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Exploring the Scope for Scale-Up of Organic Chemistry Using a Large Batch Microwave Reactor

Jason R. Schmink, Chad M. Kormos, William G. Devine, and Nicholas E. Leadbeater*

Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, Connecticut 06269-3060, U.S.A.

Abstract:

A new batch microwave reactor has been evaluated in the context of palladium-mediated transformations, condensation reactions, nucleophilic aromatic substitution reactions, and alkylations. Importantly, a linear scaling approach was taken, no changes being made to the protocol when moving from the small, developmental scale to larger scales. In some cases reactions were scaled over 18,000-fold when moving from small (0.1–1 mmol) to large (1–18 mol) runs.

Introduction

Microwave heating is a versatile and widely used tool for preparative chemistry and continually demonstrates its worth within the laboratory setting.¹ Small-scale monomode microwave units facilitate initial drug discovery and development processes. They are suitable for performing reactions on small scales, and reactions times can be dramatically shortened due to the ready access to elevated temperatures in sealed vessels. Of great interest to the process chemist is the claim that cleaner reaction profiles can be obtained when performing chemistry using microwave heating, due to the mitigation of thermal wall effects.² Since microwave irradiation heats the reaction mixture directly and standard laboratory glassware is essentially transparent when compared with the contents, the vessel walls are the coolest part of the system. Furthermore, the rapid energy transfer that is possible when using microwave irradiation means that a reaction can be heated to the target temperature in a shorter time than with conventional heating.

While the use of microwave heating for performing reactions on the millimolar scale in sealed vessels is straightforward, our group and others have been actively addressing the issues associated with scale-up.^{3,4} Possible approaches include continu-

ous-flow reactors,⁵ small-scale batch stop-flow protocols,^{6,7} or large-scale, single-batch reactors.⁸ Recent work in our laboratory and by others⁹ has been focused at exploring all three possibilities. There are a number of advantages to continuous-flow chemistry. It limits the amount of material in the microwave cavity at any given time, and as a result, the possibility of catastrophic loss of an entire reaction batch is greatly reduced. The overall scale becomes essentially limitless, and reactions can be “scaled-out” not “scaled-up.” However, continuous-flow processing has some drawbacks. Many reaction mixtures are heterogeneous, biphasic, or require long reaction times (e.g., 30–60 min) at elevated temperatures. Continuous-flow technology is generally not amenable in these cases, and extensive reoptimization must be undertaken in order to develop appropriate homogeneous reaction conditions and suitable residence times. This in itself may require additional solvent and/or catalyst screening. A stop-flow approach to scale-up has similar limitations: homogeneous conditions must be maintained throughout the cycle to avoid clogging issues. In addition, the majority of small-scale reactions are optimized under *batch* conditions. Thus, the development of a batch microwave reactor that could perform reactions on the kilogram scale would be highly desirable. Ideally, the scaling of a protocol from the milligram scale to the kilogram scale should be straightforward with little need for reoptimization. As recently addressed by Strauss,¹⁰ and due to the overwhelming body of evidence that

* Author for correspondence. E-mail: nicholas.leadbeater@uconn.edu.

- (1) A number of books on microwave-promoted synthesis have been published recently. For examples see: (a) Loupy, A., Ed. *Microwaves in Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2006. (b) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005. (c) Lidström, P., Tierney, J. P., Eds. *Microwave-Assisted Organic Synthesis*; Blackwell: Oxford, 2005.
- (2) Moseley, J. D.; Lenden, P.; Lockwood, M.; Ruda, K.; Sherlock, J.-P.; Thomson, A. D.; Gilday, J. P. *Org. Process Res. Dev.* **2008**, *12*, 30.
- (3) For a discussion of scale-up of microwave-assisted organic synthesis see: Roberts, B. A.; Strauss, C. R.; Lindström, P.; Tierney, J. P., Eds. *Microwave-Assisted Organic Synthesis*; Blackwell: Oxford, 2005.
- (4) For recent reports from our laboratories see: (a) Bowman, M. D.; Holcomb, J. L.; Kormos, C. M.; Leadbeater, N. E.; Williams, V. A. *Org. Process Res. Dev.* **2008**, *12*, 41. (b) Bowman, M. D.; Schmink, J. R.; McGowan, C. M.; Kormos, C. M.; Leadbeater, N. E. *Org. Process Res. Dev.* **2008**, *12*, 1078. (c) Iannelli, M.; Bergamelli, F.; Kormos, C. M.; Paravisi, S.; Leadbeater, N. E. *Org. Process Res. Dev.* **2009**, *13*, 634.

- (5) For examples of continuous-flow processing see: (a) Moseley, J. D.; Lawton, S. J. *Chem. Today* **2007**, *25*, 16. (b) Khadlikar, B. M.; Madyar, V. R. *Org. Process Res. Dev.* **2001**, *5*, 452. (c) Kazba, K.; Chapados, B. R.; Gestwicki, J. E.; McGrath, J. L. *J. Org. Chem.* **2000**, *65*, 1210. (d) Esveld, E.; Chemat, F. van Haveren. *J. Chem. Eng. Technol.* **2000**, *23*, 429. (e) Marquié, J.; Salmoria, G.; Poux, M.; Laporterie, A.; Dubac, J.; Roques, N. *Ind. Eng. Chem. Res.* **2001**, *40*, 4485.
- (6) Arvela, R. K.; Leadbeater, N. E.; Collins, M. J. *Tetrahedron* **2005**, *61*, 9349.
- (7) (a) Moseley, J. D.; Woodman, E. K. *Org. Process Res. Dev.* **2008**, *12*, 967. (b) Pitts, M. R.; McCormack, P.; Whittall, J. *Tetrahedron* **2006**, *62*, 4705. (c) Loones, K. T. J.; Maes, B. U. W.; Rombouts, G.; Hostyn, S.; Diels, G. *Tetrahedron* **2005**, *61*, 10338.
- (8) For examples of batch processing using one vessel see: (a) Raner, K. D.; Strauss, C. R.; Trainor, R. W.; Thorn, J. S. *J. Org. Chem.* **1995**, *60*, 2456. (b) Shackelford, S. A.; Anderson, M. B.; Christie, L. C.; Goetzen, T.; Guzman, M. C.; Hananel, M. A.; Kornreich, W. D.; Li, H.; Pathak, V. P.; Rabinovich, A. K.; Rajapakse, R. J.; Truesdale, L. K.; Tsank, S. M.; Vazir, H. N. *J. Org. Chem.* **2003**, *68*, 267. (c) Khadlikar, B. M.; Rebeiro, G. L. *Org. Process Res. Dev.* **2002**, *6*, 826. (d) Fraga-Dubreuil, J.; Famelart, M. H.; Bazureau, P. *Org. Process Res. Dev.* **2002**, *6*, 374. (e) Cleophax, J.; Liagre, M.; Loupy, A.; Petit, A. *Org. Process Res. Dev.* **2000**, *4*, 498. (f) Perio, B.; Dozias, M.-J.; Hamelin, J. *Org. Process Res. Dev.* **1998**, *2*, 428.
- (9) For a recent and comprehensive comparison of apparatus for scale-up, see ref 2.
- (10) Strauss, C. R. *Org. Process Res. Dev.* **2009**, *13*, 10.1021/op900194z.

now exists refuting any nonthermal microwave effects,¹¹ efficient stirring of reactions should negate any microwave penetration issues. While a batch microwave reactor may not be the solution when tons or hundreds of tons of a desired compound must be synthesized yearly, a batch microwave reactor capable of processing material at the kilogram scale would help bridge the gap between a small-scale protocol and larger kilo- or pilot-plant scale, adding a much needed tool to the process chemist's toolbox. However, as Moseley and co-workers recently pointed out, "there is at present no single commercially available scale-up reactor capable of meeting the needs of the pharmaceutical industry for the wide range of reactions typically required on >1 kg scale."¹²

In the development of new chemical entities (NCEs), the transition from the medicinal chemistry route to a scale where enough material can be prepared to carry out initial *in vivo* toxicology studies is often the most difficult.¹² Besides the fact that the initial route only had to be efficient enough to obtain a few milligrams of the NCE, medicinal chemists often use chemistry or methodologies, including microwave-mediated transformations, that are currently difficult to scale to the size necessary to obtain 1–5 kg of the NCE. Due to the prevalence of scientific microwave apparatus in medicinal chemistry laboratories, process chemists often are delivered protocols that used microwave heating in one or more steps. Thus, those charged with the duty of the initial scale-up often are faced with the difficult choice between running multiple reactions for the microwave-mediated steps to achieve desired throughput or having to develop modified conditions to avoid microwave heating. This second option may mean lowering temperatures, lengthening reaction times and employing different solvents and/or higher catalyst loadings. In the worst-case scenario, process chemists have to redesign the entire route to the target compound in order to avoid the microwave-mediated steps within a reaction sequence. As the likelihood of one of any given 20–50 promising NCEs becoming the active pharmaceutical ingredient in a new drug is low, companies have a vested interest in pushing any reoptimization of a route to the target molecule to the latest possible stage, ideally only after screening and toxicology tests have thinned the field to a few promising candidates.¹²

A batch microwave reactor capable of running reactions from 2000–12000 mL in a single batch has very recently become available to our research group for experimental use though is not yet commercially available. Our research group has screened a number of pharmaceutically relevant synthetic transformations using the unit, and we present the results here. We searched the medicinal chemistry literature and selected microwave-mediated protocols. Then, to the fullest extent possible, we scaled them up in a linear fashion, often over 10,000 times that at which they were first developed. The purpose of our study was three-fold. First, we wanted to probe the operating parameters of the microwave apparatus with respect to heating



Figure 1. (a) CAD rendering of the prototype reactor used in the current work. (b) CAD rendering of the unit that will soon be commercially available.



Figure 2. Interchangeable reaction flasks of (a) 5-L, (b) 9-L, and (c) 13-L capacity with working volumes of 2–4 L, 4–8 L, and 7–12 L, respectively.

profiles, maximum temperature and pressure, magnetron efficiency, and overall effectiveness. Second, we aimed to determine which reactions were directly scalable and then scrutinize those where difficulty was met. Finally, we wanted to evaluate the ease of performing reactions in a batch microwave reactor at the kilogram scale.

Results and Discussion

Equipment. The microwave unit, designed by AccelBeam Synthesis, allows for reactions to be performed on scales from 2–12 L. Engineering renderings of the prototype unit used in our trials, together with those of the unit to be commercially available soon, are shown in Figure 1. Currently, there are three interchangeable reaction vessels; 5-L, 9-L, and 13-L glass vessels with working volumes of 2–4 L, 4–8 L, and 7–12 L, respectively (Figure 2). A universal cover acts as the interface for peripherals including a stirring paddle that operates at speeds from 0–125 rpm, a fiber-optic temperature probe, the reaction ejection tube, and a port for interfacing spectroscopic tools. In addition, a small port on the cover allows for last-minute addition of catalyst, reagents, or solvent (Figure 3). The desired reaction vessel, equipped with the cover, is placed in a mechanically sealed stainless steel reaction chamber capable of operating at pressures up to 350 psi (24.1 bar). To run a reaction, the chamber is prepressurized to 250–300 psi (17.2–20.7 bar) using nitrogen gas via a high-pressure cylinder. This allows access to reaction temperatures above the normal boiling points of solvents at atmospheric pressure. The reactor employs three 2.45 GHz water-cooled magnetrons rated at 3 kW each, with an accessible power of 2.5 kW each for a total maximum allowed output of 7.5 kW. Reaction parameters such as time, temperature, pressure, and magnetron power are monitored and collected with the use of the software provided by the manufacturer. Additionally, this software allows for operation of all pressure inlet and release valves. Eventually, it will also control power modulation of the magnetrons. However, on this prototype unit, microwave power input was operator-

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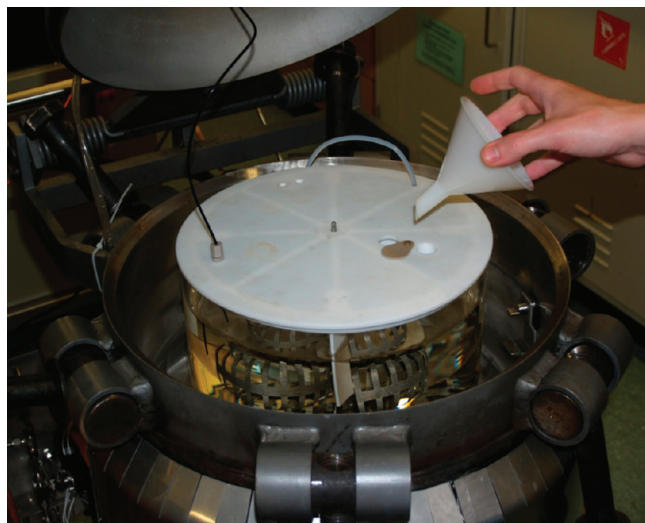


Figure 3. Last-minute addition of solvent to the reaction vessel through the port on the lid.

controlled via the built-in analog control dials of each of the three magnetron power sources. Upon completion of a reaction, a valve in the reaction ejection line is opened to allow the nitrogen pressure in the reactor to force the contents out. This flow can be directed through a water-cooled counter-flow heat exchanger, or directly into a receiving chamber at ambient pressure.

Solvent Heating. To begin our investigations, we chose to heat various solvents in the unit, as a practical “back-of-the-envelope” indication of the effectiveness of the magnetrons and to aid us in the selection of solvents for reactions. When using microwave heating, at the outset it would seem obvious to select highly absorbing solvents in order to keep ramp times short and achieve elevated temperatures easily. Indeed, it has been our experience using a wide range of dedicated small-scale microwave reactors that solvents such as ethanol, dimethylformamide (DMF), or dimethylsulfoxide (DMSO) heat well, while solvents such as dichloromethane (DCM) or tetrahydrofuran (THF) that interact poorly with microwave irradiation require significantly more power input in order to reach elevated temperatures. On the basis of conventional wisdom when using monomode microwave apparatus and our small-scale microwave experience, we expected that heating solvents such as DCM or THF would require significantly more energy input than more polar solvents such as ethanol. However, there are two significant differences between typical monomode microwave reactors and the AccelBeam unit, namely much larger reaction volumes and vessel prepressurization.

We studied seven solvents with a range of microwave absorptivities: ethanol, water, acetonitrile, ethyl acetate, THF, 2-butanone (MEK), and DCM. In all cases, 4 L of solvent was heated in the 5-L reaction vessel until they reached 150 °C using a constant 7.5 kW power delivery from the magnetrons (2.5 kW \times 3) and with the stirring set to \sim 60 rpm. The results are shown in Figure 4.

It took between 4–5 min to heat 4 L of MEK (4 min 13 s), DCM (4 min 15 s), acetonitrile (4 min 21 s), THF (4 min 28 s), or ethyl acetate (4 min 58 s) from 30–150 °C. Perhaps surprisingly, the solvents that performed the best in this study are ones often regarded as “poor” microwave absorbers. On the other hand, those generally touted as good solvents for

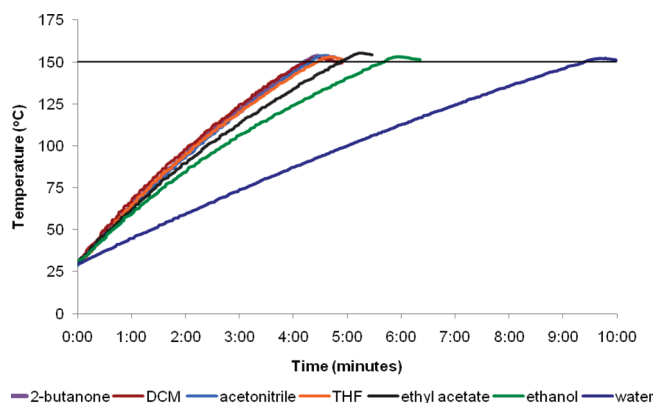


Figure 4. Heating profiles for various solvents heated using the microwave unit. In all cases 4 L of the desired solvent was heated using 7.5 kW (2.5 kW \times 3) of applied microwave power, and stirring was set at \sim 60 rpm.

microwave chemistry actually performed relatively poorly; 4 L of water takes over 9 min to reach 150 °C. An often-overlooked component to solvent selection is the heat capacity and, as a result, the required amount of energy to heat it. As a rough estimate, we calculated the amount of energy required to heat 4 L of water to 120 °C to be approximately 2.01×10^3 kJ.¹³ The same volume of ethanol requires less than half that at 924 kJ, and all the other solvents require less than 900 kJ (4 L, $\Delta = 120$ °C). Also, the vessel is charged with 280 psi (19.3 bar) N₂ prior to heating. In contrast, typical small-scale microwave reactors operating in sealed-vessel mode generate autonomic pressure. As a result, when heating with our large-scale unit, energy loss due to solvent vaporization is minimized. For example, the calculated boiling point for dichloromethane at 280 psi (19.3 bar) is 160 °C (atmospheric boiling point = 40 °C).¹⁴

The combination of heat capacity and minimal energy loss due to vaporization cannot fully explain the unexpected results we obtain. Since the solvents are being heated using microwave irradiation, their relative microwave absorptivities must have some impact. The loss tangent ($\tan \delta$) is proportional to the ability of a material to convert electromagnetic energy into heat. The loss tangent is a quotient defined as: $\tan \delta = \epsilon''/\epsilon'$; where ϵ'' is the dielectric loss which describes the efficiency of which microwave energy is converted into kinetic energy and ϵ' is the dielectric constant which indicates the polarizability of a molecule within the microwave field. Thus, the ability of a solvent to couple with the microwave field, and in turn result in heating, is generally proportional to its loss tangent as well as its dielectric loss constant. However, this is only true if the entire sample's cross-section can effectively be irradiated. On the small scale this is the case, which means solvents that are highly microwave absorbing will heat faster than those that have low microwave absorptivities. At larger scales, the depth to which the microwave energy can penetrate the contents of the vessel will vary. Less absorbent solvents such as DCM or THF have a larger cross-section that is absorbing the microwave

(13) Using the heat capacities of solvents at 20 or 25 °C. For a comprehensive table, see the Supporting Information.

(14) (a) Goodman, J. M.; Kirby, P. D.; Haustedt, L. O. *Tetrahedron Lett.* **2000**, 41, 9879. (b) The embedded applet described in ref 14a can be found at <http://www-jmg.ch.cam.ac.uk/tools/magnus/boil.html>.

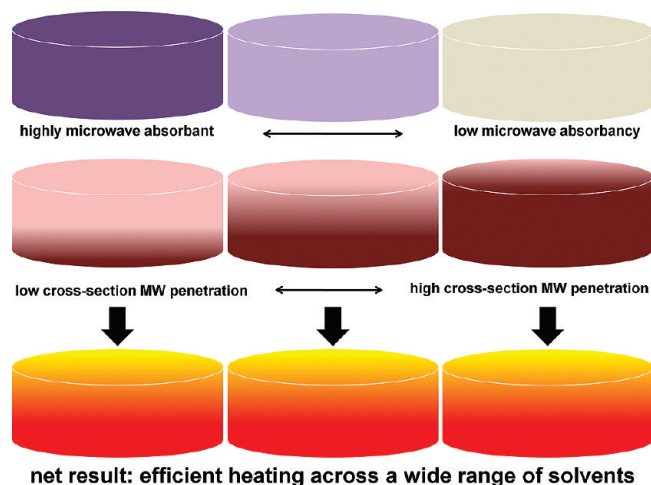


Figure 5. Illustration showing that microwave irradiation is effective at heating a wide range of solvents on a large scale, regardless of microwave absorptivity.

energy as compared to more absorbent solvents such as ethanol and water. Microwave absorptivity and heating cross section are interlinked and inversely proportional which means that dichloromethane ($\tan \delta = 0.042$) can be heated to 150 °C from 30 °C ($\Delta T = 120$ °C) in less time than it takes to heat ethanol ($\tan \delta = 0.941$) across the same temperature range using the same applied microwave power. A graphical representation of this can be seen in Figure 5.

The ramifications of these observations are significant. First, many researchers intimately involved with the scale-up of microwave chemistry, including our lab, have reluctantly viewed microwave-mediated batch scale-up as limited in scope. We and others have hypothesized that flow chemistry would be the only suitable approach for >1-kg scale-up using microwave heating, citing poor penetration depth as a potential issue. While there are a number of excellent reasons to adopt flow chemistry for large-scale synthesis, they hold true regardless of whether microwave or conventional heating is used. Our results show that, with efficient stirring and properly sized and engineered magnetrons, it should be possible to design batch reactors capable of effectively heating reactions on significantly larger scales than currently used.

As a note of caution, in light of our success with heating solvents such as dichloromethane we attempted to heat toluene. The microwave energy does not couple effectively with the solvent because it is sufficiently transparent. Instead, arcing was evidenced by a rapid increase in pressure due to decomposition of toluene vapors into molecular hydrogen and elemental carbon black. The run was abandoned after 15 s of microwave heating. However, a larger solvent cross section (e.g., 12 L instead of 4) could feasibly allow for sufficient absorption of microwave energy by the solvent and reduce the potential for arcing. Current investigations are underway. However, at this point we note that it is unadvisable to carry out reactions in toluene using nonabsorbing reagents without additives to increase the absorptivity of the load.¹⁵

Preparation of 3-Acetylcoumarin. The condensation of salicylaldehyde with ethyl acetoacetate to form 3-acetylcoumarin

acted as a platform for our preliminary studies. We have studied this reaction previously across a range of scales and in a number of commercial microwave units.^{4b,16} Furthermore, the reaction is homogeneous throughout its course, and the starting materials are readily available and inexpensive. We find microwave heating to be very beneficial in this reaction as it affords short reaction times that mitigate byproduct formation.¹⁷ It also allows for use of low loadings of the piperidine catalyst and gives the chemist flexibility in the choice of solvent used. In small-scale studies we found that 1 mol % of the piperidine catalyst is sufficient to afford moderate-to-good isolated yields of the desired 3-acetylcoumarin when the reaction is carried out in ethanol at 130 °C for 20 min. In our first attempt to scale up this reaction in the batch unit, the heat exchanger was used upon completion. Due to the crystalline nature of the product and its high concentration in ethanol (1.5 M), the product crystallized in the efficient heat exchanger, resulting in clogging. We decided to explore a flash cooling option, whereby the contents of the reaction were ejected into a 5-gal (~20 L) vented receiving flask at ambient pressure situated in a fume hood via a stainless-steel exit line. A significant quantity of the ethanol evaporated, thereby rapidly cooling the reaction contents from 130 °C to approximately 80 °C almost instantaneously. Not only did this solve the clogging issue but also provided us an unexpected benefit. Since the rapid evaporation of solvent resulted in flash cooling, a granular crystal form and very even distribution of particle size was noted. This greatly facilitated the filtration and isolation of the product. Allowing the reaction mixture to cool slowly inside the microwave unit led to flatter, plate-like crystal morphologies and required longer filtration times. The differences in the crystal morphologies obtained using each cooling mode can be seen in Figure 6.

We performed the reaction on three scales; 3 mol, 12 mol, and 18 mol, in each case running the reaction at a concentration of 1.5 M. It proved to be very scalable, affording isolated yields of 67%,¹⁸ 74%, and 81%, respectively, at the three reaction scales (Table 1, entry 1). Furthermore, as we have studied this reaction in a number of microwave units, we are able to compare heating profiles, in particular ramp times, to other reaction vessels. Intuitively, ramp times will lengthen as scale increases. At a volume of 2 L, the ramp to 130 °C from room temperature took 3 min 48 s. At the 8-L scale the ramp time was 7 min 8 s, and on the 12-L scale, it was 12 min 45 s (Figure 7). This shows that the unit is capable of heating the reaction mixture to the target temperature in an expeditious manner, even when using large volumes. For comparison, running the same reaction in the Biotage Advancer, the ramp stage takes 1 min 20 s for the much smaller volume of 300 mL.

Preparation of 4-Phenyl-3,4-dihydropyrimidine-2(1H)-one. The Biginelli condensation among a urea or thiourea, an aldehyde, and a β -keto carbonyl to afford dihydropyrimidines

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- (17) Michael addition of enolate to coumarin to form a dimer.
- (18) Product crystallized in heat exchanger, leading to low isolated yield.

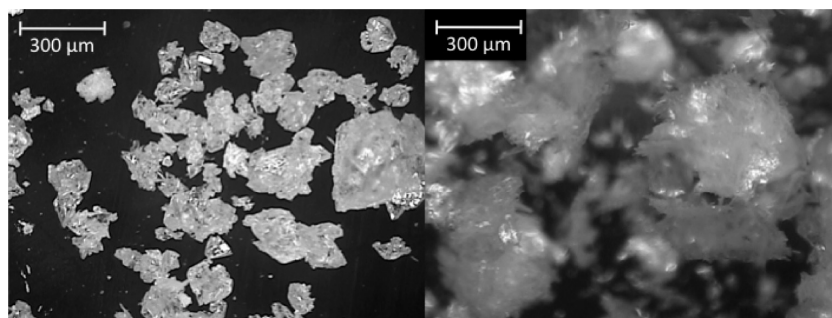


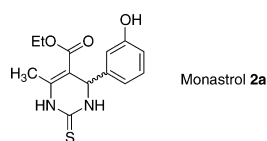
Figure 6. Comparison of 3-acetylcoumarin crystals. The left panel illustrates the granular morphology observed upon flash cooling from 130 °C to approximately 80 °C. The right panel illustrates the plate-like crystal morphology of the coumarin crystals that is observed upon slow cooling.

Table 1. Reactions performed in the large-scale batch microwave unit^a

Entry	Reaction	Small-scale results	Large-scale results
1		5 mmol, 72% 300 mmol, 71%	3.0 mol, 66.6% 12.0 mol, 74.0% 21.0 mol, 80.7%
2		2 mmol, 54%	4.0 mol, 55.0%
3		1 mmol, 73% 100 mmol, 93%	2.0 mol, 95%
4		1 mmol, 93% 50 mmol, 90%	4.0 mol, 91.8%
5		2 mmol, 70%	2.0 mol, 90.0% 4.0 mol, 93%
6		8.7 mmol, 70%	3.4 mol, 64%
7		3.4 mmol, 88% 14.7 mmol, 98%	performed conventionally
8		1 mmol, 91%	1.84 mol, 75%

^a For comparison, small-scale reactions and corresponding yields of the protocol are included. When scaling up, reactions were performed using identical conditions of time, temperature, reaction concentration, and catalyst loadings, differing only in reaction scale and ramp time. All yields represent isolated yields, except where noted.

is widely used in medicinal chemistry. An example of a pharmaceutically relevant dihydropyrimidine is Monastrol (**2a**),



first identified in 1999 by Mayer and co-workers as a potential lead candidate for new anticancer drugs.¹⁹ We chose to examine the Biginelli reaction using benzaldehyde, ethyl acetoacetate,

and urea as substrates. This reaction has been studied extensively by Kappe and co-workers using microwave heating.²⁰ Their recent protocol effects high (86% after column chromatography) to moderate (76%, isolation by filtration) yields of the desired products using acetonitrile as a solvent and 10 mol % ytterbium(III) triflate as a Lewis acid catalyst.²¹ However, as the

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(21) Dallinger, D.; Kappe, C. O. *Nat. Protoc.* **2007**, 2, 317.

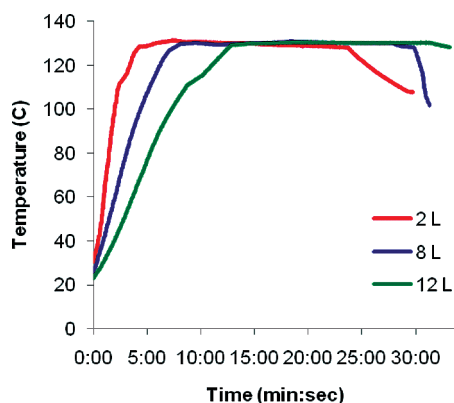


Figure 7. Heating profiles for the syntheses of 3-acetylcoumarin on 2-, 8-, and 12-L scales.

scale is increased, the lanthanide catalyst becomes rather cost prohibitive. We employed 20 mol % HCl in ethanol as an alternative, similar to the original conditions developed by Biginelli, obtaining a 55% yield on the 2 mmol scale.²² Working on the 4 mol scale, heating the reaction to 120 °C from ambient took just under 6 min at which point the microwave power was modulated to maintain this temperature for 20 min. After the reaction time elapsed, the contents of the vessel were ejected into a receiving flask (without external cooling), and the desired dihydropyrimidinone **2** was obtained in 56.0% yield without the need for further purification.

Preparation of 4-Methoxycinnamic Acid. The palladium-catalyzed Heck reaction represents a powerful methodology for the formation of carbon–carbon bonds. Furthermore, cross-coupling reactions have seen an increase in utility by pharmaceutical companies over the past 20 years.²³ Our group has examined this transformation extensively at a wide range of scales in numerous scientific microwave units,^{4a,b,6,24} thus, we thought it an excellent choice for study here. Our protocol for this reaction uses water as the solvent, potassium carbonate as base, a low loading of ligandless palladium source as the catalyst, and tetrabutylammonium bromide (TBAB) as a phase transfer agent. Previous experience has shown us that effective stirring is critical to the successful outcome of the reaction. Even at 175 °C the heterogeneous nature of the reaction mixture can lead to ineffective mass transfer and subsequently low yields. Working on the 2 mol scale and with a total reaction volume of 4 L, the microwave unit took approximately 15 min to heat to the desired temperature of 175 °C. We then aimed to modulate the microwave power to hold the reaction mixture at this temperature for 15 min, this taking less than 100 W total (~25–30 W × 3). However, as the reaction proceeded, carbon dioxide was generated due to decomposition of the carbonate base. The pressure gradually rose and approached the limits of the vessel after 5 min at 175 °C. The microwave power was then modulated to stay below the 350 psi (24.13 bar) pressure limit, and by the end of the 15 min hold time, the reaction temperature was measured to be 165 °C. Although the temperature was not at optimal for the full 15 min, we isolated

339 g of 4-methoxycinnamic acid (**3**), this corresponding to a 95.2% isolated yield (Table 1, entry 3), which compares favorably with our previous efforts performing the reaction on the 0.1 mol scale (92% isolated yield).^{4b} We repeated the reaction a further two times, reducing the TBAB loading from a full equivalent initially to 0.5 equiv and then 0.25 equiv. In the case of the former, the isolated yield was comparable to that in our initial protocol (95% isolated yield). When we reduced the TBAB loading to 0.25 equiv, the yield suffered (65% isolated yield). This could be due, at least in part, to the decreasing solubility of the substrates in the reaction mixture as the quantity of phase transfer agent is decreased. In addition, TBAB can stabilize palladium colloids; as a result as we decrease the quantity used, the palladium species may be agglomerating, which decreases the catalytic activity.

Preparation of 4'-Methoxybiphenyl. Another reaction on which our research group has focused considerable attention is the palladium-catalyzed Suzuki–Miyaura coupling.²⁵ It is possible to perform the reaction using very low loadings of palladium chloride in a water–ethanol solvent mixture. The power and utility of this protocol becomes increasingly evident at larger scales, as the use of inexpensive solvents, the elimination of the need for expensive phosphine ligands, and the very low palladium loadings make this coupling economically feasible. Performing the reaction on the 4 mol scale required a mere 1.6 mg of palladium (0.015 mmol Pd). Heating the 8 L reaction mixture to 150 °C using 7500 W (2500 W × 3), took 13.3 min. At this point the magnetron power was modulated to remain at the desired 150 °C (300 W; 100 W × 3) for an additional 5 min before ejecting the contents into a receiving flask. A 91.8% isolated yield of the desired biaryl (**4**) was obtained (Table 1, entry 4), corresponding to a catalyst turnover number of 243,000. Previously, we have performed this reaction on the 50 mmol scale in a sealed vessel using an identical protocol.^{4b} Using the larger batch reactor here, we are able to scale this 40-fold in a linear manner and obtain identical results.

Performing a Four-Step Reaction Sequence. In order to simulate a situation where multiple sequential microwave steps were employed in order to reach a desired target compound, we developed a sequence of reactions as a medicinal chemist might at the <10 mmol scale in order to synthesize a drug-like molecule (Scheme 1). We then scaled up each step in a linear manner. We began with a base-mediated condensation between thiourea and ethyl acetoacetate in ethanol to afford 6-methylthiouracil using an adaptation of a literature procedure (Table 1, entry 5).²⁶ On the 1–2 mmol scale we obtained a 70% yield of the desired product (**5**). We scaled this up in the batch reactor initially to 2 mols. The 4-L reaction volume was heated to 125 °C and held for 25 min, a 90.0% yield of **5** being obtained. We scaled the reaction further to 4 mol (8-L volume), obtaining an isolated yield of 94.6%. The reaction performed significantly better at scale when compared to the 1–2 mmol optimization runs. We attribute this to the fact that, over the course of the reaction, the sodium salt of the thiouracil product is formed,

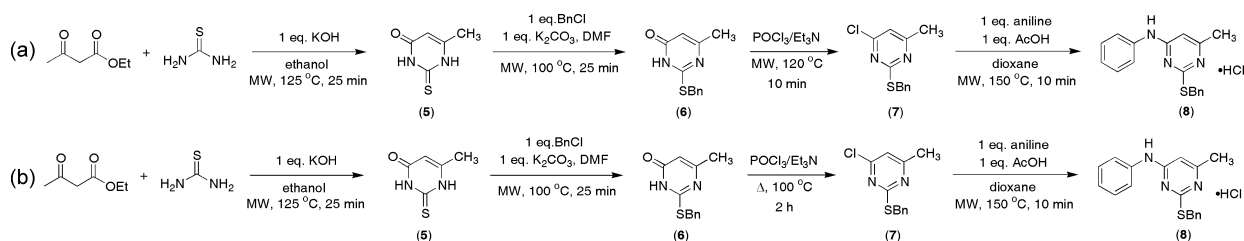
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Scheme 1. Four-step reaction sequence^a



^a (a) Small-scale: 39% isolated yield over 4 steps. (b) Large-scale: 38% isolated yield over 4 steps (1.82 moles).

and even at 125 °C in ethanol, the product readily precipitates (Figure 8). On the small scale, a monomode microwave unit was used, and reactions were stirred using a magnetic stir bar placed into the vessel. We speculate that this becomes ineffective as the precipitate forms, thus hindering the reaction and resulting in lower yields. Conversely, on the larger scale with mechanical stirring, this problem is mitigated, and an appreciable increase in product yield is achieved. However, when we attempted to scale up to 6 mols (12 L volume), the quantity of precipitate proved too significant for the stirring mechanism. As such, we deemed it prudent to discontinue heating to avoid the potential of scorching the static load. As such, the reaction contents reached only 100 °C, where it was held for 30 min before the contents were ejected, leading to a comparably low isolated yield of only 74.9%, although still higher than the small-scale, magnetically stirred reactions.

In the second step of our reaction series, we performed the selective benzylation of the sulfur functionality on 6-methylthiouracil (Table 1, entry 6) to form benzylthiouracil (**6**). We built on a protocol reported by Botta and co-workers, where they used microwave heating (130 °C for 5 min), an equivalent of either of the halobenzyl compounds of choice, DMF as solvent, and K₂CO₃ as a scavenger base. We found that using benzyl chloride and heating the reaction mixture to 100 °C and holding for 25 min was optimal in our case. Performing the reaction on the 8.4 mmol scale using a monomode microwave unit, a 70% isolated yield of **6** was obtained. A comparable yield (64.0%) was obtained upon scaling up to 3.4 mols using the batch reactor.



Figure 8. The sodium salt of **7** precipitates during the course of the reaction. Upon completion, the solvent is ejected, rapidly cooling the product which remains in the vessel as a spongy solid that is easily isolated by filtration.

A POCl₃/Et₃N deoxygenation protocol was next performed (Table 3, entry 7). On the small scale, a 3.0 M suspension of **6** in POCl₃ was prepared, to which 1 equiv of triethylamine was added. At this point, the reaction was heated to 120 °C for 10 min. A careful quench of the reaction with cold, saturated bicarbonate solution followed by extraction with ethyl acetate afforded 88% isolated yield of the 3-chloropyrimidine (**7**) at the 3.4 mmol scale and 98% isolated yield at the 14.7 mmol scale, both with purities >95%. However, after calorimetry studies (at the 9.0 mmol scale) indicated an exotherm of approximately 120 kJ/mol upon addition of the amine to the reaction mixture and because the chlorination reaction proceeds smoothly at lower temperatures albeit with longer reaction times, we opted to carry out the reaction at lower temperatures in separate batches, using conventional heating. This allowed us to use the exotherm to heat the reaction initially, and then heat to 100 °C and hold at this temperature until TLC indicated reaction completion about 90 min at 100 °C, giving a total reaction time of 2 h.

The final step of our multistep sequence was an acid-catalyzed nucleophilic aromatic substitution (S_NAr) protocol, directly following a literature procedure, originally developed on the 0.1 mmol scale.²⁷ Aniline, **7**, and 1 equiv of acetic acid was heated in dioxane to 150 °C and held for 10 min. On the 1 mmol scale a 91% yield of 2-(benzylthio)-6-methyl-4-(phenylamino)pyrimidine hydrochloride (**8**) was obtained. Scaling to 1.84 mols using the batch reactor afforded a 75% yield of **8**, representing a greater than 18,000-fold increase in scale over the original published procedure but with no changes made (Table 1, entry 8).

Overall, the sequence employed three microwave steps and afforded 473 g of **8** in 38% overall yield for four steps from thiourea and ethyl acetoacetate (Scheme 1b). This is almost identical to the 39% overall yield obtained on the small scale (Scheme 1a). Thus, using three identical reaction steps (out of 4) with no adjustment other than quantity of reagents used for a sequence of four reactions developed at the 1 mmol scale, comparable results were obtained, making this of great potential benefit to the process chemist.

Summary

We have explored the scope for scale-up of organic chemistry using a large batch microwave reactor. The unit is capable of processing 2–12 L per batch, allowing the process

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chemist access to the multimole and >1 kg scale. Initial studies into heating efficiencies illustrate the ability of the unit to heat a wide range of solvents effectively. The results also show that penetration depth was not an issue when heating larger volumes of solvents. A range of reactions have been scaled up by using the unit, and these include homogeneous condensations, heterogeneous reactions, and phosphine-free palladium-catalyzed transformations carried out in water. The unit, with a microwave output of 7.5 kW, allowed us to heat reaction mixtures to the target temperature in an expeditious manner. Of note is that no reaction we examined required more than 450 W (150 W \times 3) to keep the reaction at the desired temperature, regardless of volume, reagents, or solvent. The batch microwave unit performs on par with its smaller monomode cousins, allowing us to scale reactions without the need for reoptimization of conditions. This should prove a boon to process chemists faced with performing microwave-mediated reactions originally developed at small scale. In addition, this unit should prove an effective tool for the development of kilo-scale microwave chemistry.

Experimental Section

Preparation of 3-Acetylcoumarin on the 12 mol Scale.

To the 9 L reaction flask was added 1.26 L (12.0 mols, 1,470 g) salicylaldehyde and 1.56 L (12.0 mols, 1560 g) ethyl acetoacetate. This mixture was diluted to 8.00 L with ethanol (1.50 M). The lid was placed on the reaction and the fiber optic temperature probe was inserted into the reaction mixture. The stirring paddle was fitted to the motor and the ejection tubing was inserted into the reaction vessel. At this point, piperidine (120 mmol, 10.2 g) was added through a small access port. The reaction chamber was securely closed and prepressurized to 280 psi (19.3 bar) with nitrogen. The reaction was heated to 130 °C using 7500 W (2500 W \times 3), the ramp time taking approximately 7 min (4 min for 2 L scale, 13 min for 12 L scale). At this point the magnetron power was modulated to remain at the desired 130 °C (300–600 W; 100–200 W \times 3) for 20 min. After this time, microwave heating was stopped, and the contents were ejected without cooling into a 5-gal (~20 L) receiving vessel containing 1500 mL ethanol; 1.664 kg (73.7%) 3-acetylcoumarin (**1**) was collected via vacuum filtration, rinsed with 1000 mL ethanol, and allowed to dry at ambient temperature for 3 days. ¹H NMR (300 MHz, CDCl₃) δ : 8.51 (s, 1H), 7.67 (m, 2H), 7.39 (m, 2H), 2.73 ppm (s, 3H). ¹³C NMR (75.5 MHz, CDCl₃) δ : 195.4, 159.2, 155.3, 147.4, 134.4, 130.2, 125.0, 124.5, 118.2, 116.7, 30.5.

Preparation of Dihydropyrimidinone 2 on the 4 mol Scale. To the 5 L reaction flask was added ethyl acetoacetate (4.4 mols, 557 mL), urea (4.0 mols, 240 g), and benzaldehyde (4.0 mols, 404 mL), and the mixture was diluted to 4 L with ethanol (1.0 M). Without waiting for the urea to dissolve, the lid was placed on the reaction, and the fiber optic temperature probe was inserted into the reaction mixture. The stirring paddle was fitted to the motor, and the ejection tubing was inserted into the reaction vessel. At this point, 67 mL 12.0 M HCl (aq, 20 mol %) was added via an inlet port on the reaction lid. The reaction chamber was securely closed and prepressurized to 280 psi (19.3 bar) with nitrogen. The reaction was heated to 120 °C using 7500 W (2500 W \times 3), the ramp time taking

approximately 6.5 min. At this point the magnetron power was modulated to remain at the desired 130 °C (300–600W; 100–200 W \times 3) for 20 min. After this time, microwave heating was stopped, and the contents were ejected without cooling into a 5-gal (~20 L) receiving vessel containing 1500 mL ethanol. The product was allowed to cool, and the solid was collected via vacuum filtration and rinsed with ethanol. The solid was then allowed to dry overnight in an oven (100 °C) to yield 576 g (55.4%) of **2**. ¹H NMR (300 MHz, DMSO-*d*₆) δ : 9.19 (s, 1H), 7.74 (s, 1H), 7.32–7.26 (m, 5H), 5.16 (s, 1H), 3.98 (q, 2H, *J* = 7.1 Hz), 2.26 (s, 3H), 1.09 ppm (t, 3H, *J* = 7.1 Hz). ¹³C NMR (75.5 MHz, DMSO-*d*₆) δ : 165.8, 152.6, 148.8, 145.3, 128.8, 127.7, 126.7, 99.8, 59.6, 54.4, 18.2, 14.5.

Preparation of 4'-Methoxycinnamic Acid on the 2 mol Scale.

To the 5 L reaction vessel was added 4-bromoanisole (250 mL, 2.0 mol), methyl acrylate (360 mL, 4.0 mol), and tetrabutylammonium bromide (161, 322, or 644 g; 0.5, 1.0, or 2.0 mol; 0.25, 0.5, or 1.0 equiv). A 3.7 M aqueous solution of potassium carbonate (2 L solution, 415 g, 7.4 mol) was added to the reaction flask. The lid was placed on the reaction, and the fiber optic temperature probe was inserted into the reaction mixture. The stirring paddle was fitted to the motor, and the ejection tubing was inserted into the reaction vessel. A second solution was prepared containing 4 mL of a 1.006 mg/mL palladium stock solution diluted to 1 L with deionized water. This second solution was added to the reaction vessel, and the reaction chamber was securely closed and prepressurized to 280 psi (19.3 bar) with nitrogen. The reaction was heated to 175 °C using 7500 W (2500 W \times 3), the ramp time taking approximately 11.5 min. At this point the magnetron power was modulated to remain at the desired 175 °C (300 W; 100 W \times 3) for 15 min. At the end of the reaction, the solvent was ejected into a receiving flask containing 2 L water, allowed to cool to ambient temperature, and acidified using concentrated HCl to a pH = 2. The resulting solid was filtered under vacuum, washed with 2 L water, and dried at 100 °C overnight to yield 339 g (95.2%, >95% purity by ¹H NMR). The white solid (**3**) was recrystallized from ethanol. ¹H NMR (300 MHz, CDCl₃) δ : 12.2 (bs, 1H), 7.62 (d, 2H, *J* = 9 Hz), 7.59 (d, 1H, *J* = 16 Hz), 6.93 (d, 2H, *J* = 9 Hz), 6.40 (d, 1H, *J* = 16 Hz), 3.77 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ : 168.3, 161.4, 144.2, 130.3, 127.3, 117.0, 114.8, 55.7.

Preparation of 4'-Methoxybiphenyl on the 4 mol Scale.

A solution was prepared by adding 4-bromoanisole (502 mL, 4.00 mol) to enough ethanol to make 4.0 L of solution. A second solution containing phenylboronic acid (536 g, 4.4 mol), sodium hydroxide (320 g, 8.0 mol), and enough water to make 3.8 L was prepared. A third solution was prepared by diluting 1600 μ L of a commercially available palladium stock solution (Aldrich 207349, 1.001 mg/mL in 5% aq HCl, 1600 μ g of palladium, 15.0 μ mol, 0.0004 mol %) to 200 mL with deionized water. The first two solutions were combined in the 9-L reaction flask. The lid was placed on the reaction, and the fiber-optic temperature probe was inserted into the reaction mixture. The stirring paddle was fitted to the motor, and the ejection tubing was inserted into the reaction vessel. The reaction chamber was securely closed and prepressurized to 280 psi (19.3 bar) with nitrogen. The reaction was heated to 150 °C using 7500 W

(2500 W \times 3), the ramp time taking approximately 13.3 min. At this point the magnetron power was modulated to remain at the desired 150 °C (300 W; 100 W \times 3) for an additional 5 min. At the end of the reaction, the reaction contents were ejected into a receiving flask containing 2.0 kg ice. The white solid was collected via vacuum filtration, rinsed with 2.0 L water, and dried for three days at 50 °C to yield 669 g of 4-methoxybiphenyl, **4** (91.8%). ¹H NMR (400 MHz, CDCl₃) δ : 7.60 (t, 4H, J = 8.9 Hz), 7.47 (t, 2H, J = 7.8 Hz), 7.36 (t, 1H, J = 7.4 Hz), 7.04 (d, 2H, J = 8.8 Hz), 3.90 ppm (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 159.4, 141.1, 134.0, 129.0, 128.4, 127.0, 126.9, 114.4, 55.6.

Preparation of 6-Methylthiouracil on the 4 mol Scale.

To the 9-L reaction flask was added ethyl acetoacetate (4.0 mols, 506 mL), a suspension of thiourea (5.2 mols, 400 g) in 1 L of ethanol, and potassium hydroxide (4.0 mols, 404 mL) solution in 2.5 L of ethanol and was diluted to 8 L with ethanol (0.5 M). The lid was placed on the reaction, and the fiber-optic temperature probe was inserted into the reaction mixture. The stirring paddle was fitted to the motor, and the ejection tubing was inserted into the reaction vessel. The reaction chamber was securely closed and prepressurized to 300 psi (20.7 bar) with nitrogen. The reaction was heated to 125 °C using 7500 W (2500 W \times 3), the ramp time taking approximately 10 min (6 min for the 4-L reaction). At this point the magnetron power was modulated to remain at the desired 125 °C (300–600 W; 100–200 W \times 3) for 25 min. At the end of the reaction, the solvent was ejected into a receiving flask containing 2 L of water, leaving behind a spongy white solid in the reaction flask, which was suspended in the ejection contents. The suspension was adjusted to pH 6 with HCl (conc.) and allowed to cool overnight. This precipitate was vacuum filtered, suspended in 2 L of water, refiltered, and dried overnight at 100 °C to yield 514 g of white solid. A second crop was collected from the mother liquor after being allowed to stand at room temperature for 1 day. It was filtered, washed with 500 mL of water, and dried overnight at 100 °C to yield a further 24 g of white solid, bringing the total isolated yield of 6-methylthiouracil (**5**) to 538 g (94.6% theoretical). ¹H NMR (DMSO-*d*₆) δ : 12.25 (bs, 2H), 5.88 (s, 1H), 2.08 (s, 3H). ¹³C NMR (DMSO-*d*₆) δ : 176.3 161.4, 153.6, 104.1, 18.5.

Preparation of Benzylthiouracil on the 3.42 mol Scale.

6-Methylthiouracil (486 g, 3.42 mol), potassium carbonate (472 g, 3.42 mol), and 5.8 L of *N,N*-dimethylformamide were added to the 9-L reaction flask at which point benzyl chloride (394 mL, 3.42 mol) in 1.0 L of *N,N*-dimethylformamide was added. The lid was placed on the reaction, and the fiber-optic temperature probe was inserted into the reaction mixture. The stirring paddle was fitted to the motor, and the ejection tubing was inserted into the reaction vessel. The reaction chamber was securely closed and prepressurized to 100 psi (6.9 bar) with nitrogen. The reaction was heated to 100 °C using 7500 W (2500 W \times 3), the ramp time taking approximately 5.5 min. At this point the magnetron power was modulated to remain at the desired 100 °C (300 W; 100 W \times 3) for 25 min. At the end of the reaction, the solvent was ejected into a receiving flask containing 2 L of water and acidified using 12 M HCl. The resulting solid was filtered using vacuum filtration and dried

at 100 °C overnight to yield 510 g (64%) of **6** as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ : 7.49 (d, 2H, J = 7.6 Hz), 7.34 (t, 2H, J = 7.3 Hz), 7.28 (t, 1H, J = 7.3 Hz), 5.99 (s, 1H), 5.70 (s, 1H), 4.47 (s, 2H), 2.27 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ : 164.5, 164.4, 137.9, 129.5, 128.89, 128.87, 127.7, 107.2, 34.1, 23.6.

Conventional Preparation of 2-(Benzylthio)-4-chloro-6-methylpyrimidine on the 1 mol Scale.

A 1-L, three-necked round-bottom flask was charged with 232 g (1.00 mol) of *S*-benzyl-6-methylthiouracil (**6**) and placed in a heating mantle. To the flask was added 333 mL of POCl₃ (3.6 mol) and fitted with an addition funnel, an overhead stirring shaft, and a thermometer. To the stirred solution, Et₃N (102.0 g, 1.00 mol) was added dropwise at a rate to maintain approximately 80 °C, taking approximately 30 min. The heating mantle was turned on, and the reaction was heated to 100 °C and held at this temperature until the reaction reached completion as indicated by TLC, approximately an additional 90 min. At this point, heating was discontinued, and the reaction was allowed to cool to 50 °C. The reaction contents were slowly added portionwise to 1500 mL of a saturated aqueous solution of NaHCO₃ which was simultaneously being stirred vigorously with an overhead stirrer, adding additional NaHCO₃ as needed (upon cessation of CO₂ generation). Approximately 2 kg of bicarbonate was needed to completely quench the reaction contents and bring the pH \approx 7. This aqueous layer was decanted from the solid precipitate into a 4.0-L separatory funnel. The precipitate was rinsed with \sim 300 mL of ethyl acetate. The aqueous layer was extracted with 900 mL of ethyl acetate in three 300-mL portions. The organic extracts were combined, washed sequentially with 300 mL of water and 100 mL of saturated sodium chloride, and dried over MgSO₄; the solvent was removed under reduced pressure to yield 219.5 g (87.5%) of **7** as a reddish brown oil of a purity greater than 95% (¹H NMR) that was used without further purification in the next step. ¹H NMR (300 MHz, CDCl₃) δ : 7.46 (d, 2H, J = 6.9 Hz), 7.29 (m, 3H), 6.86 (s, 1H), 4.40 (s, 2H), 2.44 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ : 172.1, 169.0, 160.7, 137.2, 129.2, 128.4, 127.3, 115.9, 35.5, 23.8.

Preparation of 2-(Benzylthio)-6-methyl-4-(phenylamino) Pyrimidine Hydrochloride on the 1.8 mol Scale.

The 5-L reaction vessel was charged with 2-(benzylthio)-4-chloro-6-methylpyrimidine (**7**) (461 g, 1.838 mol), aniline (172 g, 1.84 mol), and acetic acid (110 g, 1.84 mol) in dioxane (3.5 L solution, 0.53 M). The lid was placed on the reaction, and the fiber-optic temperature probe was inserted into the reaction mixture. The stirring paddle was fitted to the motor, and the ejection tubing was inserted into the reaction vessel. The reaction chamber was securely closed and prepressurized to 280 psi (19.3 bar) with nitrogen. The reaction was heated to 150 °C using 7500 W (2500 W \times 3), the ramp time taking approximately 11 min. At this point the magnetron power was modulated to remain at the desired 150 °C (300–600 W; 100–200 W \times 3) for 10 min. After this time, microwave heating was stopped, and the solution was ejected into a receiving flask containing 2 L of water, leaving behind a spongy solid in the reaction flask. The solid was allowed to cool and then filtered under vacuum

and dried overnight at 100 °C to yield the pale-yellow solid (433 g, 68.4%). The aqueous solution was extracted using ethyl acetate (4 × 300 mL). The organic extracts were combined, washed with brine (100 mL), and dried over MgSO₄; the solvent and residual 1,4-dioxane were evaporated under reduced pressure to yield an additional 40.0 g of pale-yellow solid bringing the total yield of 2-(benzylthio)-chloro-6-methyl-4-(phenylamino)pyrimidine to 473 g (74.7%). A small sample of this solid was combined with 2.0 M NaOH (aq) and extracted using ethyl acetate. The organic layer was washed with brine and dried over MgSO₄; the solvent was removed under vacuum to afford the freebase of **8**. ¹H NMR (500 MHz, CDCl₃, freebase) δ: 7.44 (d, 2H, *J* = 7.4 Hz), 7.38 (t, 2H, *J* = 7.3 Hz), 7.32 (m, 4H), 7.26 (t, 1H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 7.3 Hz), 6.74 (s, 1H), 6.27 (s, 1H), 4.43 (s, 2H), 2.33 ppm (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ: 170.7, 166.6, 160.8, 138.17, 138.13, 129.4, 129.0, 128.4, 127.0, 124.8, 122.5, 98.8, 35.1, 24.1. HRMS: *m/z* 308.1227, expected: 308.1216.

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Supporting Information Available

General experimental details as well as ¹H NMR and ¹³C NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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