−1.5 kg per day was achievable. This study confirms that the stop-flow approach in combination with rapid microwave heating can be equivalent to conventional continuous flow technology with comparable productivities.

Introduction

Microwave-assisted organic synthesis (MAOS)[1,2] has become hugely successful in the past few years in both academia and especially industry, where it is now routinely used for initial drug discovery synthesis.[1b] Microwave heating provides many well-known benefits at small scale, most of which are also advantageous at larger scale. For example, increased reaction rates, improved impurity profiles, reduced catalyst loadings, access to superheated solvents (possibly leading to novel chemistries such as near critical water chemistry for example),[3] and possible energy savings,[4] are all as highly desirable at large scale as at small scale.

However, the scale-up of microwave reactions in organic synthesis has not been easy for a number of reasons, and so far only a limited scale-up has been achieved.[5] The various approaches to scale-up have followed a number of strategies. Successful synthesis in small-scale sealed tubes (2−10 mL), as exemplified by the Biotage Initiator and CEM Discover microwave reactors, has led to synthesis in larger sealed tubes (20−35 mL), and thence to larger sealed vessels, for example in the Milestone MicroSYNTH. The problem with these larger vessels (100−3000 mL) is that a superheated solvent generates considerable pressure at the temperatures typically required. To contain these pressures, the vessel must be strong whilst being microwave transparent. The materials typically chosen (ceramic, glass, PTFE) are all thermal insulators, with the result that whilst the heating time is fast, the cooling time is often poor, and becomes worse as the vessel size grows. A way around this is to use multiple small vessels in parallel, as for example in the Anton Paar Synthos 3000, which achieves a larger volume, whilst keeping the pressure in any individual vessel within acceptable limits. However, for larger-scale synthesis, it would be tedious to load multiple vessels with multiple reagents and solvents, and so this approach also has a limited effective scale-up capability.

An open vessel system using conventional laboratory glassware as in the CEM MARS avoids this problem, and some impressive synthetic reactions have been performed in this apparatus on 5 L scale.[6] However, it is limited to the boiling point of the solvent used for the reaction, which may limit the chemistry compared to the original microwave tube-scale reaction. And a further limiting factor for all open or closed vessel systems is the penetration depth of microwaves,[7] which is only a few cm in most solvents at 2450 MHz.[8] Therefore, even the open vessel system cannot be scaled up beyond about 5 L. Consequently many have concluded that for effective scale-up, a continuous flow (CF) system will have to provide the answer. Many prototypical or modified commercial CF microwave reactors have been reported,[9] starting with the pioneering example of Strauss in the mid 1990s,[10] and at least one viable commercial instrument (the Milestone FlowSYNTH) is now available. However, most if not all of these microwave reactors suffer the same general limitation of CF reactors in requiring a homogeneous solution both to enter and exit the reactor vessel.

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Even so, a further hybrid microwave-CF reactor configuration is also possible, that of an automated stop-flow microwave reactor, which exists in one form as the commercially available CEM Voyager SF. This instrument relies on a small vessel (80 mL) to circumvent the microwave heating issues that limit larger vessels as discussed above, and automation to facilitate repetitious vessel charging. As with other CF reactors, homogeneous or near homogeneous solutions are required, and it could be argued that this system has the disadvantages of CF without the benefits of conventional batch reactors (i.e., simplicity, scale and ubiquity). However, automated charging combined with microwave heating on a small chemical inventory means that this reactor effectively processes multiple small vessels in series, rather than in parallel as for other microwave reactors; or by comparison to conventional CF, it could be considered to process segments of reaction material passing through a tube, but in stop-start fashion, rather than in a continuous stream.

By retaining the small vessel size, the advantages of microwave heating are easier to realise, such as for example the overall rapid processing of batches, rapid heating and cooling profile, and lower mechanical pressures due to superheated solvents. The combination with automated charging makes processing many small batches practicable, where it would not be so in other cases. In common with CF generally, the workup procedure must be considered separately, but here also there are several minor advantages; batches can be combined to provide workup batches of whatever convenient size required (to fit vessels or for GMP considerations), and occasional out-of-specification batches result in a trivial loss of output compared to the possible impact on small batch numbers from large batch reactor manufacture.

We present here our results using the CEM Voyager in stop-flow mode for a number of pharmaceutically relevant reactions. These reactions were chosen because they are typical of those used within the pharmaceutical industry, and because they would benefit from microwave heating to increase the reaction rate. They were also chosen because they all provided a homogeneous solution which could easily be processed in the Voyager. The Voyager is capable of processing some heterogeneous reaction mixtures, although the results have been mixed.[11] On the other hand, we wanted to test the instrument on typical (albeit homogeneous) pharmaceutical reactions, and at typical concentrations, by running many multiple batches; it is only by running in CF mode for an extended period that the true capability of the technology can be proven. In this case, we were not disappointed.

Figure 1. **CEM Voyager.**

Results and Discussion

Description of the CEM Voyager. The CEM Voyager is essentially a pump unit consisting of a peristaltic pump, two valves and associated lines, which sits on top of the versatile 300 W Discover base unit.[12] The two units have integrated software control and are connected by a single cable. The Discover unit can be used separately from the Voyager unit, and it takes only a couple minutes to switch between the two functionalities. The combined Voyager unit will fit comfortably in a standard depth fume cupboard and occupies no larger footprint than the Discover itself, except for the need for feed and receiver vessels, and so occupies no more than half the width of a standard fume cupboard in total (Figure 1). With a small footprint, multiple units can be accommodated easily if larger quantities are required (a scale-out option). Furthermore, once the reaction conditions are optimised, the automation reduces the interaction required by the chemist. A significant drawback is the need to have homogeneous or nearly homogeneous reaction solutions. Although the instrument uses a peristaltic pump which can in principle transfer slurries, and is fitted with an anticlog device, in practice the lines (1.5 mm i.d.), valves and pump are prone to blocking with slurries, as noted by Lehmann.[11c] However, it has been used successfully with fine slurries as reported by others.[11a,b] Although continuous addition and sampling whilst heating are not formally possible, the multiple inlet and outlet lines could be used to mimic these techniques if required, although with the potential to isolate many small batches, this is probably of less interest. Finally, the small reaction mass in a glass-walled reactor heats and cools quickly and so the cycle time per batch is fast. Coupled with genuine automation for rapid charging and discharging, this small instrument has a lot to offer.

In fuller detail, the Voyager SF has an 80 mL Pyrex glass vessel with 50 mL operating capacity and a fibre optic probe to measure the temperature, sited in a sapphire thermowell

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Figure 2. **Voyager head unit, reaction vessel and fibre optic probe in thermowell.**

(Figure 2). (There is also a true continuous flow model (Voyager CF), which has a 5 mL capacity coil in place of the 80 mL glass vessel, and requires a different pump unit, but this has been little used in comparison). Magnetic stirring provides the agitation, and cooling is provided by compressed air which cools the vessel and contents at the end of the heating cycle. The vessel can also be cooled whilst heated if desired. The Voyager will operate across the standard temperature and pressure range for most scientific microwaves (i.e., up to ~200 °C and 20 bar).

The vessel is charged through three inlet lines (made of PTFE or stainless steel), two for starting material solutions (SM1 and SM2) and one for solvent; however, this could equally serve as an SM3 inlet line also. And there are three outlet lines for product, waste and air. The air line can also be used as an inlet line for other gases, either for inertion or for other reaction gases. There is also an overflow line which simply operates as a drain if the vessel is overfilled. The lines can be blown clear with air from valve 1 backwards, but because there is only one pump, it is not possible to flush the lines beyond this valve with solvent without first occupying the vessel and then blowing back (see Figure 3). The line connecting valve 1, the pump, valve 2 and the vessel is therefore common to all, which has to reach to the bottom of the vessel if it is to discharge the contents efficiently; the air line and overflow reach only to the top. The Voyager therefore in essence provides automated charging and discharging of the reaction vessel in a stop-flow mode, so it can be programmed to charge, heat, cool and discharge repeatedly, for as many batches as are required. The total volume to be processed is entered into the interface, and the software calculates the number of batches required. Some idea of the cycle time is a good idea however, if one wants to know when it is likely to finish. The cycle can also be paused, halted or canceled.

A sequence of batches uses a method which is made up of individual steps (add, microwave, remove or clean), and each of these steps has additional substeps. The add step adds a fixed volume from any one of the input lines into the reaction vessel. It is wise to calibrate the pump first for this procedure, and to note the calibration constants, as different solvents and reaction mixtures have markedly different viscosities. However, the calibration constants stay with each add step and do not need to be redone even if switching regularly between solvents. The add step also blows the lines clear of reagent, and two solvent charges can be added with further air blows to further ensure the lines are clear for the next reagent or product. Finally, it is worth noting that the pump speed can be adjusted down from 100% to a minimum of 20%, if particularly fine control for a small charge is required; or the charges can be controlled on time alone if preferred.

The microwave step operates as expected, heating to a set point temperature in a specified time, and then holding for a specified time, before cooling to a set temperature. All the usual parameters can be altered, including heat-up and hold times, adjusting the wattage or using fixed power, heating-with-cooling, and designing multistage heat-up procedures. The remove step simply empties the vessel through the appropriate outlet line, and is best run on fixed time, although there is also a solvent sensor to detect when the vessel is empty. The clean steps are designed to rinse the vessel and the lines, either to ensure all product has been removed to the receiver vessel, or in preparation for the next batch. They are basically simplified add and remove steps combined in one operational step. Vessel rinses can also be built into a method by using add and remove steps separately, but we found in general that it is a more efficient to use the functionality built into the instrument software.

Preparing the Chemistry. Chemistry for trial in the Voyager should first be assessed in a small-scale scientific microwave reactor; indeed the chemistry may well have come from a microwave reaction. If it is from conventional heating, a tube-scale reaction should be tried. The trial should obviously be at the same concentration as the planned scale-out reaction. This will give an idea of the operating parameters required for successful reaction (i.e., time and temperature) and also an early indication of any potential hazards (e.g., unexpected pressure build-up). However, this is unlikely as the maximum scale is only 50 mL, so few reactions should be problematic. Even so, stepwise scale-up (2 mL to 20 mL to 50 mL) when superheating reaction mixtures is still wise (and recommended by the manufacturers). A DSC test or Carius tube experiment will provide sufficient data in cases of concern. Furthermore, it is a simple calculation to determine the pressure generated from a particular solvent at a set temperature with a given vessel fill volume.

Once standard parameters for a tube-scale reaction have been determined, and chemical and physical hazard issues addressed if necessary, trials in the Voyager can begin. It is not worth over-optimising the small-scale microwave reaction conditions in our experience, as they will vary slightly when transferred to the Voyager. This is because the vessel has a slightly different geometry from a microwave tube, the stirring will be slightly different, and the Voyager has the same size magnetron (300 W) as the smaller reactors to heat a much larger reaction mass. As with other CF apparatus, considerable starting material is needed for trials, depending on the concentrations to be run. Presumably, this will be available if the aim is to process large

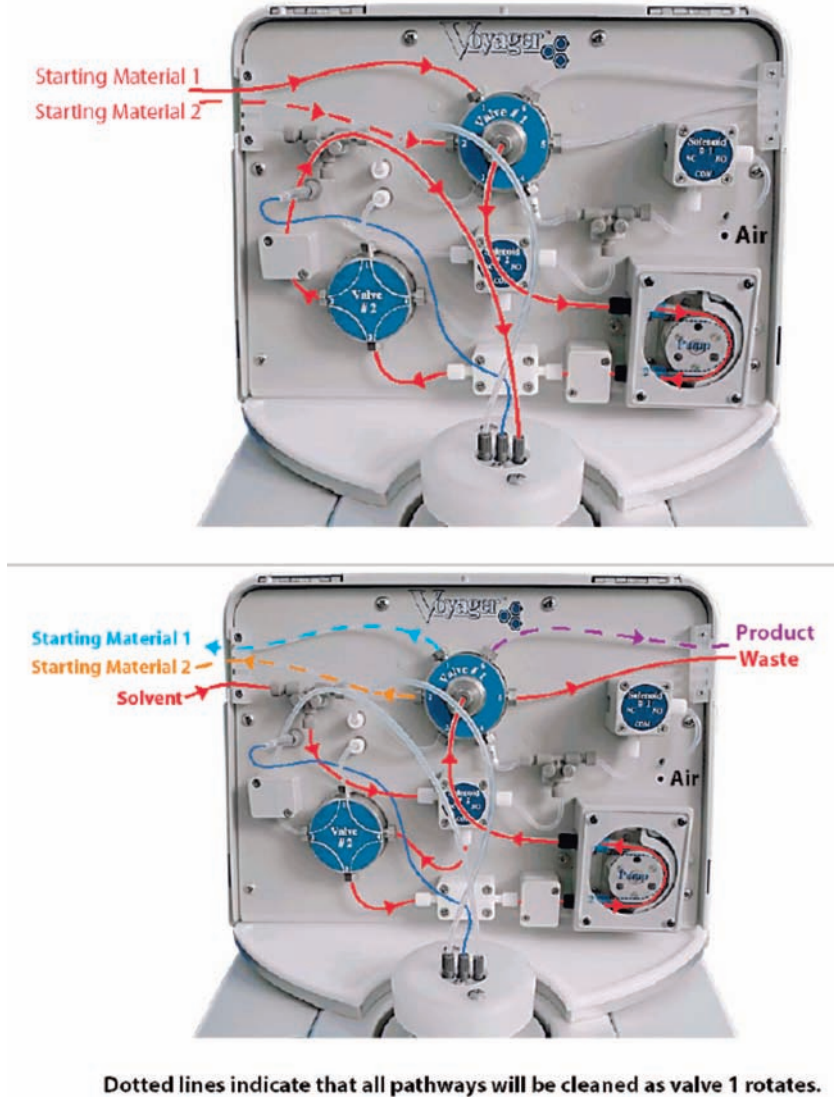
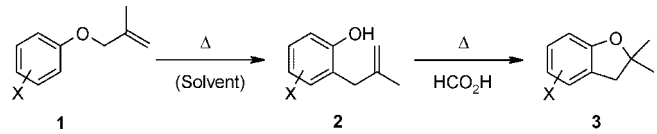


Figure 3. **Schematic overlay of Voyager pumping operations for "add" (top) and "clean" (bottom) steps.**

quantities of material, and for many chemists, the initial product from unoptimised batches will still be very useful for ongoing studies. It also makes sense to fill the vessel to capacity (50 mL) unless there is good reason to do otherwise, as this will maximise the through-put. The Voyager will actually allow 60 mL into the vessel, so there is some scope for increasing productivity, although stirring and cooling might be less efficient. There is obviously a pay-off in terms of cycle time for heating and cooling a larger batch (which takes slightly longer) than in heating and cooling a smaller batch. Other factors may determine what is the most efficient protocol overall. What the Voyager will not allow is more than 60 mL in the vessel if it thinks this volume has been exceeded; this can happen if the pump calibration volume deviates significantly from the actual input volume. Whilst in principle it is not essential to have these figures close together, in practice it is more helpful to have the calibration volume fairly close to the actual volume.

Overall, preparing the chemistry in practice from microwave tube reactions to a suitable Voyager method can take typically between 0.5 and 3 days, depending on familiarity with the chemistry, the complexity of the method and problems encountered. Once the method is developed however, little further work is required, other than to keep the instrument running, and of course to isolate the product.

Scheme 1



ortho **Claisen Rearrangement and Benzofuran Formation.** The Claisen rearrangement is a valuable and venerable reaction, first reported in 1912, and has most recently been reviewed by Martin-Castro.[13] We chose to focus on the *ortho*-Claisen rearrangement and subsequent ring closure to the benzofuran (Scheme 1) since this aligned with a recent AstraZeneca project.

The readily prepared aryl-*O*-allylethers **1** were conveniently used for scouting trials in small microwave tubes. Of these, we chose to concentrate on the naphthyl compound **4** since considerable quantities of this material were available from investigating the preceding O-allylation reaction; and also because it is converted to its Claisen product **5** under more facile

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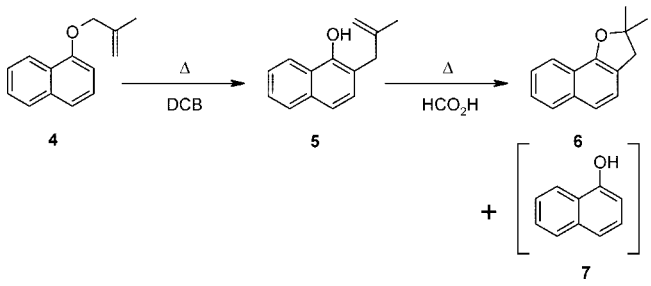
Scheme 2



conditions more readily within the scope of the Voyager (Scheme 2). Typical conditions for the *ortho*-Claisen rearrangement require several hours in high-boiling solvents such as DMF or diethylaniline, or heated neat without solvent. Although we tried a range of classic and nonclassic solvents for this rearrangement, we found that conversions for all substrates were cleanest when conducted neat. Compound **4** was also a light oil, so could be flowed into the Voyager. This reaction therefore provided an example of a high-temperature, single-phase reaction. The small-scale tests on **4** were conducted on 1.0 g (4 mmol) scale in each tube, but because the reaction was neat, we conducted a DSC test to determine that there were no thermal stability issues before scaling up in the Voyager.

Initially we attempted to combine the Claisen rearrangement and the acid-catalysed ring-closure step into a two-step sequence to convert **4** into **6** (Scheme 2). Scouting studies in a tube-scale microwave reactor indicated that the Claisen reaction required heating at 200 °C for 10 min, followed by ~140−150 °C for 5 min for the ring closure, depending on the quantity of formic acid used. Conversions were good with only ~2−3% **4** left and 5% 1-naphthol (**7**) formed (presumably by acid-catalysed hydrolysis of unreacted **4**); this could be washed out of the product with dilute alkali solution. To simplify the process, an all-in reaction with a roughly equal volume of formic acid was attempted with an extended heating time, to convert **4** directly to **6**. However, the level of **7** regenerated was now 13%, with an unknown impurity present at 10% (by HPLC area), and although all starting material **4** was otherwise converted to product **6**, an overall conversion and purity of ~75% was judged too low to justify this one-step procedure.

Concurrently, pumping trials in the Voyager had revealed that although **4** appeared to be a mobile oil, it was viscous enough to trigger the clog detector in the pump periodically, causing it to reverse the flow briefly. This was not desirable for the multiple-batch manufacture we were planning, so the starting material was diluted with an inert solvent to reduce the viscosity. This would also allow us to build in small solvent washes to rinse the line of residual formic acid in-between batches in the two-step procedure. Model studies in microwave tubes worked well using between a quarter and one equal volume of toluene to starting material **4**, even though the formic acid was biphasic with the toluene reaction mixture at RT. We rationalised that at high temperature the reaction mixture would be either monophasic or sufficiently well stirred to achieve good mixing.

Studies in the Voyager could now begin. A solution of **4** in toluene was prepared suitable for a small number of batches and a three-batch trial was run. This is the minimum realistic number for a trial; the first batch always behaves slightly differently due to starting from cold or if the instrument has been left idle for a period; the second batch should give a reliable indication of performance; and the third batch provides some measure of reproducibility. Once the conditions have been fine-tuned on the Voyager, a five-batch trial provides further confirmation just before starting a large cycle. In this case however, the three-batch trial failed because the 300 W magnetron, which had been more than adequate for a tube-scale reaction, could not heat 25 mL of this very low polarity reaction mixture beyond about 140 °C. Xylene was also considered, but we have found 1,2-dichlorobenzene (DCB) to be a good substitute for aromatic solvents such as toluene and xylene in microwave reactions, aided by its higher bp (180 °C) and dielectric constant (9.9).[1d] This necessitated another quick check on tube scale, which heated considerably faster than the comparable toluene solution, confirming our choice of DCB. Heating trials for the first stage were now successful in the Voyager, although the magnetron had to work hard to hold the batch at 200 °C. By dropping the temperature back to 195 °C, and heating for 2 extra minutes, the magnetron reached the set-point temperature more quickly and held it at 195 °C more comfortably on relatively low power. In fact, the reaction mixture tended to overshoot the set-point temperature up to ~200 °C once it reached ~190 °C, which we assumed was the heat of reaction. The volume of DCB used was also reduced to half with respect to **4**, which may also have aided the heating time.

With the first step fixed, we attempted to fine-tune the second. The crude Claisen product **5** was cooled to 120 °C and 20 mL of formic acid charged through the SM2 line, followed by a 3 mL line wash with fresh DCB through the solvent line. This mixture was reheated to 150 °C for 5 min, and also tended to overshoot the set-point considerably, up to 165 °C. This caused a problem because enough formic acid had decomposed to generate residual pressure greater than the normal 50 psi limit for venting the vessel, although this limit can be adjusted upwards. An alternative was to limit the microwave power available in this step to 200 W, which then kept the temperature somewhat closer to the desired set-point, and resulted in less gaseous formic acid decomposition products. However, longer heating was still required to get the pressure down to an acceptable level, even when the temperature was already well below 90 °C. The batch was removed from the vessel through the product line, where it immediately became biphasic. Two vessel rinses with fresh DCB of ~10 mL each were used to clean the vessel of residual formic acid through the waste line in preparation for the next batch. The overall cycle time was 37 min for 10 g of starting material **4** (50 mmol) with ~90% conversion to naphthofuran **6**.

Unfortunately, analysis of both phases of these batches indicated incomplete reaction in two out of three cases, even though the small-scale tube reactions had been excellent. Since there was no starting material **4** left, but some Claisen product **5** without much of the usual 1-naphthol (**7**), this suggested that it was the second, ring-closing reaction that was the problem (since conversion of **4** to **5** was complete, and **5** converts readily to **6**, incomplete reaction could only arise if the second reaction

Table 1. **Comparison of reaction data**

reaction	cycle time (min)	temperature (°C)	hold time (min)	conversion (%)[a]	relative volume[b]	concentration (g/batch)	through-put[c] g/h
Claisen (one step)	21	195	12	95	0.5	21	60
Heck #1 (**10**)	8.6	140	2.0	93−98[d]	12	3.3	23
Heck #2 (**13**)	8.6	140	2.0	93−98[d]	10	4.0	28
hydrolysis	9.5	110	1.5	99	30	1.5	9.5
hydrolysis + alkylation	11	110	2.0	99	30	1.5	8.2
NKR #1 (**14a**)	16	200	10	99	2	16	60
NKR #2 (**14b**)	27	210	20	99	5	8.3	18
NKR #3 (**14c**)	28	210	20	95	4	10	21

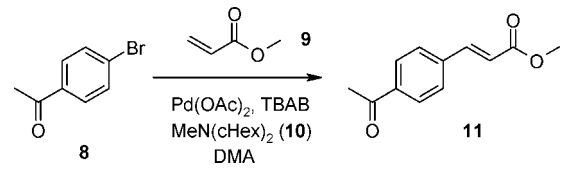
[a] Determined by HPLC. [b] Relative to starting material mass. [c] Through-put of starting material. [d] Total conversion to products **11** and **12**.

failed in some manner). It was thought likely that the explanation was due to an intermittent mechanical problem with the stirring on the instrument, which can sometimes be discerned by the sound. Poor stirring of the probably biphasic reaction mixture in the larger reaction vessel could account for the incomplete reaction in some batches. At the time, we decided to press on with the single-stage (Claisen) reaction to establish the precedent of a 1 kg-scale manufacture in the Voyager. However, we have discussed this attempt in some detail because it illustrates a number of points in the use of this technology.

ortho **Claisen Rearrangement.** Having decided to fall-back on the single-step Claisen reaction, virtually no additional development work was required. The batch size was increased to 30 mL to improve the productivity, since volume in the reaction vessel was not needed for the formic acid. The full capacity was not used since the cycle time increased significantly when trying to heat 50 mL to the temperature limit around 200 °C. As noted, 195 °C for 12 min gave precisely 95% conversion with ~5% starting material **4** left and a trace of 1-naphthol. Reducing the heating to 10 min resulted in ~94% conversion, which we felt was just too low, whilst heating for 15 min gave only a 1% improvement to 96%, and was not worth the gain in yield versus the cycle time. Some time was saved by venting the product from the vessel at 100 °C which shortened the cooling time, so that overall the planned cycle time was 21.0 min for this simple Voyager three-step method (full details of which can be found in the Supporting Information). The three-batch proving trial worked exactly as planned, so two 24-batch cycles using a total of 1006 g of **4** diluted with 500 mL of DCB were processed over two 8.4 h days. Batches were combined into groups of six or seven, and HPLC showed conversions for all fell between 94.8 and 95.1%. Output volumes were exact multiples of 30 mL (180 or 210 mL), demonstrating very good control by the pump, and no operator input was required during the day other than to supply the receiver vessels.

Total reaction time for 48 batches was 16.8 h, or 21.0 min per 21 g batch as planned. This averaged 1.000 g min^{-1} or 60.0 g h^{-1} comparative to CF mode, a good rate for a reaction requiring 195 °C for 12 min, which is notably above what is achievable by most standard pharmaceutical laboratory and pilot plant equipment. Of the 21.0 min, the typical heating time was 3.5 min and cooling time was 3.3 min; the remaining nonheating time of 2.2 min was taken up with pumping and valve switching. Further details are given in Table 1. Overall, productivity was very high because this reaction is almost neat.

Scheme 3



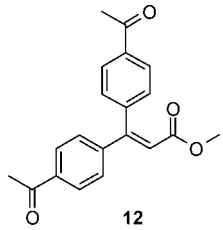
However, it does demonstrate what one small instrument can achieve for a suitable reaction operating in a type of CF mode, albeit stop-flow in this case. Furthermore, it also demonstrates how microwave technology, in combination with a scale-up/-out option, can deliver useful quantities of product that would be difficult to achieve on pilot-plant scale due the normal temperature limits there. A further comparison with other reactions considered here is given later in Table 2.

Heck Reaction #1. Although not as old as the Claisen reaction, the Heck reaction has also established itself as an invaluable synthetic transformation.[14] It also served our purposes in being an example of a second order reaction. The requirement for moderately high temperatures in combination with a metal catalyst made it ideal for investigation under microwave heating. Preliminary investigations reacting 4-bromoacetophenone (**8**) with methyl acrylate (**9**) using $Pd(OAc)_2$ as the catalyst had established that a homogeneous reaction mixture could be obtained. This is a standard model substrate for the Heck reaction, and several microwave scale-up preparations have been reported using low loading of catalyst (0.1 mol %).[15] Our conditions[16] were slightly different from those reported, using dimethylacetamide (DMA) as the solvent and methyldicyclohexylamine (**10**) as the base, which has been found to work well in more demanding cases (Scheme 3).[17]

All components of the reaction mixture could be made up in a single solution at 10 volumes in DMA (relative to the acetophenone **8**) and stored for some time; there was no background reaction at RT. The $Pd(OAc)_2$ catalyst was loaded at 0.1 mol % with tetrabutylammonium bromide (TBAB) at 0.4 mol %, and was completely soluble in DMA at this volume. As a precaution, reaction mixtures for large sequences were filtered to remove any residual particles. Small-scale microwave tube trials showed that the reaction was 95% complete after 5

(14) (a) Beletskaya, I.; Cheprakov, A. *Chem. Rev.* **2000**, *100*, 3009–3066. (b) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553–1582.
(15) (a) Leadbeater, N. E.; Williams, V. A.; Barnard, T. M.; Collins, M. J. *Synlett* **2006**, 2953–2958. (b) Arvela, R. K.; Leadbeater, N. E.; Collins, M. J. *Tetrahedron* **2005**, *61*, 9349–9355.
(16) Murray, P. M. Personal communication; manuscript in preparation.
(17) (a) Gurtler, C.; Buchwald, S. *Chem. Eur. J.* **1999**, *5*, 3107. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

min at 130 °C and 100% complete at 140 °C. These conditions were transferred to the Voyager on 47 mL scale, but the reaction mixture regularly overshot the 140 °C set point temperature up to ~150 °C. A DSC test established this was not due to a reaction exotherm (and also established there were no other thermal hazards), but was presumably due to the highly polar reaction medium coupling well with microwave heating. Cutting down both the microwave power available and heating time did not minimise this temperature overshoot. Instead, we decided to make use of it, and cut the heating time to 1 min to reduce the cycle time. The heating profile was therefore effectively 150 °C for 1 min, although only 140 °C for 1 min was programmed in the method. Conversions were >98%, with <2% residual starting material; however, part of the conversion (5−7%) was due to the formation of an impurity identified by MS as the bis-coupled adduct **12** (and which is probably over-reported by HPLC based on UV detection).



12

The overall cycle time was 7.5 min with cooling to 80 °C. Three-batch sequences worked well for the first batch, but the subsequent batches had a tendency to block in the outlet lines due to residues of the highly crystalline HBr salt of **10** seeding the second and third batches. To overcome this, a small line wash with fresh DMA was charged after the product was removed from the vessel to rinse the outlet lines, and the outlet temperature was raised to 90 °C. The reaction volume was also cut down to 9.5 volumes to allow for the line wash. Unfortunately, successful reaction batches were clearly on the limits of solubility at these temperatures and concentrations, as the lines blocked solid after the first batch and had to be replaced. Thus, the reaction volume was increased to 12 volumes of DMA, and both a vessel wash and a line wash were built into the Voyager method. The vessel wash of 10 mL of fresh DMA from the solvent line cleared reaction residues from the lines between valve 1, the pump and the vessel (cf. Figure 3), which were the most important lines to keep clear, being common to all pumping operations. Since the wash was relatively large compared to the residues removed, this was rinsed to the waste line and discarded. The second smaller line wash (5 mL) also rewashed this section of line, making sure it was clear, but then flushed the product outlet line also, sweeping any remaining reaction residues into the receiver vessel, and ensuring this line was clear to accept the next batch. In this regard, running a Voyager sequence was very much like running a pilot plant. Lastly, an additional 20 s air blow was added to the method to get the lines as clear as possible. The overall cycle time was increased to 8.5 min, but the method was now robust, and calculations predicted 20 g h^{-1} through-put.

During this work, the conversion appeared to have dropped off slightly, so for the final fine-tuning of the reaction conditions on a five-batch sequence, the heating time was increased to 2 min, and the reaction volume to 48 mL. To save wasting material, and to avoid the slightly lower conversion of the first batch when the instrument is cold, the first batch through the cycle was simply blank solvent. The four following reaction batches gave good and consistent conversions (97.5%) with reliable output volumes (53 mL each) and a cycle time now of 9.2 min (due to the increased reaction time). None of the lines blocked.

Figure 4. **Pd-coated reaction vessel and stirrer bar.**

A 50-batch sequence was performed in a single day on 2650 mL of filtered reaction mixture, heated to 140 °C for 2 min. Total run time was 7.2 h, or 8.56 min per batch (the discrepancy in cycle time is likely to be due to the instrument not being fully hot during the short proving sequence). Total processed mass of acetophenone **8** was therefore 163 g. Initial batches were combined into groups of four, and showed conversions of 89−94%, slightly low compared to the expected results. Volumes for combined batches were around 212 mL (i.e., 4 × 53 mL), and the wash volumes consumed were also exactly as planned, demonstrating again very good control by the pump. Further details are given in Tables 1 and 2.

After the first 20 batches had been collected in groups of four, the final 30 were collected in one vessel. Surprisingly, the conversion for this group had dropped to 80% of product **11**, with still ~5% of diadduct **12** but 15% of unreacted acetophenone **8**. However, when the vessel was opened and examined, it became obvious what had changed; the vessel was heavily plated with a Pd mirror (Figure 4). The fibre optic probe's thermowell was also plated down most of its length (not shown) and significantly the window at the tip was obscured. Operating above ~110−120 °C was likely to produce Pd nanoparticles,[18] and residual Pd-black could be seen in the product reaction mixtures (Figure 5). However, this vessel had been running batches more or less continually with trial batches and it was not until more than 50 batches had been performed,

(18) (a) Reetz, M.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165. (b) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickz, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285–3288. (c) Reetz, M.; de Vries, J. *Chem. Commun.* **2004**, 1559.

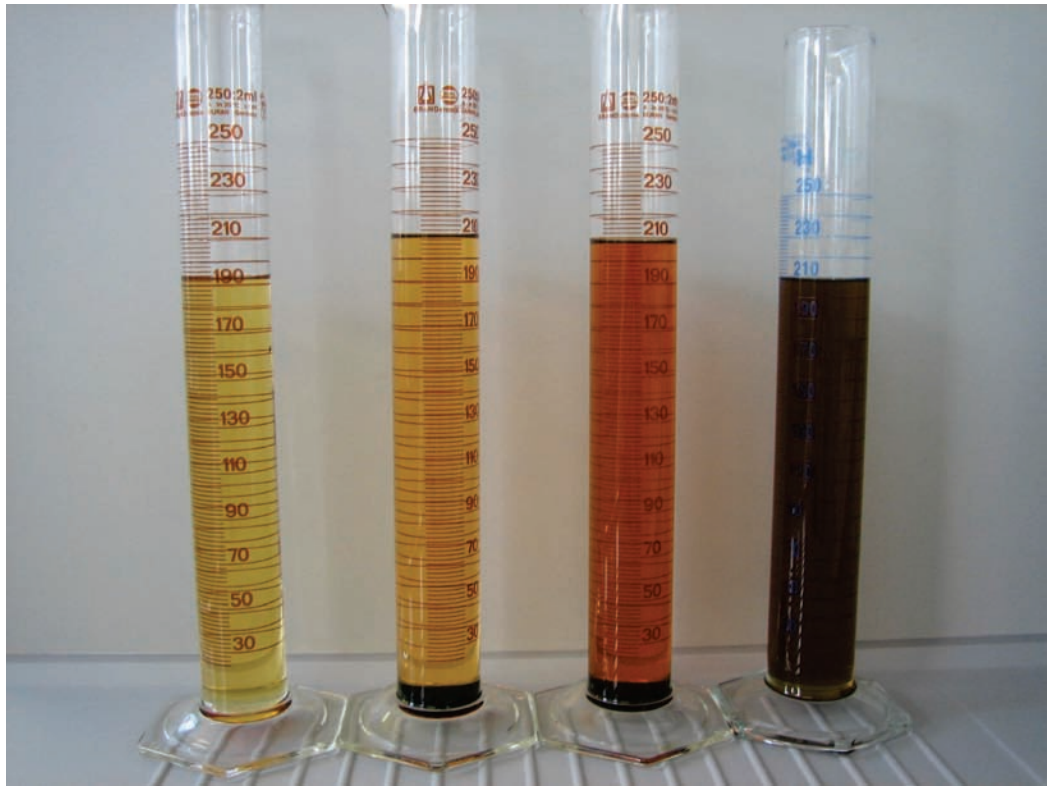
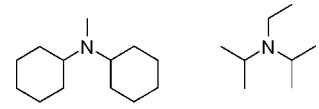


Figure 5. **Heck reaction product solutions. Left to right: (a) unreacted solution, (b) partially reacted solution, (c) fully reacted solution, (d) partially reacted solution showing Pd nanoparticles before settling. Note: Pd residues have settled out in tubes (b) and (c).**

during the middle of this large-scale sequence, that performance started to significantly degrade. We speculate that the Pd mirror will couple very well with the microwaves, thus perhaps giving hot surfaces in contrast to the usual performance with microwave vessels. Of more importance though is the likely increased temperature reading on the *inside* of the Pd-coated window by the fibre optic probe. This will cause the probe to read a higher temperature than the bulk reaction mixture, which will not then receive the full microwave heating required for complete reaction (and which is presumably not compensated by any additional heating from hot Pd-coated walls).

Aside from this issue, the workup and isolation of the product was relatively straightforward. The reaction liquors were diluted into double their volume with water which precipitated a yellow solid. This was isolated by filtration and washed with water to give the cinnamate product **11** as an off-white, slightly grey solid (residual Pd levels will be reported separately). Quality was excellent, and batches with conversions of >90% gave isolated product **11** with typically 97−98% quality, the balance being shared by residual acetophenone **8** and diadduct **12**. Even lower quality batches gave generally good quality product on workup. However, residual amine **10** was seen at 33−50 mol % in the ^{1}H NMR spectra. This was removed by reslurrying in water and washing with 0.5−1.0 equiv of concentrated HCl for several hours, re-isolating and washing with water, which completely removed all amine residues. Quality was further improved to >99%, and the recovery was typically 95%. The HCl washing procedure was then built directly into the workup for later batches which simplified the process, and gave an overall yield of 80−90% with quality ∼97%.

Heck Reaction #2. The second Heck reaction attempted was essentially identical, but with Hunig's base (**13**) in place of the much more expensive **10**. Aside from being cheaper, especially for the quantities required for this CF chemistry, its HBr salt did not crystallise in the Voyager's lines. This allowed the Voyager method to be simplified, since the vessel and line washes in the previous reaction had not been required for the chemistry, but were only needed to ensure the lines were free from blockage. This would save cycle time, but only if **13** was a suitable substitute for **10**. Small-scale tube experiments demonstrated equivalent performance for acetophenone **8** in combination with acrylate **9**; this is not to suggest that more demanding coupling partners would react so readily, however.



10 **13**

Other minor changes were also made. The methyl acrylate charge was reduced to 1.05 equiv in the starting material solution. The DMA volume was reduced back to 10 volumes relative to acetophenone **8**, and the batch size was increased from 47 to 50 mL, in both cases to increase productivity. A small line wash was added, initially of 3 mL but 1 mL was found to be adequate. This was added to wash traces of residual starting material solution out of the SM1 line and into the vessel, so that they did not contaminate the product on the way out. This translated into a simple three-step Voyager method of add, microwave and remove (full details in the Supporting Information), with a cycle time of 8.6 min. Proving trials on a three-

batch sequence then worked as planned, with the 1.0 mL line wash proving to be reliable and accurate, and conversions of 93% product **11**, <2% starting material **8**, and 6% diadduct **12**, in agreement with the small-scale studies.

However, when a 50-batch sequence was attempted, all the initial batches showed only a trace of conversion which gradually increased up to ~10%. Running the reaction mixture in a small-scale microwave reactor proved that the reaction material solution was good. Examination of the reaction vessel, which was new, showed slight blackening from Pd residues which were also present on the fibre optic probe. The fibre optic probe was thoroughly recleaned, and a clean reaction vessel was used which had previously been used for some base hydrolyses. The next batches then worked successfully. We speculate that the surface of this vessel may have been either cleaned or deactivated by the base in some manner, thus allowing successful reaction.

It is not known what caused this failure, whether some unseen contamination on the new reaction vessel, or residues left on the fibre optic probe that had not been cleaned completely. With only ~4 mg of catalyst entering the vessel with every batch, poisoning of the catalyst by a small amount of contaminant could have been significant. This might also explain why the reaction was very slowly improving over the course of the first 20 batches. In either case, the Voyager itself was clearly not at fault. Changing it over to Discover mode (small-scale tube) gave complete conversion as expected, and the reaction mixture was clearly being heated sufficiently in Voyager mode because the metallic Pd nanoparticles could be seen in the reaction product (Figure 5). Further studies are ongoing.

Once this problem had been avoided (if not solved), a further sequence of 20 batches was prepared which were grouped into batches of four for analysis and which showed conversions >90% as expected. Workup was as described before, but adding acid during the drown-out provided essentially quantitative yield of the product cinnamate **11** of 98.6% quality by HPLC, with 0.6% of **8** and 0.8% of diadduct **12**. Further details are included in Table 1.

The reactor vessel showed some level of Pd plating after another 25 batches of this Heck chemistry and so was removed and cleaned along with the probe. Fifty-batch sequences were now set in train, using the method described above with **13** as the base, to determine how many batches could be run before the vessel and probe needed to be cleaned. The results for the conversions of **8** to **11** and **12** are collected in Figure 6 and showed some surprising trends. For example, the first few batches of each sequence tended to perform particularly poorly, whether starting from a clean vessel (batches 1−5) or restarting after an overnight break (batches 51−55; the vessel was not cleaned in between). This trend also got worse, so that after the second overnight break at batch 100, it took more than 15 batches to get the conversion back to a barely acceptable ~80%. After the first 50 batches, the upper part of the vessel was plated with Pd, but the lower part and the probe were relatively clean; after the second group of 50, the vessel and especially the probe were heavily coated in Pd residues. Cleaning the probe, but not the vessel itself, did not help, as batches 126−130 show,

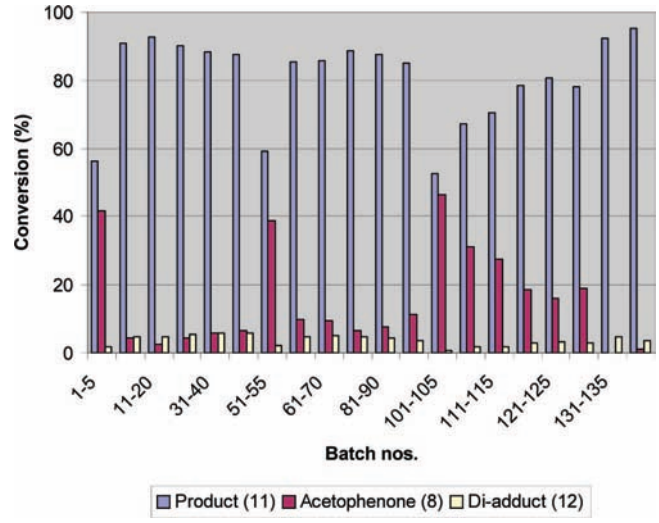


Figure 6. **Vessel performance showing conversions of 8 to 11 and 12 over multiple batches (note irregular batch scale).**

but recleaning the probe and installing a clean vessel in mid-sequence did restore very good performance (batches 131−140). The cycle time also improved to 7.5 min for these latter batches, compared to 8.6 min for the previous ones with incomplete conversions.

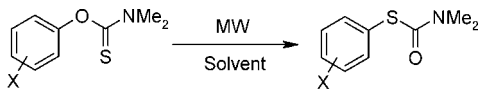
In summary, it appears that about 50 batches taking typically 7 h can be conducted before the performance starts to deteriorate significantly below the 90% conversion level (it should be noted that production of diadduct **12** actually represents part of the forward reaction conversion, albeit undesired over-reaction). It also appears that performance might be better if run continually, rather than leaving the reaction vessel empty overnight. However, in the worst case, the probe may need to be cleaned and the reaction vessel swapped for a clean one once a day, which is the work of a few minutes.

The workup for these batches was as before, and could conveniently be conducted on 20-batch scale (1050 mL). The reaction liquors could be decanted from settled Pd residues (cf. Figure 5) and any crystallised Hunig's base HBr salts, and an equal volume of warm water added with stirring, which gave a better form than previously of the product as a yellow precipitate. Adding acid was not necessary to remove residual Hunig's base as this washed out easily, so that typical isolated yields were in the range 81−87% with no base or residual solvent as determined by ^{1}H NMR. Quality by HPLC was excellent, showing 95−96% product **11** and 4−5% diadduct **12** with no residual starting material **8** in these cases.

Newman−Kwart Rearrangement. Like the Claisen rearrangement, the Newman−Kwart rearrangement (NKR)[19] presents another example of a single-phase unimolecular rearrangement which requires high temperatures and has been reviewed recently (Scheme 4).[20] Hence, high-boiling solvents are often used, or it can be performed as a melt. Since we have reported on this reaction previously[5b] and several aspects are similar to the Claisen rearrangement, only brief comments specific to the Voyager work will be made here.

(19) (a) Newman, M. S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980–3984. (b) Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 410–412.
(20) Lloyd-Jones, G. C.; Moseley, J. D.; Renny, J. S. *Synthesis* **2008**, 661–689.

Scheme 4



14a-c **14/15a**; X = 2-NO_2 **15a-c**
14/15b; X = 4-NO_2
14/15c; X = 3-Me-4-NO_2

Small-scale tube studies were conducted as for other reactions, generally at 4 volumes in DMA (or NMP). Reaction conditions were then readily transferred to the Voyager, using a simple three-step method similar to that used for the Claisen rearrangement (i.e., add, microwave and remove). Short automated sequences were run for all three *O*-thiocarbamates **14a-c**. Under standard conditions for **14a** (200 °C for 10 min in 4 volumes of DMA), a five-batch run of **14a** gave >99% conversion for each batch of **15a**, with a cycle time of 16 min per batch, and an unoptimised yield of 77%. A three-batch run of **14a** under similar but more concentrated conditions (2 volumes) gave complete conversion with a 93% isolated yield in similar cycle time. This would equate to 460 g per 8 h day (30 batches).

Compound **14b** required a slightly longer time and was run in a six-batch sequence to give again complete conversion with an unoptimised yield of 79% with a cycle time of 27 min. In this case, the discharge from the vessel was slowed to the maximum possible (~3 min) to mimic a direct aqueous drown-out of the product into 12 volumes of water. This naturally lengthened the cycle time by bringing part of the workup within the Voyager sequencing. However, it did establish that a slow pump-out could be achieved, if for example the unquenched reaction mixture was unstable, and required immediate neutralisation. Such a quench could also be achieved by neutralising inside the vessel, but this would give issues with removal of precipitated solids, and also residual water in the vessel for the next batch. Overall, there was no benefit to the form of the product isolated in this case, and given the additional time involved, it was not as efficient as the previous example. The isolated yields from the individual batches were in the range 76−84%, which was felt to be more a test of the reproducibility of the workup than of the Voyager.

Lastly, compound **14c** was heated at 4 volumes of DMA to 210 °C for 20 min in a five-batch cycle to give ~95% conversion for each batch with an overall isolated yield of 82%. At this concentration with this yield and a cycle time of 28 min, 160 g per day could be produced. Running the reactions below complete conversion proved beneficial in this case as the unreacted *O*-thiocarbamate **14c** was more readily removed on aqueous drown-out than some very minor impurities if the reaction was forced to completion. The aqueous drown-out was performed off-line from the Voyager runs so that both conversion and yield data could be obtained for each batch as a measure of reproducibility. Figure 7 shows excellent reproducibility for both aspects, which was also typical of the related NKR examples. Furthermore, in every case above, the quality of the products was excellent (>98%) with only aqueous drown-outs for purifications. Comparison data with other reactions performed here are included in Tables 1 and 2.

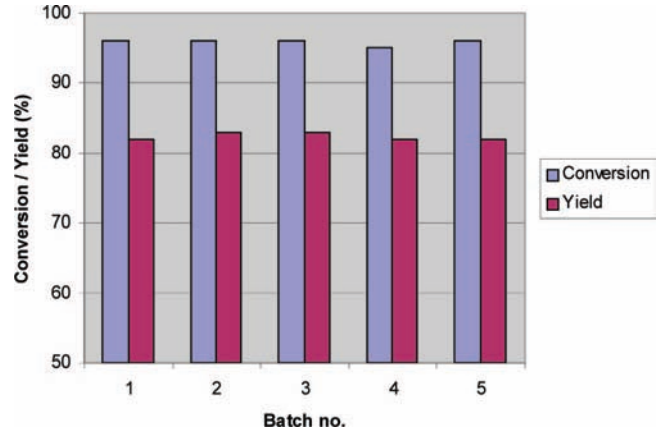


Figure 7. **Conversions and yields for individual batches of 15c.**

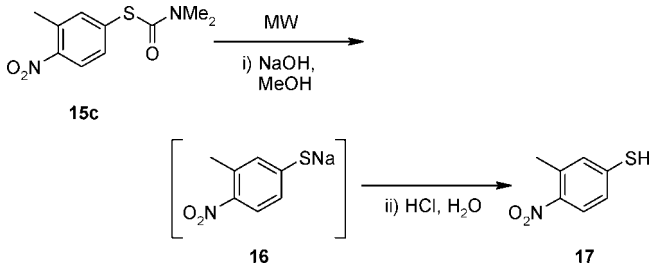
These were the first examples performed in the Voyager, and larger runs could not be performed at the time due to lack of materials. This is why individual batches were isolated and analysed, to give an idea of the batch-to-batch reproducibility. In later work, batches were combined into larger groups (5−20 batches) for the Claisen, Heck and hydrolysis reactions, when we knew the reproducibility was good. Note that slightly higher temperatures could be achieved for these reactions than for the Claisen rearrangement (210 °C compared to 195 °C); this was possible because both the solvent (DMA) and the substrates (**14a−c**) heated much better than **4** and DCB, and even 20 min at 210 °C did not require the magnetron to work at full power. The limit for the Voyager on a 30−50 mL sample appears to be about 220−230 °C in a favourable case. Finally, it should be noted that these compounds (**14a-c**) have also been converted to their *S*-thiocarbamate products **15a−c** in a Milestone FlowSYNTH,[21] which is a true continuous flow, large-scale microwave reactor.

Hydrolysis of *S*-Thiocarbamates. Another second-order reaction worth trying in the Voyager was the hydrolysis of the *S*-thiocarbamates produced earlier. Furthermore, hydrolysis of the *S*-thiocarbamate group, which behaves somewhat like an amide, would complete the sequence from phenol to thiophenol, the usual rationale for the NKR.[20] We were also hopeful this would provide another homogeneous reaction mixture. Unfortunately, the *S*-thiocarbamates generally had low solubility in methanol; the 2-nitro compound **15a** would not dissolve below 30 volumes, and whilst the 4-nitro compound **15b** did dissolve, it hydrolysed too quickly to be worth testing under microwave conditions. The 3-methyl-4-nitro compound **15c** however would dissolve in about 25−30 volumes of methanol, and we decided this would provide a good test of productivity for a dilute reaction mixture on the limit of acceptable volumes for process scale-up (Scheme 5).

Small-scale screening reactions quickly established that complete hydrolysis could be achieved after ~2 min at 110 °C with 1.5 equiv of 1.0 M aqueous NaOH. The stoichiometry was also tested, and at this temperature fast and complete conversions were still obtained down to about 1.1 equiv (Figure 8). However, some reaction tubes showed slight variability at lower stoichiometries, and so 1.3 equiv was chosen as a robust

(21) Moseley, J. D.; Lawton, S, J. *Chem. Today* **2007**, *25* (2), 16–19.

Scheme 5



level for reaction. Having performed this brief survey of reaction parameters, fine-tuning of conditions began on the Voyager. Since there was a high background rate of reaction at RT, the *S*-thiocarbamate and the NaOH were not premixed. Although additional (non-microwaved) reaction in the feed vessel is in principle desirable, premixing the reagents would result in considerable precipitation of products in the feed vessel, which would block the SM1 line. We also wanted to model a situation where premixing was undesirable due to potentially deleterious side reactions, so the reagents were segregated. This also provided the opportunity to use the SM2 line for a second reagent, and the requirement to use the solvent line for a wash (to avoid precipitate in the lines).

Furthermore, the reagent charge of NaOH was going to be relatively small compared to the starting material solution, which would test the pump calibration and reproducibility more thoroughly than previously, since small errors in a small reagent charge could significantly affect the stoichiometry in each batch (cf. Figure 8). A concentration of 2.0 M had been chosen as a compromise between not adding too much water to the reaction mixture compared to the methanol volume (in case of precipitating either the starting material or the product), but not too small such that errors in the charging became too critical for the stoichiometry.

The Voyager sequence was therefore as follows: charge 47 mL of starting reaction mixture (**15c**) through SM1; charge 4.6 mL of 2.0 M NaOH (1.3 equiv) through SM2; wash the lines twice with 3 mL of fresh methanol through the solvent line (i.e., 6 mL total); heat to 110 °C and hold for 1.5 min; cool to 65 °C and remove the product from the vessel (full details are given in the Supporting Information). The overall cycle time was relatively long at 9.45 min, and one reason for this was

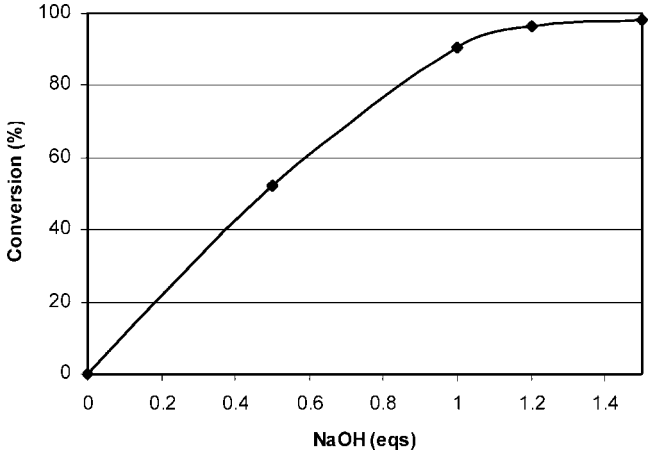


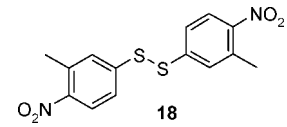
Figure 8. **Affect of NaOH stoichiometry on reaction conversion for hydrolysis of 15c to 17.**

the need to cool the vessel contents to 65 °C; above this temperature, the methanol was superheated, and hot vapours condensed in the air line as a bright orange liquid as soon as the valve opened. Although this appeared to have no practical drawback (most of the liquid was blown into the vessel when it was emptied), it seemed a less than ideal way to run the process. If a higher temperature could be accepted at this point or a higher-boiling alcohol was used, then less cooling would be required before emptying the vessel.

A solution of 101 g of **15c** in 3050 mL (30 volumes) of methanol was prepared and filtered to remove residual fines and charged through the SM1 line, whilst the NaOH was charged from a measuring cylinder through the SM2 line. Fresh methanol was fed from a vessel through the solvent line. The three-batch proving trial worked exactly as planned, so a single 64-batch sequence using a total of 96 g of **15c** in 2880 mL of methanol was processed over one 10.1 h period. Batches were combined into groups of three initially and then 10, and HPLC showed conversions for all were >99%. Output volumes were exactly 58 mL, once again demonstrating very good control and reproducibility by the pump for repeated multiple charges.

Total reaction time for 64 batches was 10.1 h, or 9.45 min per 1.5 g batch. Further details are given in Table 1. Overall, productivity was low because, although the reaction time and temperature were low and the cycle time was fast, the reaction was very dilute. However, it does demonstrate that worthwhile laboratory-scale quantities of product (50−100 g) can be obtained per day using this instrument even in an unfavourable case. Kilo-scale manufacture would be possible with two such instruments operating for a week. Productivity would be further enhanced if improvements to the cycle time or concentration could be made. Further data and comparisons are given in Table 2.

The workup was developed first on preliminary batches, then on groups of 10, and finally on the remaining bulk reaction mixture, 44 batches at one time. The reaction liquors were reduced to about one-third volume, water was added, and then concentrated HCl was added (2.5 equiv) to neutralise the remaining base, which resulted in precipitation of the product **17**. This was isolated by filtration and washed with more water to remove inorganic salts. The overall quality of **17** was 93% by HPLC (>99% by ^{1}H NMR), with 6% of the disulfide impurity **18** (which may be over-reported by HPLC), unchanged from the level in the crude reaction mixture. The final isolated yield was 62 g (91%).



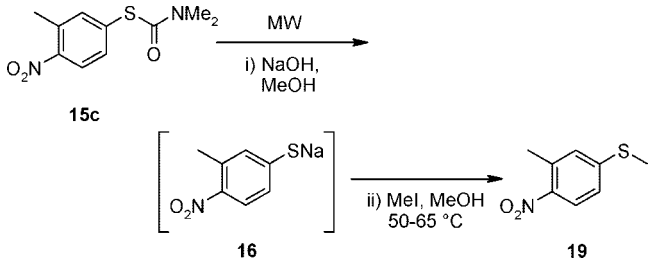
Combined Hydrolysis and Alkylation Reaction. Having performed the hydrolysis reaction successfully, we now determined to combine this with an alkylation reaction, taking advantage of the intermediate thiophenolate **16** generated in situ (Scheme 6). Although in principle a trivial reaction, this provided an opportunity to use all three input lines for the starting material and two reagents. This would require foregoing the solvent wash since there was no spare solvent line. It also

Table 2. **Overall comparison of productivities**

reaction	total batches	cycle time (min)	total run time (h)	relative volume[a]	actual mass processed[b] (g)	calculated mass processed[b] in 8 h (g)	calculated mass processed[b] in 24 h (g)
Claisen (one step)	48	21	16.8	0.5	1006	480	1440
Heck #1 (**10**)	50	8.6	7.2	12	163	184	552
Heck #2 (**13**)	>300	8.6	~7[c]	10	>1000	222	666
hydrolysis	64	9.5	10.0	30	96	76	228
hydrolysis + alkylation	30	11	5.5	30	45	66	197
NKR #1 (**14a**)	5	16	n/a	2	80	480	1440
NKR #2 (**14b**)	6	27	n/a	5	50	144	432
NKR #3 (**14c**)	5	28	n/a	4	50	168	504

[a] Relative to starting material mass. [b] Based on input starting material. [c] Per 50 batches.

Scheme 6



involved two small reagent charges (NaOH, then methyl iodide) which would further test the pump accuracy on a combined reaction sequence. To reduce the criticality of the charge of methyl iodide, which is very dense ($d = 2.28$), it was diluted with methanol, although perhaps this was overcautious, since the small line wash of 1.0 mL in Heck reaction 2 had worked very reliably.

Small-scale scouting trials in the small microwave reactors with fresh reaction liquors of **16** quickly showed that the alkylation reaction would go to completion at modest temperatures with only a modest excess of methyl iodide (1.2 equiv). From this screen, 1.5 equiv at 40 °C gave almost instantaneous reaction and were chosen as the reaction conditions. Running the reaction "all-in" was not possible since about 10% of unreacted starting material **15c** was left, even though all **16** had been converted to **19**; therefore the two-step reaction was required as planned. Although microwave heating was not required for the second step, the reaction mixture still needed to be cooled to below 65 °C to stop intermediate product getting into the air line when the vessel was opened. There was no point heating again, so the methyl iodide solution (3.2 M in methanol) was added through the solvent line, and cooling was continued for a fixed period of 30 s. This was achieved by using a microwave step with the wattage set to 0 W, and the heating-with-cooling function used, simply to cool the vessel further (bp of methyl iodide is 41−43 °C). Once this step was complete, the reaction mixture was already well below the bp of methanol (65 °C) and so could be discharged from the vessel.

Slight changes had been made to the previous hydrolysis method, reducing the initial input volume of **15c** to 45 mL for example to account for the small (3.3 mL) methyl iodide solution charge. The solvent washes had to be removed, and only the air blows could be used to ensure the lines were clear. There was also no interbatch clean-out, but this was unlikely to present a problem; the "all-in" reaction was nearly successful, so residues from the previous batch were unlikely to be critical. With these changes, the overall cycle time was now 11.0 min.

The three-batch proving trial worked exactly as planned with no residual **15c** or **16** left. From this a 30-batch sequence was then prepared. Unfortunately, the only remaining large batch of **15c** left in hand was highly coloured, and although it looked identical to other materials by HPLC and ^{1}H NMR, ~10% of its mass did not dissolve in methanol when the reaction solution was filtered. This mass has been accounted for in subsequent calculations presented here, but the immediate consequence was that the stoichiometric charges of NaOH and methyl iodide were slightly higher than those planned. This did not affect the chemistry adversely and, if anything, improved it. In all other respects, the reaction proceeded as expected in the Voyager method, which now involved three separate charges and no solvent line washes. The chemistry was unaffected by the lack of solvent washes, which improved the cycle time for this more complex sequence. Conversions were 99% for all batch groups assayed, and the total mass of **15c** processed was 43 g in 5.5 h. The reaction product was initially isolated by extraction to give analytically pure product, but an aqueous drown-out was developed which was simpler and provided good quality product without chromatography. Finally, is should be noted that we had been concerned that running multiple batches of hot alkaline solutions might damage the integrity of the glass vessel. However, there was no visible sign of deterioration, and its mass was unchanged after both long hydrolysis sequences.

Summary of Continuous Flow. In regard to the continuous flow aspects of this study, the Voyager SF microwave reactor has much in common with conventionally heated continuous flow instruments and the learning was similar. The first priority is to have a homogeneous reaction mixture. CF studies can use a lot of material/volume to develop the process, but the development time required should be relatively short (0.5−3 days in our experience) and easily developed from tube-scale microwave reaction conditions in a largely scale-up free manner. Once developed, minor modifications are easily incorporated, and large quantities of product are manufactured with relative ease. The first batch (and possibly the second and third) through the system will be different from the standard later batches. This will be the same as starting up a conventional CF instrument, and heating blank reaction solvent in the instrument will warm it up before starting the sequence properly, which will save some material or avoid a possible out-of-specification batch at the start. One final significant point of learning was

the need to run long sequences of many batches to really test the reliability of the instrument, as noted for the Heck reaction; only by running multiple batches over long periods can the true reliability and out-put of the technology be fairly evaluated.

Summary of the Voyager. In regard to the Voyager, the overall reliability and reproducibility, batch after batch in a long sequence, was excellent. Once the pump calibration had been set, the volumes pumped were reliable down to small values (1 mL), even when changing between multiple solvents of varying viscosities. It was worth the effort invested to get the pump calibration and volumes correct at the start of development for each reaction. The heating profile was also very reproducible between batches, except when the chemistry affected the process as in the Pd-plating seen in the Heck reaction. Running short trial sequences was essential before committing larger quantities of material; this was useful to confirm both the chemistry and sequencing operations were performing as planned, and also to produce initial supplies of material for downstream studies. It was not worth overdeveloping the chemistry beforehand, however, as subtle changes from small-scale microwave tube reactions were inevitable; fine-tuning of conditions should be completed on the Voyager. Overall this development time took typically 0.5 to 3 days per reaction, but the ease of subsequent manufacture was well worth the effort invested.

Two-step and more complex procedures were successfully accommodated on the Voyager, even to using the third inlet line as a reagent line. As with other CF instruments, line blockages were a potential issue, either on entry or exit. However, line washes and vessel rinses were useful to avoid or ameliorate this problem, and the Voyager functionality made it easy to incorporate these. In fact it was best to use the functionality of the instrument as it was generally more efficient than designing other protocols. One interesting observation that we made was the need to consider the Voyager like a mini-pilot plant when sequencing reactions; and once a long sequence was running, it behaved somewhat like a pilot plant in manufacturing product at a greater rate than could comfortably be accommodated in a research laboratory setting! Furthermore, for certain concentrated high-temperature reactions in particular, the combination of CF with microwave heating means that it can out-perform most standard pilot-plant reactions in reaching >200 °C to produce kg-scale quantities of product per day (Table 2).

Conclusions

In summary, we have presented results from scaling-out six different reactions used in the pharmaceutical industry which can benefit from microwave heating. For these typical pharmaceutical reactions, the Voyager stop-flow microwave can produce daily through-puts of between 50 and 250 g. For more concentrated reactions, such as the Claisen and NKR reactions discussed above, up to 0.5 kg is possible in a normal 8 h day, or more if run continuously. Others have also demonstrated kg-scale capability on a daily basis for concentrated reactions.[11a,22] The scale-out option of using multiple Voyagers, and/or 24-h operation would bring even the dilute hydrolysis reaction discussed above within the kg-scale range in less than one week. Our experience strongly suggests that the Voyager is fully capable of performing reliably over continuous 24-h periods, and therefore of kg-scale production for homogeneous reactions.

Experimental Section

HPLC Methods. Reaction mixtures and products were analysed by reverse phase HPLC on an Agilent 1100 series instrument according to the following conditions: **method 1**; column, Waters Symmetry C18 3.5 μm, 50 mm × 3.0 mm i.d.; eluent A, purified water with 0.1% v/v formic acid; eluent B, acetonitrile with 0.1% v/v formic acid; flow rate 1.25 mL/min.; wavelength 230 nm; temperature 45 °C; injection volume 2 μL; at $t = 0$ min, 5% eluent B; at $t = 6$ min, 95% eluent B; at $t = 7$ min, 95% eluent B; post time 1.5 min; **method 2**; column, HiChrom ACE Phenyl 3.0 μm, 50 mm × 3.0 mm i.d.; eluent A, purified water with 0.03% v/v formic acid; eluent B, methanol with 0.03% v/v formic acid; flow rate 1.25 mL/min.; wavelength 220 nm; temperature 45 °C; injection volume 2 μL; at $t = 0$ min, 5% eluent B; at $t = 6$ min, 95% eluent B; at $t =$ 7.5 min, 95% eluent B; post time 3 min; **method 3**; column, Genesis C18 3 μm, 100 mm × 3.0 mm i.d.; eluent A, 95% purified water, 5% acetonitrile, 0.1% v/v formic acid; eluent B, 95% acetonitrile, 5% purified water, 0.1% v/v formic acid; flow rate 0.75 mL/min.; wavelength 254 nm; temperature 35 °C; injection volume 5 μL; at $t = 0$ min, 40% eluent B; at $t =$ 5 min, 70% eluent B; at $t = 7$ min, 70% eluent B; post time 3 min. Typical retention times (RT) are noted in each case.

General Procedures. Melting points were determined using a Griffin melting point apparatus (aluminium heating block) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 400 spectrometer at 400 and 100.6 MHz respectively with chemical shifts given in ppm relative to TMS at $\delta = 0$. Electrospray (ES+) mass spectra were performed on Micromass ZQ or a Micromass Platform LC. Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of self-indicating Merck Kieselgel 60 F_{254} and visualised by UV light at 254 nm. Preparative scale silica gel flash chromatography (for purification of analytical samples only) was carried out by standard procedures using Merck Kieselgel 60 (230−400 mesh). Where not stated otherwise, assume standard practices have been applied.

Typical Small-Scale Microwave Procedures. Small-scale microwave reactions were performed in thick-walled glass sealed tubes in Biotage *Initiator* or CEM *Discover* focused 300 W microwave reactors with IR temperature monitoring and noninvasive pressure transducer. Procedures were typically performed on 1−2 mmol scale exactly as described for the large-scale microwave procedures. However, analytically pure samples, if required, were more often purified by flash silica chromatography than the aqueous drown-out procedures used on the larger scales. The heating time to reach the set temperature was typically 30−90 s, depending on the scale, the maximum wattage supplied (100−300 W) and the temperature required (100−250 °C). The heating time is not included in the quoted hold time for any given procedure.

(22) Leadbeater, N. E.; Smith, R. J.; Barnard, T. M. *Org. Biomol. Chem.* **2007**, *5*, 822–825.

Preparation of Reaction Mixture for Claisen Rearrangement of 4 to 5. 1-(2-Methyl-2-propenyl)oxynaphthalene (**4**) (1006 g, 5.07 mol) was diluted with DCB (500 mL) to give a dark-coloured solution (1500 mL) which was used in the CEM Voyager microwave reactor as described in the Discussion section, and according to the detailed protocol which can be found in the Supporting Information. An analytically pure sample could be obtained by flash silica gel chromatography in 9:1 isohexane/ethyl acetate, to yield 2-(2-methyl-2-propenyl)-1-naphthol (**5**) as a colourless oil; HPLC (method 1, RT 4.89 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H, m), 7.76 (1H, m), 7.36−7.48 (3H, m), 7.18 (1H, m), 5.76 (1H, s), 4.98 (2H, m), 3.53 (2H, s), 1.75 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.1, 144.7, 133.8, 128.9, 127.4, 125.7, 125.2, 124.9, 124.5, 120.1, 117.6, 112.7, 40.6, 22.0.

Preparation of Reaction Mixture for Heck Reaction of 8 and 9 Using Dicyclohexylmethylamine (10). Methyl acrylate (79 mL, 880 mmol, 1.10 equiv) and dicyclohexylmethylamine (**10**) (257 mL, 1200 mmol, 1.50 equiv) were added to a solution of 4-bromoacetophenone (159 g, 800 mmol) dissolved in DMA (1700 mL) and thoroughly mixed. In a separate flask, tetrabutylammonium bromide (0.89 g, 3.2 mmol, 0.4 mol %) was added to a solution of $Pd(OAc)_2$ (180 mg, 0.8 mmol, 0.1 mol %) dissolved in DMA (210 mL) to give a dark orange solution. This solution was added to the first solution to give the reaction mixture as an overall light orange solution. (Note: if any particulates were visible, the combined solution was filtered through a grade 3 sinter at this point.) The reaction mixture could be used immediately, or stored in a sealed vessel for some time if required (at least one week if volatile components could not evaporate). The reaction mixture was used in the CEM Voyager microwave reactor as described in the Discussion section, and according to the detailed protocol which can be found in the Supporting Information. A typical workup procedure follows.

Preparation of Reaction Mixture for Heck Reaction of 8 and 9 using Hunig's Base (13). Methyl acrylate (95 mL, 1050 mmol, 1.05 equiv) and di-*iso*-propylethylamine (**13**) (262 mL, 1500 mmol, 1.50 equiv) were added to a solution of 4-bromoacetophenone (199 g, 1000 mmol) dissolved in DMA (1700 mL) and thoroughly mixed. In a separate flask, tetrabutylammonium bromide (1.11 g, 4.0 mmol, 0.4 mol %) was added to a solution of $Pd(OAc)_2$ (225 mg, 1.0 mmol, 0.1 mol %) dissolved in DMA (290 mL) to give a dark orange solution. This solution was added to the first solution to give the reaction mixture as an overall light orange solution. (Note: if any particulates were visible, the combined solution was filtered through a grade 3 sinter at this point.) The reaction mixture could be used immediately, or stored in a sealed vessel for some time if required (at least one week if volatile components could not evaporate). The reaction mixture was used in the CEM Voyager microwave reactor as described in the Discussion section, and according to the detailed protocol which can be found in the Supporting Information. A typical workup procedure follows.

Typical Workup Procedure of the Heck Reaction using Hunig's Base. The combined dark orange reaction liquors from 20 successful batches (1050 mL, 424 mmol) were poured into a solution of concentrated HCl (11.6M, 18.2 mL, 21.2 g, 212 mmol, 0.50 equiv) and water (1050 mL) over 1 h with good agitation. Considerable heat of mixing is generated and a dense white or pale yellow precipitate forms. Once the mixture has cooled back to RT (with cooling water if required), the precipitate is isolated by filtration and the product cake slurry washed twice with water (250 mL). The solid is dried in a vacuum oven at 40 °C with an air bleed to yield methyl 3-(4-acetylphenyl)acrylate (**11**) as an off-white solid (70−75 g, 81−87%). HPLC (method 1, RT 3.63, 97−99%); mp 98−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, dt, J = 8.8, 1.8 Hz), 7.71 (1H, d, J = 16.0 Hz), 7.61 (2H, dd, 6.8, 1.6 Hz), 6.53 (1H, d, J = 16.0 Hz), 3.83 (3H, s), 2.62 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 197.2, 166.9, 143.2, 138.66, 138.0, 128.8, 128.1, 120.3, 51.8, 26.6.

NKR Reaction of 14b to 15b with Aqueous Drown-Out. Six batches of a warm solution of *O*-thiocarbamate **14b** in DMA held at 60 °C were sequentially charged by automation through a CEM Voyager equipped with a fibre optic probe and magnetic stirrer bar (each batch contained 10.0 g of **14b** (41.6 mmol) in 40 mL DMA (4 vols)). Each batch was heated with magnetic stirring to 210 °C over 3.5 min with 300 W available power, held at 210 °C for 20 min, then cooled by compressed air to 70 °C over 5 min. The individual batches were collected separately and drowned out with varying quantities of water from which it was determined that 12 volumes of water was most efficient to precipitate the product. The products were isolated by filtration, washed with more water and dried in a vacuum oven at 50 °C to give 4-nitrophenyl-*S*-thiocarbamate (**15b**) as a pale yellow or buff solid (combined yield 41.2 g, 82%). R_f 0.33 (2:1 isohexane/ethyl acetate); HPLC (RT 3.01, 99.7%); mp 118−120 °C (lit.[19a] 122−124 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (2H, d, J = 8.0 Hz), 7.68 (2H, d, J = 8.0 Hz), 3.11 (3H, bs), 3.06 (3H, bs); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.58, 147.88, 137.65, 135.57, 123.54, 36.89 (2C); MS (ES+) 227 (M + 1, 5%), 142 (60%), 101 (100%).

NKR Reaction of 14c to 15c (Aqueous Drown-Out Separate). Five batches of a warm solution of *O*-thiocarbamate **14c** in DMA held at 60 °C were sequentially charged by automation through a CEM Voyager equipped with a fibre optic probe and magnetic stirrer bar (each batch contained 10.0 g of **15c** (41.6 mmol) in 40 mL DMA (4 vols)). Each batch was heated with magnetic stirring to 210 °C over 3.5 min with 300 W available power, held at 210 °C for 20 min, then cooled by compressed air to 70 °C over 5 min. The individual batches were collected separately and drowned-out with varying quantities of water from which it was determined that 12 volumes of water was most efficient to precipitate the product. The products were isolated by filtration, washed with more water and dried in a vacuum oven at 50 °C to give 3-methyl-4-nitrophenyl-S-thiocarbamate (**15c**) as a pale orange solid (combined yield 41.2 g, 82%). HPLC (RT 3.8, 96%); mp 74−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, d, J = 8.5 Hz), 7.48 (2H, m), 3.10 (3H, bs), 3.05 (3H, bs), 2.60 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.96, 149.03, 139.02, 135.30, 133.90, 133.31, 124.81, 36.97, 20.38; MS (ZQ) (ES+) 241 (M + 1, 100%).

Preparation of the Reaction Mixture for Hydrolysis of 15c to 17. 3-Methyl-4-nitrophenyl-*S*-thiocarbamate (**15c**) (100.6 g, 418 mmol) was dissolved in methanol (3050 mL) and the solution filtered through a grade 3 sinter to remove any fines. This solution was added to the CEM Voyager through the SM1 line, sodium hydroxide (2.0M) through the SM2 line, and fresh methanol through the solvent line. These solutions were charged to the CEM Voyager microwave reactor as described in the Discussion section, and according to the detailed protocol which can be found in the Supporting Information. A typical workup procedure follows.

Typical Workup Procedure for the Hydrolysis Reaction of 15c to 17. The combined dark red reaction liquors of 10 successful batches (580 mL, 30 vols) were reduced to 10 vols under reduced pressure. Water (200 mL, 13.5 vols) was added to the solution with stirring followed by hydrochloric acid (11.6M, 13.0 mL, 156 mmol) which precipitated a pale yellow solid. The precipitate was isolated by filtration and the product cake slurry washed with water (10 mL). The solid was dried in a vacuum oven at RT with an air bleed to yield the desired product, 3-methyl-4-nitrothiophenol (**17**) (10.7 g, 101%). This procedure was repeated with another 10 successful batches (10.8 g) and then repeated on a larger scale using the remaining 44 batches to yield a pale orange solid (40.1 g) giving a total overall yield for 64 batches of 61.7 g (91%). HPLC (method 2, RT 3.81, 92.7% with 6.1% disulfide **18**); mp 59−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, d, J = 10.0 Hz), 7.18 (1H, s), 7.16 (1H, m), 3.66 (1H, s), 2.58 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.7, 135.0, 131.6, 129.6, 126.3, 125.7, 20.8.

Preparation of the Reaction Mixture for the Combined Hydrolysis/Alkylation Reaction of 15c to 19. 3-Methyl-4-nitrophenyl-*S*-thiocarbamate (**15c**) (50.1 g, 208 mmol) was dissolved in methanol (1500 mL) and the solution filtered through a grade 3 sinter to remove undissolved dark material (3.3 g). This solution was added to the CEM Voyager through the SM1 line, sodium hydroxide (2.0 M) through the SM2 line, and a methyl iodide/methanol solution (containing 20.0 mL methyl iodide (321 mmol) made up to 100 mL with methanol) through the solvent line. These solutions were charged to the CEM Voyager microwave reactor as described in the Discussion section, and according to the detailed protocol which can be found in the Supporting Information. A typical workup procedure follows.

Typical Workup Procedure for the Combined Hydrolysis/Alkylation Reaction of 15c to 19. The combined reaction liquors of two successful batches (104 mL, 30 vols) were reduced to 10 vols under reduced pressure. Water (150 mL, 50 vols) was added to the solution with stirring to form a brown precipitate. The precipitate was isolated by filtration and the product cake slurry washed with water (3 mL, 1 vol). The solid was dried on the filter to yield *S*-methyl-3-methyl-4-nitrophenylsulfide (**19**) as a brown solid (1.92 g, 84%). This procedure was repeated in five-batch portions for the 30 batches generated in the Voyager trial. HPLC (method 3, RT 5.08, 98.4%); mp 40−42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, d, J = 8.4 Hz), 7.12 (2H, m), 2.62 (3H, s), 2.53 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 146.7, 145.5, 134.7, 128.5, 125.4, 122.9, 21.2, 14.8.

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Supporting Information Available

Detailed protocol. This material is available free of charge via the Internet at http://pubs.acs.org.

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