JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Design and Performance Validation of a Conductively Heated Sealed-Vessel Reactor for Organic Synthesis

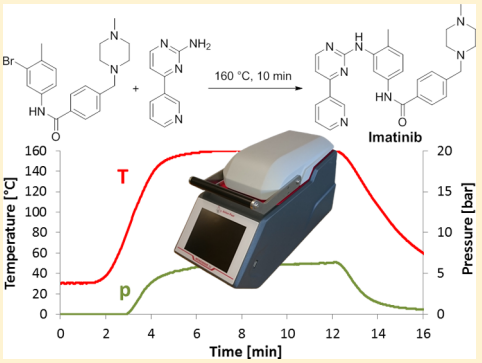
David Obermayer,[†] Desiree Znidar,[†] Gabriel Glotz,[†] Alexander Stadler,[‡] Doris Dallinger,*[,†] and C. Oliver Kappe*[,†]

[†]Institute of Chemistry, University of Graz, NAWI Graz, Heinrichstrasse 28, 8010 Graz, Austria

[‡]Department of Analytical and Synthetic Chemistry, Anton Paar GmbH, Anton-Paar-Strasse 20, 8054 Graz, Austria

Supporting Information

ABSTRACT: A newly designed robust and safe laboratory scale reactor for syntheses under sealed-vessel conditions at 250 °C maximum temperature and 20 bar maximum pressure is presented. The reactor employs conductive heating of a sealed glass vessel via a stainless steel heating jacket and implements both online temperature and pressure monitoring in addition to magnetic stirring. Reactions are performed in 10 mL borosilicate vials that are sealed with a silicone cap and Teflon septum and allow syntheses to be performed on a 2−6 mL scale. This conductively heated reactor is compared to a standard single-mode sealed-vessel microwave instrument with respect to heating and cooling performance, stirring efficiency, and temperature and pressure control. Importantly, comparison of the reaction outcome for a number of different synthetic transformations performed side by side in the new device and a standard microwave reactor suggest that results obtained using microwave conditions can be readily mimicked in the operationally much simpler and smaller conventionally heated device.



INTRODUCTION

High-speed microwave-assisted organic synthesis has attracted considerable interest since its initial conception in the mid-1980s.[1] In particular the introduction of dedicated sealed-vessel single-mode microwave reactors around 2000 has paved the way for the rapid implementation of this enabling technology into modern synthetic laboratories. Today, microwave reactors are virtually omnipresent in both academia and industry and the technology has become an indispensable tool for performing organic synthesis at elevated temperature regimes. The many advantages and benefits of this nonclassical heating method for various synthetic applications have been thoroughly investigated and documented in numerous publications, reviews, and books.[2−4] Most of the published examples document a significant reduction of reaction times when performing reactions in sealed-vessel microwave reactors at temperatures well above the boiling point of the solvent at atmospheric conditions (Arrhenius-based rate acceleration).[2−4] In addition, an increase in yield and product purity can often be achieved using this technique.[2−4] In contrast to conventionally heated reactions, dedicated microwave devices also allow a higher degree of process control, allowing accurate online monitoring of temperature and pressure, and increase the safety by avoiding the use of round-bottom flasks in combination with water-cooled reflux condensers, oil-baths, or other electric heating sources.

Since the early beginnings of microwave chemistry, the dramatic rate accelerations were often suspected of being caused by so-called *specific* or *nonthermal* microwave effects (in addition to the well-understood Arrhenius-based *thermal* effects).[2] Although occasionally still being controversially debated,[5] most of the allegedly found evidence for such microwave effects can be traced back to erroneous or incorrect temperature sensing in the microwave setup.[6] Clearly, the vast majority of the effects that can be experienced in microwave-assisted organic synthesis are the result of purely thermal (Arrhenius-based) bulk temperature phenomena.[5] Therefore, the idea of implementing the main advantages of microwave-assisted synthesis, namely rapid heating and cooling of a reaction mixture in a sealed-vessel environment with adequate process control, into a technically simpler setup, avoiding microwave technology altogether, appears rather obvious.[7]

In 2013 we reported a novel type of resistance-heated sealed-vessel reactor that employed a modified silicon carbide (SiC) vial as reaction vessel.[8,9] This comparatively easy to assemble a resistance-heated SiC autoclave can effectively mimic a standard sealed-vessel microwave experiment. Rapid heating and cooling, superheating of reaction mixtures above their boiling points, and excellent control over reaction temperature and pressure could all be duplicated in the SiC reactor, in which the electrically conductive SiC ceramic served as an integrated reaction-vessel/heating element. Importantly, with a series of model reactions and control experiments we could demonstrate that the outcome of the chemical transformations in the SiC reactor did not differ from the microwave-heated processes

Received: September 12, 2016
Published: November 7, 2016

DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788−11801

under otherwise identical reaction conditions (temperature profile, reaction time).[8]

We now present a technically simplified device that utilizes a standard 10 mL sealed Pyrex microwave vessel as the reaction environment and allows rapid heating and cooling of reaction mixtures to 250 °C and 20 bar pressure at rates not unlike those achieved with modern single-mode microwave reactors. The reactor employs conductive heating of a stainless steel heating jacket and implements both online temperature and pressure monitoring in addition to magnetic stirring. Appropriate software algorithms ensure proper control over reaction temperature. With a series of model reactions it is demonstrated that this novel device, based entirely on conductive heating principles, can adequately mimic the results achieved in modern microwave reactors.

RESULTS AND DISCUSSION

Reactor Design. The basis for the reactor is a standard 10 mL Pyrex microwave vial, which is immersed in a precisely fitting stainless steel heating jacket (Figure 1). The heating jacket is equipped with an appropriate heating coil, and the pitches between the windings act as cooling fins when cooling the vial after the reaction. The reaction vial rests on a standard negative temperature coefficient (NTC) temperature sensor at the bottom of the heating jacket. This contact sensor gives feedback to the controller, which calculates the actual reaction temperature from the measured surface temperature via a specifically programmed software algorithm. Comparing the current temperature with the programmed settings, the instrument's power is regulated between 0 and 315 W to reach and maintain the target temperature. Additionally, a pressure sensor embedded in the instrument cover measures the evolving pressure during the reaction up to a maximum of 20 bar (Figure 1). In the case of a substantial pressure build-up, the overpressure is safely released via an exhaust port until it drops to below 20 bar. A key feature for temperature homogeneity and reproducible results is the built-in magnetic stirrer.[10] Setting an appropriate stirrer speed (according to the viscosity of the reaction mixture) is essential for accurate temperature control. Only if sufficient heat distribution by agitation is ensured will the contact sensor provide a representative temperature value allowing the controller to determine the reaction temperature for the entire bulk accordingly.[10] To serve a wide scope of homogeneous and heterogeneous mixtures and various viscosities, the stirrer speed can be set between 0 and 1200 rpm. The reaction vial is closed with a silicone cap containing a Teflon septum, and the instrument cover is manually closed by a handle to seal the vial.

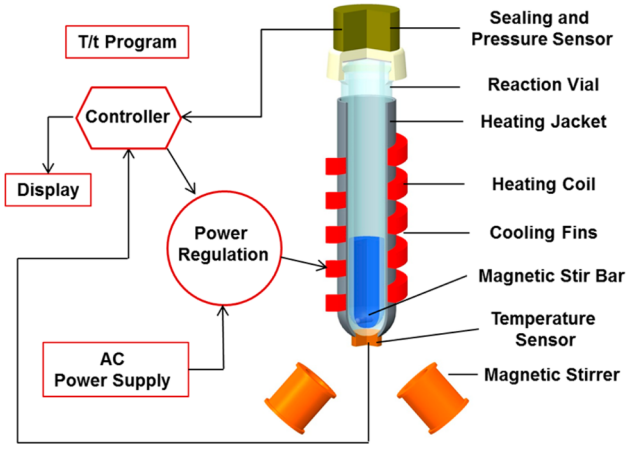


Figure 1. Concept of a conductively heated sealed vial reactor employing a 10 mL glass vial. Apart from temperature and pressure monitoring, magnetic stirring and air cooling are integrated into the reactor. Image copyright Anton Paar GmbH (ref 11).

Methods programming for temperature-controlled experiments in the reactor termed Monowave 50 (Figure 2, Anton Paar GmbH)[11] is carried out via a built-in capacitive touchscreen and allows experiments up to 250 °C for a maximum of 4 h. Reaction mixtures can be heated in an "as fast as possible" mode (AFAP) or by applying a defined ramp time to reach the target temperature. After an experiment is completed, the vial is automatically cooled within minutes by an integrated heat exchanger. The heating and cooling characteristics of the instrument are comparable to the performance of standard single-mode microwave reactors. The most significant difference from a microwave device is probably the initial delay of the heating phase, because the sealed-vessel reactor needs a preheating time to heat the heating jacket. Once the working temperature is reached (after ca. 30 s), the heating profiles appear nearly identical to those experienced with a single-mode microwave instrument (Figure 3). The more polar the utilized solvent (i.e., the higher its tan δ value),[12] the more significant the difference in heating rate between microwave dielectric heating and the convective heating principle used in the Monowave 50 device. The cooling concept is also slightly different from that of standard single-mode microwave reactors. Instead of a jet stream of compressed air alongside the vessel surface, the heat is withdrawn from the heating jacket by a standard heat exchanger fan. Cooling fins in the heating jacket enlarge its surface, ensuring efficient heat transfer to cool the reaction mixture efficiently. In the case of a potentially remaining overpressure after cooling, the safety measures of the instrument ensure a safe release when opening the instrument cover. When the handle is unlocked, the pressure piston slightly moves to allow the silicon cap to expand. The overpressure is immediately released via an exhaust channel to the rear of the instrument.

Figure 2. Monowave 50 reactor (Anton Paar GmbH) with open cover and 10 mL glass vials with silicone cap, septa, and stirring bar. Image copyright Anton Paar GmbH (ref 11).

DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788−11801

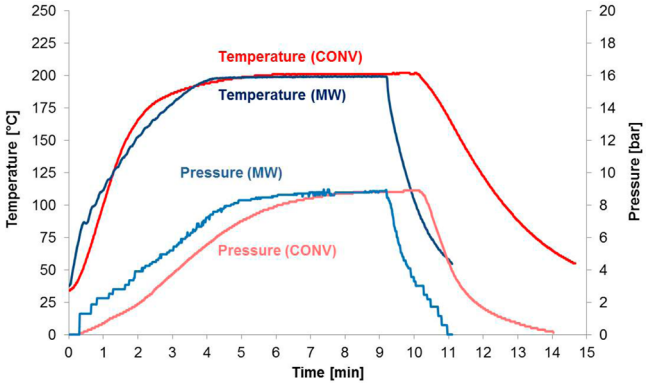


Figure 3. Temperature and pressure profiles for heating and cooling a sample of toluene (6 mL) AFAP to 200 °C (5 min hold time, target temperature for cooling 50 °C) comparing the performance of a standard single-mode microwave reactor (Monowave 300, MW, blue) with the conventionally heated Monowave 50 reactor (CONV, red). The ca. 30 s preheating phase of the Monowave 50 reactor is not shown for better comparison.

After complete manual opening of the instrument cover, the vial is at atmospheric pressure and can be safely removed from the heating jacket (Figure 2).

Heating and Cooling Performance. To evaluate the heating performance and the quality of temperature control in the newly designed reactor, a series of standard solvents for organic synthesis was processed. First, to validate the principle of the contact thermometer and the algorithm to determine the reaction temperature, preliminary heating experiments have been conducted with simultaneous internal temperature sensing in an instrument prototype setup. As shown in Figure 4, the calculated reaction temperature derived from the

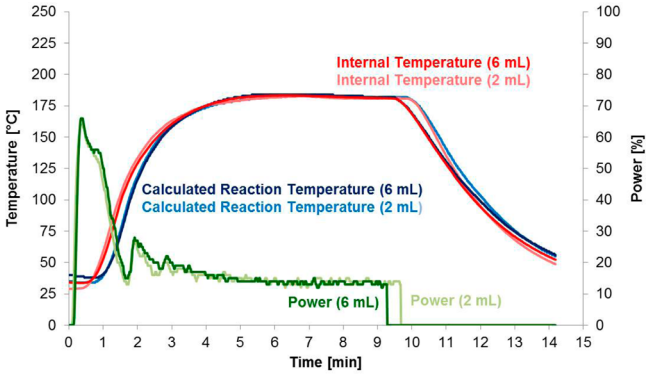


Figure 4. Temperature profiles for heating 2 and 6 mL of ethanol to 180 °C (5 min hold time) in the Monowave 50 reactor: calculated reaction temperature (blue) and measured internal temperature (red). The power graphs (green) indicate that significant energy is required only to heat the heating coil, and that power consumption is virtually independent of the vial content. A NiCr−Ni type K thermoelement (500 × 0.5 mm) was used as internal temperature probe.

measurement of the surface temperature of the glass vial agrees nicely with the actual temperature inside the reaction vial determined by an internal temperature probe. Furthermore, the filling volume has no significant influence on the heating profile. Heating the minimum filling volume (2 mL) and the maximum filling volume (6 mL) only differs by a few seconds.

With this optimized algorithm in hand, the performance of the new reactor regarding heating efficiency of frequently used organic solvents was compared to a standard single-mode microwave reactor. The small matrix comprises polar (high tan δ) as well as nonpolar solvents (low tan δ) to demonstrate that, unlike applying microwave dielectric heating,[12] the dielectric properties of the solvents have no influence on the heating efficiency. In the operation range of 2 to 6 mL most tested solvents are heated virtually within the same time frame of approximately 3.5−5 min (corrected time without ca. 30 s preheating phase) to the respective target temperatures (Figure 5).

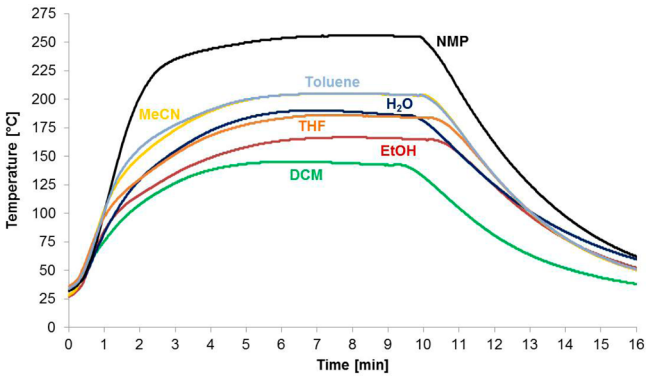


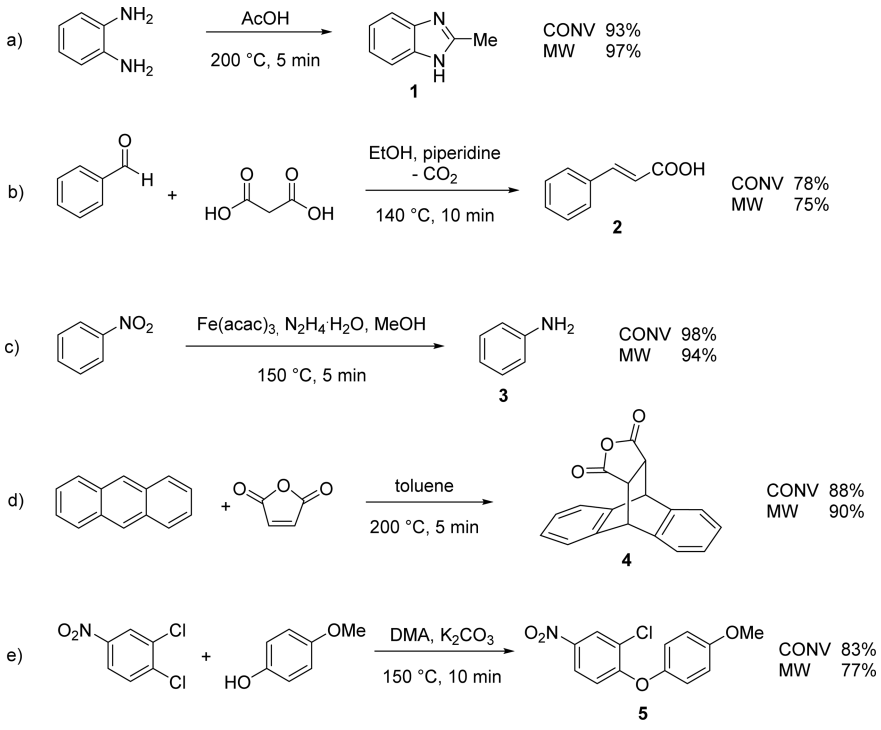
Figure 5. Heating profiles (AFAP) of common solvents (6 mL) to individual target temperatures: DCM (green), 140 °C; EtOH (red), 160 °C; THF (orange) and water (blue), 180 °C; MeCN (yellow) and toluene (light blue), 200 °C; NMP (black), 250 °C. For clarity, monitored pressure is not shown.

To ensure a high degree of accuracy in achieving the programmed target temperature, heating efficiency was sacrificed. Because when applying convective heating, the heating process will continue even when power is already reduced, it appeared advantageous to regulate the power more conservatively to prevent any significant thermal overshoots, especially when exothermic reactions are processed. This invariably leads to the comparatively slow heating ramps of ca. 3.5−5 min as shown in Figure 5. Notably, polar solvents with high heat capacity (such as NMP, ethanol, H_2O) still tend to slightly exceed the programmed target temperatures. In contrast, using microwave reactors, the in-core heating immediately stops when the power is off, therefore target temperatures are reached faster and more accurately, although slight overshoots can also be observed for some solvents (see Figure S1, Supporting Information). Consequently, in direct comparison, heating with microwave reactors, (dielectric) heating will always be more rapid. Notably, the cooling principle of the Monowave 50 reactor utilizing a standard heat exchanger fan is less complex than the one used in standard single-mode microwave reactors (compressed air flow). The efficiency of the integrated fan, which makes the instrument independent of external sources of compressed air, is still sufficient to cool most solvents within 4−5 min but lacks the speed of the compressed air support. Therefore, overall cycle times including heating, hold time, and cooling are invariably longer compared to a microwave experiment.

Standard Chemistry Examples. The assumption that slower heating and minor thermal overshoots have no significant influence on the reaction outcome has been validated with selected model transformations. All chemical transformations performed during this validation (Scheme 1)

DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788−11801

Scheme 1. Model Reactions for Performance Validation[a]



[a]Reactions were performed in the Monowave 50 reactor (CONV) based on optimization data previously obtained using microwave conditions (hold time, temperature). For detailed reaction conditions in the single-mode microwave reactor, see ref 8. For detailed reaction conditions in the Monowave 50, see Experimental Section.

are known in the literature and have been previously investigated and optimized in our laboratories using microwave dielectric heating and/or using the SiC reactor mentioned above.[8,9] The results obtained with the conductively heated Monowave 50 reactor demonstrate that the only relevant parameter is the hold time at the target temperature, rather than the time required to achieve the target temperature (ramp time). The efficiency of other features such as stirring (influence of scale/filling volume) and pressure buildup/release were also verified with appropriate chemical transformations.

For all model reactions shown in Scheme 1, virtually identical results in terms of conversion, purity profile, and/or product yields were obtained using the Monowave 50 reactor based on conventional heating principles (CONV) compared to experiments utilizing dielectric heating in a single-mode microwave reactor (MW).[8,9] Although the heating jacket reaches very high temperatures to ensure a rapid heating of the vessel contents, wall effects due to the hot vessel surface apparently do not play a significant role in the outcome of the model reactions. This is in agreement with earlier investigations and findings from our laboratory comparing conventional heating with microwave dielectric heating.[9,13]

As an initial example, the formation of 2-methylbenzimidazole (**1**) from *o*-phenylenediamine and acetic acid (Scheme 1a) was performed on different scales.[8] When a reaction temperature of 200 °C was utilized, the resulting autogenic pressure was close to the 20 bar limit of the Monowave 50 instrument. At both of the applied scales (2 and 6 mL, respectively) identical product yields (93%) were obtained. Additionally, a gas-evolving Knoevenagel condensation (Scheme 1b) was performed demonstrating the feasibility of the instrument's pressure control system.[8] On small scale (2 mL), the overpressure from CO_2 remaining in the vial after cooling (~7 bar) was not an issue. Even on larger scales (6 mL), the overpressure (~15 bar) was safely released upon opening the instrument cover (see above). Of particular interest in this evaluation were exothermic reactions such as the nitro group reduction shown in Scheme 1c, to assess how the control system is able to handle these types of transformations in terms of temperature accuracy. Even on small scale, this reaction is difficult to control under microwave conditions, leading to a significant exotherm that is accompanied by a pressure rise close to the 30 bar limit of the microwave reactor (Figure S2, Supporting Information).[14] As outlined above, when applying the conductive heating principles realized in the new reactor (Figure 1), the thermal overshoot cannot be expected to be controlled. Under identical reaction conditions as in the microwave reactor on a 2 mmol scale, a similar exotherm and pressure buildup above the instrument's limit of 20 bar was observed, which led to the termination of the experiment (Figure S3, Supporting Information). For the nitro reduction to be performed successfully in the Monowave 50, the scale had to be reduced to 1 mmol, leading to a more diluted reaction mixture. Under these conditions, the temperature overshoot could be completely prevented and the pressure remained in the operational range of the Monowave 50 (Figure S3, Supporting Information). In any event, virtually identical product yields were obtained for both processes. Finally, the influence of filling volume and solid material on stirring efficiency was investigated using a Diels–Alder reaction involving large quantities of solid starting materials (Scheme 1d) and a substitution reaction where potassium carbonate (1.5 equiv) was used as heterogeneous base (Scheme 1e).[15] On small scale (2 or 3 mL, respectively), the Diels–Alder reaction

DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788–11801

furnishes identical high yields in both reactor types. When moving to larger scale (6 mL), efficient stirring to quickly dissolve the substrates becomes more an issue due to the amount of solid material (>1.5 g) present, which may lead to inhomogeneous temperature distribution within the vial and consequently to diminished yield (very similar to the situation under microwave conditions).[10] Higher stirring speed (1200 rpm) overcomes this problem, and the yield can be even increased to >90% (Table 1). In the substitution reaction,

Table 1. Influence of Filling Volume and Stirrer Speed on the Diels–Alder Cycloaddition[a]

reactor	scale (mmol)	toluene (mL)	stirring (rpm)	yield (%)
CONV	2.45	2	600	88
CONV	7.35	6	600	85
CONV	7.35	6	1200	94
MW	2.45	2	600	90
MW	7.35	6	600	84
MW	7.35	6	1200	92

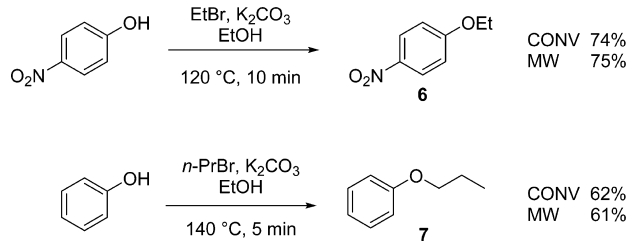
[a]Conditions: equimolar amounts of anthracene and maleic anhydride, heating AFAP to 200 °C, hold time 5 min. Yield refers to isolated product. For detailed reaction conditions on a 2.45 mmol scale in the Monowave 50 (CONV), see Experimental Section.

K_2CO_3 remains present as solid material in the reaction mixture during the entire process.[15] The observable trend is similar to the Diels–Alder reaction: on smaller scale, the amount of K_2CO_3 can be agitated efficiently and the reaction proceeds smoothly furnishing high yields (83%). In the 6 mL range (>600 mg of K_2CO_3), stirring becomes important to allow accurate temperature control. If the stirring speed is too low, the admixing of the solid base with the reaction mixture is insufficient, resulting in lower yields (ca. 60%).[15] Furthermore, a significant thermal overshoot can be observed due to inaccurate temperature measurement caused by the solid base being immobilized on the bottom of the vial.[10] With a stirring speed of 1200 rpm, yields can be improved again but are still lower (70–80%) compared to the smaller scale. With the information from these initial experiments, further chemistry examples with respect to educational purposes and also medicinal chemistry relevance have been investigated.

Educational Chemistry Examples. For synthetic organic reactions that are implemented in an undergraduate laboratory course, several criteria need to be met: they have to be operationally straightforward and relatively inexpensive and should cover standard organic reaction mechanisms. Owing to the simplicity of use and small footprint of the Monowave 50 reactor, its use in undergraduate (and graduate) teaching laboratories appears to be of significant potential interest. In university-type teaching laboratories, the long reaction times experienced for many standard synthetic organic chemical transformations (even at reflux conditions) often form a significant obstacle for their implementation into a laboratory course. Microwave instruments have therefore become increasingly popular in many undergraduate teaching laboratories.[16] We have therefore investigated the adaptation of several proven microwave chemistry protocols currently used in an undergraduate teaching laboratory to the Monowave 50 reactor.[17] These involve Williamson ether syntheses, oxidation of double bonds and alcohols, and a Knoevenagel and a Grignard reaction. All reactions were conducted under identical conditions (scale, hold time, temperature) in both a single-mode microwave reactor (MW) and the Monowave 50 instrument (CONV).

4-Nitrophenetol (**6**) and propoxybenzene (**7**) were synthesized via the Williamson ether synthesis from the corresponding phenols using bromoethane or 1-bromopropane, respectively (Scheme 2). The employed method was adapted from a

Scheme 2. Williamson Ether Syntheses[a]



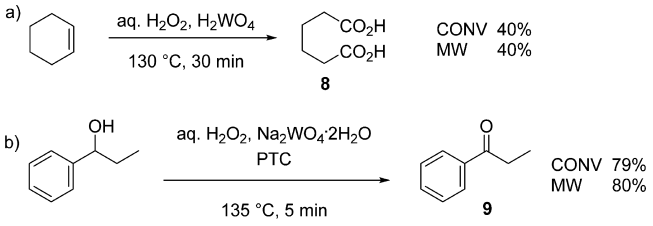
[a]For detailed reaction conditions, see Experimental Section.

protocol where a biphasic system of K_2CO_3 in MeOH was found to be effective.[18] Equimolar amounts of the phenol and base (5 mmol) were reacted with 1.2 equiv of alkyl bromide in EtOH as solvent. For the more volatile bromoethane (bp 38 °C), a temperature of 120 °C had to be selected in order not to exceed the pressure limit of the instruments (20 bar), whereas for 1-bromopropane (bp 71 °C), 140 °C was possible. To approach the set temperature more smoothly in the Monowave 50, the "ramp to temp" setting was selected and virtually identical isolated yields for both experiments were obtained (Scheme 2). In addition, to emphasize that only thermal effects and thus the Arrhenius equation applies, a standard reflux (EtOH at 78 °C) experiment under otherwise identical conditions as described above was performed for the synthesis of propoxybenzene (**7**). After 2 h, an HPLC conversion of 50% to the product was reached. Further heating overnight did not improve the reaction progress (for a kinetic study, see Figure S4 in Supporting Information), and 39% of ether **7** was isolated, indicating that 1-bromopropane is presumably vaporized and therefore removed from the reaction mixture already after 2 h. Consequently, a closed vial approach is beneficial in cases, where volatile reagents are involved.

The direct oxidation of cyclohexene to adipic acid using aqueous hydrogen peroxide (H_2O_2) as a green and inexpensive oxidation reagent (only water is formed as byproduct) and tungstic acid (H_2WO_4) as catalyst using high-temperature microwave chemistry was demonstrated in 2013.[19] If stirring is not sufficient in this biphasic system, H_2O_2 decomposes to H_2O and O_2 which is a highly exothermic process. Furthermore, the rise in temperature from the exotherm increases the rate of decomposition.[19] To prevent these events, a ramp time of 5 min to reach the 130 °C reaction temperature was mandatory. Under these conditions, a temperature overshoot of only 8 °C and a maximum pressure of 11 bar was experienced (for the heating profiles, see Figure S5 in Supporting Information) and adipic acid (**8**) was isolated in 40% after heating for 30 min (Scheme 3a). A similar protocol was applied for the oxidation of the secondary alcohol 1-phenyl-1-propanol to propiophenone (**9**); however, 1 mol % of the phase-transfer catalyst (PTC) methyltrioctylammonium hydrogen sulfate was necessary (Scheme 3b).[20] Initially, a 3 min ramp was tested, but a rapid temperature increase, resulting in an overshoot of 22 °C, was experienced accompanied by a pressure rise (for the

DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788–11801

Scheme 3. Oxidation Reactions[a]



[a]For detailed reaction conditions, see Experimental Section.

Monowave 50 heating profiles, see Figure S6 in Supporting Information). Therefore, also the 5 min ramp was applied and **9** could be generated successfully.

For the Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate, we adapted the original undergraduate laboratory protocol[21] to a microwave-heated version. Toluene was employed as solvent, and 1 mol % of β-alanine was used as catalyst. After 8 min at 150 °C (AFAP), 75% of cinnamic ester **10** was isolated under microwave conditions and 73% when performed under identical conditions in the Monowave 50 instrument (Scheme 4). Also in this case a conventional reflux experiment was conducted: after 2 h, full conversion was achieved and 70% of product **5** was isolated (for a kinetic study, see Figure S7 in Supporting Information).

Performing a Grignard reaction in a microwave reactor is not a trivial affair, because arcing phenomena of magnesium turnings during the formation of the Grignard reagent may occur.[22] For this very reason, no direct comparison of microwave and conventional sealed vial heating in the Monowave 50 reactor was attempted. The Grignard reaction of bromobenzene and ethyl benzoate to form triphenylmethanol (**7**) was therefore only performed in the Monowave 50 instrument (Scheme 5), with conditions adapted from previously published work using microwave conditions.[17] The generation of the Grignard reagent **11** was performed in dry THF as solvent, taking advantage of the higher boiling point compared to traditional Et_2O. After cooling, ethyl benzoate was added to the vial containing phenylmagnesium bromide (**11**), and the reaction mixture was further heated for an additional 15 min at 85 °C to provide triphenylmethanol (**12**) in 58% isolated yield. This reaction showcases one of the few examples where microwave heating cannot be generally applied, and thus the conventionally heated sealed vial reactor proved to be the better solution.

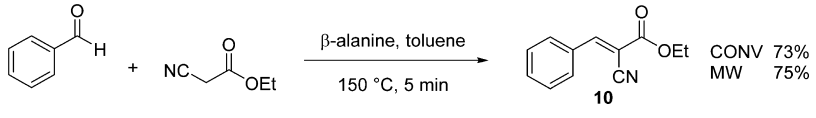
A more advanced example represents the generation of a derivative of a pyrazole-based NFAT transcription factor regulator, which, due to cost-efficiency reasons for educational laboratory courses, is a modification of a three-step microwave protocol originally developed for the synthesis of a related amide analogue (Scheme 6).[23] The first step implements the generation of pyrazole **14** from hydrazine **13** and acetylacetone. 4-Nitrophenylpyrazole **14** is then further converted to the corresponding amine **15** via a catalytic transfer hydrogenation employing 2 mol % Pd/C as catalyst and cyclohexene as hydrogen donor. To prevent a temperature overshoot in the Monowave 50 due to the exothermic reaction, a ramp time of 3 min is necessary. The final amidation step involves heating of aromatic amine **15** with carboxylic acid **16** in the presence of phosphorus trichloride (PCl_3), furnishing amide **17** in 50% isolated yield using microwave conditions and 55% in the Monowave 50 reactor. Again, in this three-step synthesis of amide **17** virtually the same isolated yields were obtained for each single step in both the microwave instrument and the conventionally heated Monowave 50.

Medicinal Chemistry Examples. Microwave heating has become a fundamental enabling technology in the pharmaceutical industry, in particular for rapid reaction optimization on laboratory scale and for the fast development of synthetic steps toward the synthesis of APIs (active pharmaceutical ingredients).[2,24] In this context, we herein describe rapid process-intensified synthetic protocols for the synthesis of olanzapine (**18**), imatinib (**19**), and glibenclamide (**20**), approved drugs of high importance for the pharmaceutical industry. The reaction conditions were first optimized employing standard single-mode microwave heating, followed by additionally performing all synthetic steps in the Monowave 50 instrument. Compared to the conventional (often reflux) protocols, a dramatic reduction in reaction times from several days to only a few minutes could be achieved, along with high product yields and simplified overall processes.

Synthesis of Olanzapine. Olanzapine or zyprexa, a thienobenzodiazepine, is a second generation (atypical) antipsychotic agent which is prescribed for the treatment of schizophrenia and bipolar disorder.[25] It was developed and launched in 1996 by Eli Lilly and is still among the top-ten best-selling drugs and generics.[26] Albeit different synthetic approaches toward the molecule have been reported in the literature,[25] we decided to adapt the continuous flow route deployed by Kirschning and co-workers (Scheme 7).[27]

For the initial Buchwald–Hartwig reaction involving aryl iodide **21** and 2-aminothiophene **22**, different Pd catalysts, two metal chelating ligands (XPhos and Xantphos), and organic and inorganic bases were screened. It was found that selectivity is highly dependent on the catalyst and ligand system. The best results concerning conversion and selectivity could be achieved by using $Pd(OAc)_2$ as a catalyst, Xanthphos as a ligand, and sterically hindered DBU as base. After heating at 130 °C for 10 min and filtration through a plug of silica, intermediate **23** could be directly used for the next step, the reduction of the NO_2 group. For this purpose, the hydrazine-mediated reduction catalyzed by in situ-formed iron oxide nanocrystals was employed.[14] Workup involved simple filtration through a plug of silica, providing aniline **24** in 96% product yield and in sufficient purity for the subsequent step. Gratifyingly, the acid-promoted cyclization of aniline **24** to benzodiazepine **25** proceeded smoothly following the published protocol.[27] Heating a solution of compound **24** under acidic conditions

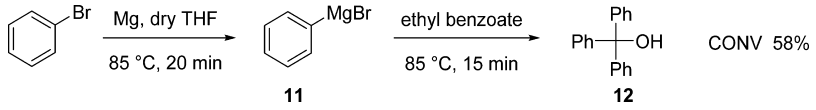
Scheme 4. Knoevenagel Condensation of Benzaldehyde and Ethyl Cyanoacetate[a]



[a]For detailed reaction conditions, see Experimental Section.

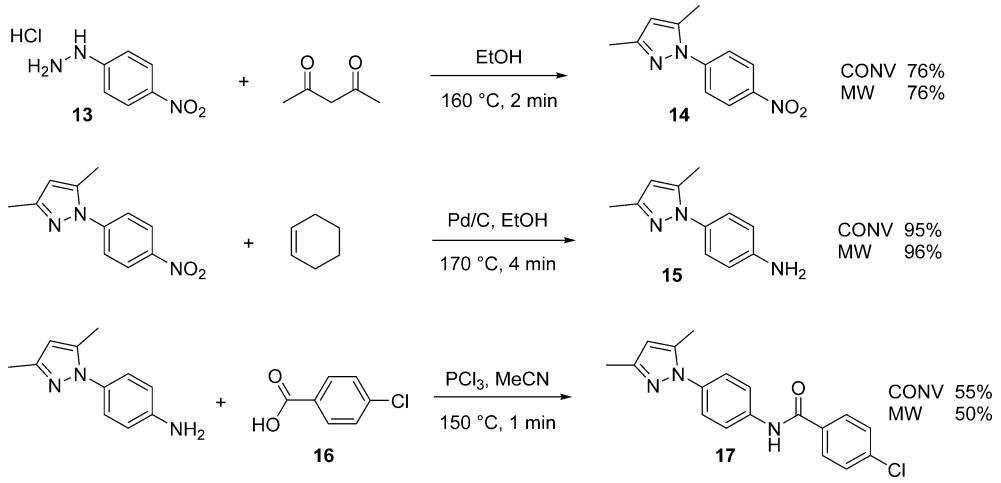
DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788–11801

Scheme 5. Synthesis of Triphenylmethanol via the Grignard Reaction[a]



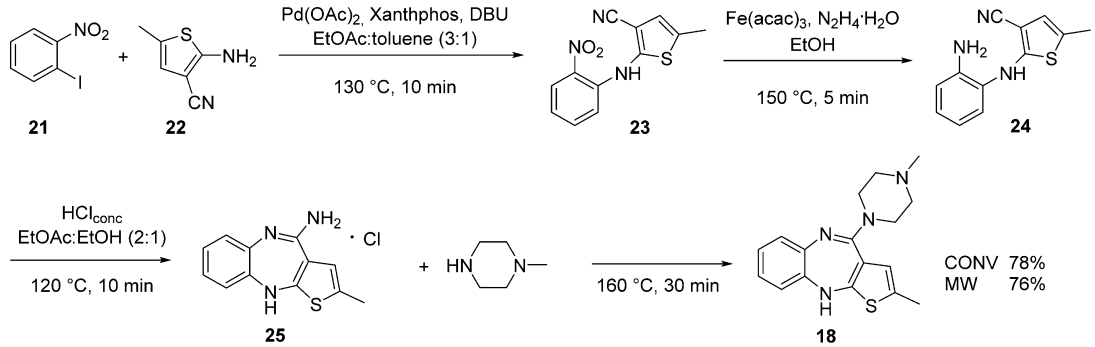
[a]For detailed reaction conditions, see Experimental Section.

Scheme 6. Three-Step Synthesis of Amide 17[a]



[a]For detailed reaction conditions, see Experimental Section.

Scheme 7. Synthesis of Olanzapine 18[a]



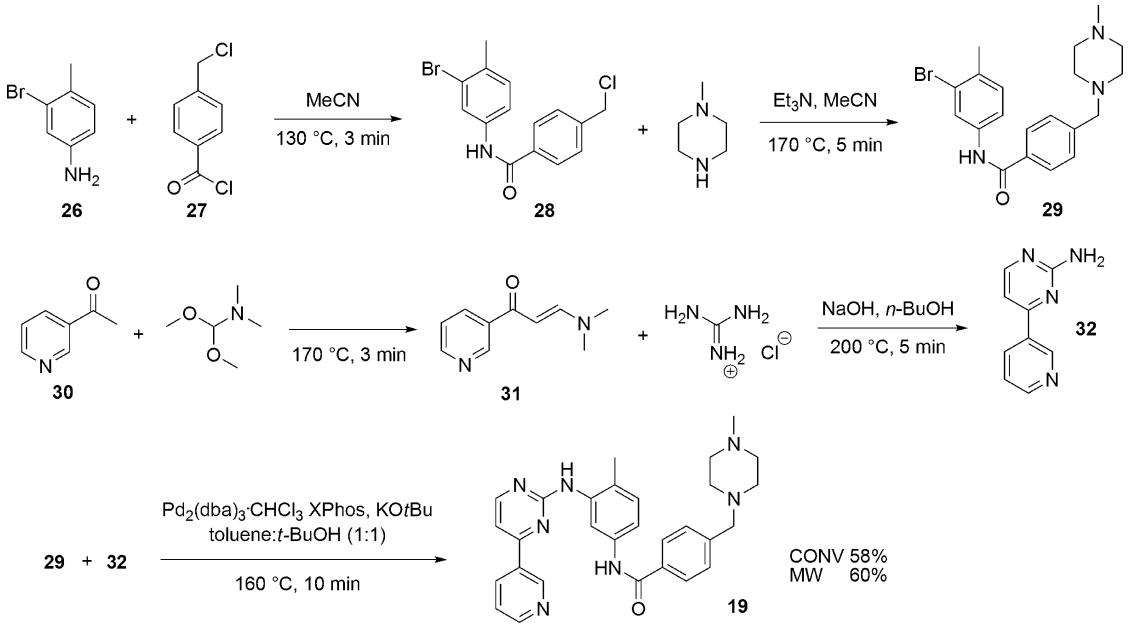
[a]For detailed reaction conditions, see Experimental Section.

at 120 °C for 10 min led to full conversion. For the final reaction step, the batch protocol of Kirschning was adapted to microwave conditions. In our hands, employing $BF_3{\cdot}Et_2O$ as Lewis acid catalyst[27] in EtOH at various temperatures and reaction times mainly resulted in hydrolyzation of **25** to the corresponding diazepinone. Finally, it was found that simply heating of intermediate **25** in neat *N*-methylpiperazine at 160 °C for 30 min and subsequent purification by flash chromatography provided pure olanzapine (**18**) in 96% yield. Performing the four-step synthesis of **18** in the Monowave 50 using identical conditions and instrument settings as for the MW experiments resulted in a virtually identical isolated overall yield of olanzapine.

Synthesis of Imatinib. Imatinib (**19**), the API in the drug Gleevec, is an anticancer agent which is used for the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumor (GISTs).[28] It has proven to be a popular target drug for synthetic chemistry; thus, several processes have been published.[29] We essentially used the synthetic route published by Ley and co-workers[29b] but had to replace some of the original procedures with protocols more compatible with microwave synthesis (see Scheme 8). The building blocks **29** and **32** for the final coupling step were synthesized via two different synthetic routes. For the initial amidation step toward building block **29**, commercially available aniline **26** and acyl chloride **27** were subjected to microwave heating in MeCN for 3 min at 130 °C. After a simple extraction, the condensation product **28** was obtained in 91% yield with >99% purity (HPLC). Running the exothermic reaction in the Monowave 50 reactor and applying the same settings as in the microwave instrument (AFAP mode) led to a significant temperature overshoot of 25 °C (see Figure S8 in Supporting Information). Nevertheless, the amidation remained clean and **28** could be isolated in very similar yields and high purity. Full conversion of benzylic chloride **28** to **29** was obtained by reaction with 3 equiv of *N*-methylpiperazine and 3 equiv of triethylamine at 170 °C for 5 min. To further simplify the protocol, both steps could be performed as a sequential one-pot reaction, and after

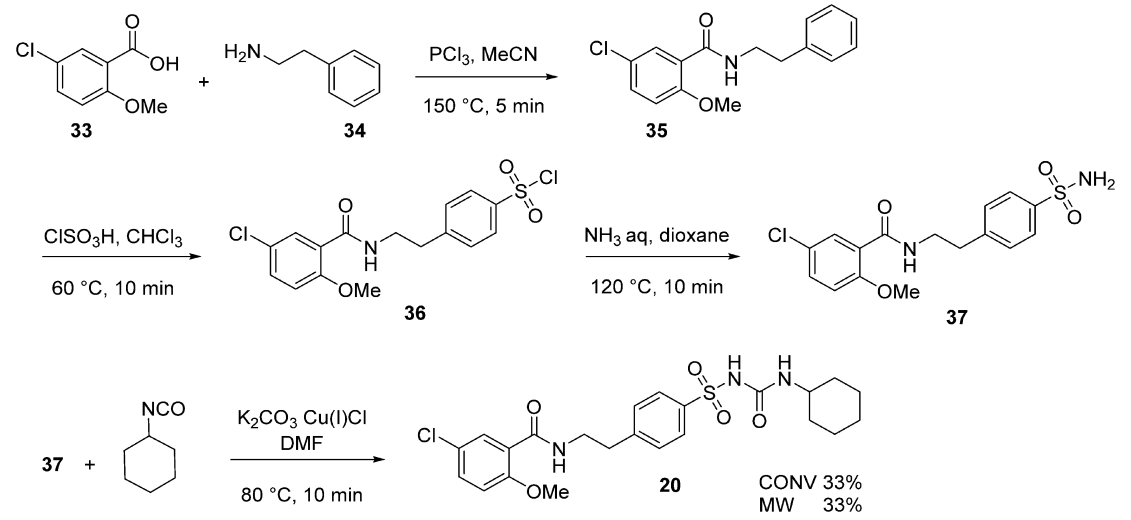
DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788−11801

Scheme 8. Synthesis of Imatinib 14[a]



[a]For detailed reaction conditions, see Experimental Section.

Scheme 9. Synthesis of Glibenclamide (20)[a]



[a]For detailed reaction conditions, see Experimental Section.

crystallization from water, **29** was obtained in 93% overall yield. Although amine **32** is commercially available, it was readily synthesized starting from acetylpyridine (**30**) and DMFDMA within a few minutes.[29,30] This condensation was performed under neat conditions due to side-product formation upon reaction with the solvent; e.g., in the case of MeOH, >30% of nicotinic acid methyl ester was detected by GC-MS. Clean and complete condensation of **31** producing the heterocyclic key intermediate **32** was obtained using guanidine hydrochloride, NaOH as base, and *n*-BuOH as solvent at 200 °C within 5 min.

Crystallization from ice/water provided **32** in 70% yield and sufficient purity for the final step. Intermediates **29** and **32** were coupled via a Buchwald–Hartwig reaction using $Pd_2(dba)_3$ with XPhos as catalyst–ligand system according to the Ley protocol.[29b] For reaction optimization, a number of different bases and solvent mixtures were tested. Performing the reaction in the presence of the commonly employed base Cs_2CO_3 caused stirring problems, and the coupling was almost completely suppressed. KO*t*-Bu was found to be a more suitable base, and in toluene/*t*-BuOH (1:1) as solvent mixture complete conversion to **19** (HPLC) in high selectivity was achieved. For the Buchwald–Hartwig coupling, a 3 min ramp to reach and keep the set target temperature of 160 °C was necessary in the Monowave 50, because under AFAP conditions a temperature overshoot of ca. 20 °C was experienced. Pure imatinib (**19**) was obtained after automated flash chromatography. While the yield of the last step was similar to that described in the flow procedure (69% vs 71%),[29b] the overall yield could be increased significantly (32% vs 58%).

Synthesis of Glibenclamide. Glibenclamide or glyburide is a hypoglycemic agent, which decreases the blood sugar level;

DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788–11801

therefore, it is used in the treatment of diabetes mellitus type II.[31] We first transformed the synthetic route reported by Velingkar and co-workers[32] from conventionally heated open-vessel to sealed-vessel microwave conditions and were able to significantly reduce reaction times from many hours down to several minutes (Scheme 9). For the initial amidation step leading to amide **35**, the original method was slightly modified. Instead of a two-step procedure including a preceding acid chloride formation of carboxylic acid **33** and subsequent amidation with **34**, we applied the one-step protocol already described in Scheme 6 employing phosphorus trichloride as reagent. Isolation by simple extraction provided pure **35** in 95% yield. Intermediate **36** was obtained in high purity (HPLC) and 88% yield by sulfonation of **35** using chlorosulfonic acid as sulfonation agent and $CHCl_3$ as solvent within 10 min at 60 °C. The subsequent formation of sulfonamide **37** was performed with NH_4OH as amination reagent and dioxane as solvent. Isolation by extraction provided sulfonamide **37** in 68% yield. For the last step, the synthesis of sulfonylurea glibenclamide (**20**), we followed a protocol that was originally performed at room temperature for 24 h employing Cu(I)Cl as catalyst.[33] Using 0.5 equiv of K_2CO_3, 2.4 equiv of cyclohexyl isocyanate, and heating at 80 °C for 10 min, 80% conversion and a 54% isolated yield of **20** could be obtained. Performing the four-step synthesis of **20** in the Monowave 50 reactor using exactly the same reaction conditions and instrument settings as in the microwave instrument provided glibenclamide (**20**) in exactly the same overall yield (see Scheme 9).

CONCLUSION

In summary, we have demonstrated the design and construction of a conventionally heated sealed-vessel reactor (Monowave 50) that is capable of mimicking many of the features common to modern single-mode microwave reactors with respect to heating and cooling efficiency, temperature, and pressure monitoring and the ability to efficiently agitate the reaction mixture in a cylindrical vessel using magnetic stirring. Similar to a standard sealed-vessel microwave instrument, reaction temperature, and time (hold time) is programmed via a graphical interface, with vessel handling (sealing, opening, introduction to the cavity) all being very similar to a standard microwave instrument. Although heating and cooling cycles are somewhat slower in the new device compared to a standard microwave instrument (leading to extended processing times), no direct impact on the outcome of the investigated chemical transformations in terms of conversion, selectivity, or purity profiles could be observed. Temperature overshoots as a result of exothermic reactions can typically be overcome by adding a ramp time to the set temperature. On the basis of conductive heating principles, the heating efficiency of the reaction mixture/solvent is not dependent on its dielectric properties; thus, nonpolar solvents can also be employed conveniently in this reactor. In addition, the main advantages of microwave heating, such as superheating of reaction mixtures above their boiling points accompanied by faster reaction rates, and excellent control over reaction temperature and pressure, are all duplicated with the new reactor. Therefore, sealed-vessel microwave conditions on laboratory scale (2−6 mL reaction volume, 250 °C, 20 bar) can easily be mimicked in a reactor of much reduced complexity, smaller footprint (no compressed air required), and lower cost. It can thus be argued that in both teaching and research laboratories this technology will be very useful, providing a simplified and more affordable solution for carrying out sealed-vessel microwave experiments.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were recorded on a 300 MHz instrument. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. GC-MS spectra were recorded using a GC coupled with a DSQ II (EI, 70 eV). A HP5-MS column (30 m × 0.250 mm × 0.25 μm) was used with helium as carrier gas (1 mL min^{-1} constant flow). The injector temperature was set to 280 °C. After 1 min at 50 °C, the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 4 min. The MS conditions were as follows: positive EI ionization, ionization energy 70 eV, ionization source temperature 280 °C, emission current 100 μA, full-scan-mode. GC-FID analysis was performed on a GC with a flame ionization detector using a HP5 column (30 m × 0.250 mm × 0.025 μm). After 1 min at 50 °C, the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 4 min. The detector gas for the flame ionization was H_2 and compressed air (5.0 quality). Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 μm) at 37 °C using mobile phase A (water/MeCN 90:10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.5 mL min^{-1}. The following gradient was applied: linear increase from solution 30% B to 100% B within 10 min. LC-MS analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 μm) at 37 °C using mobile phases A (water/MeCN 90:10 (v/v) + 0.1% HCOOH) and B (MeCN + 0.1% HCOOH) at a flow rate of 0.6 mL min^{-1}. The following gradient was applied: linear increase from solution 30% B to 100% B in 17 min, hold at 100% solution B for 4 min. HRMS analysis was performed on a TOF LC/MS instrument using APCI in positive mode. Melting points were obtained on a standard melting point apparatus in open capillary tubes. Microwave irradiation experiments were carried out in a Monowave 300 single-mode microwave reactor using 10 mL borosilicate glass vials. The reaction temperature was monitored by an external infrared sensor (IR) that was housed in the side-walls of the microwave cavity, measuring the surface temperature of the reaction vessel. Reaction times refer to hold times at the temperature indicated, not to total irradiation times. All previously optimized syntheses were additionally carried out in a Monowave 50 reactor[11] using 10 mL borosilicate glass vials with silicone caps. The temperature was monitored by an external contact sensor placed at the cavity bottom, measuring the surface temperature of the reaction vessel (Figure 1). All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification. Products were characterized by ^{1}H NMR and identified by comparison of the spectra with those reported in the literature. All compounds synthesized herein, except for compounds **15** and **17**, are known in the literature. Proof of purity was obtained by ^{1}H NMR, GC-FID, and HPLC-UV spectroscopy.

The experimental procedures given below refer to syntheses performed in the Monowave 50. The experiments have additionally been performed in a single-mode microwave reactor under identical conditions (temperature and hold time), unless otherwise stated.

2-Methylbenzimidazole (1). Into a 10 mL process vial, equipped with a stir bar, were placed *o*-phenylenediamine (10 mmol, 1.08 g) and 2 mL of acetic acid. The vial was closed, and the reaction mixture was heated to 200 °C with a 5 min ramp and 600 rpm stirring speed and was then kept at this temperature for further 3 min. After cooling, AcOH was removed under reduced pressure, and the product was precipitated using a saturated K_2CO_3 solution and further extracted with EtOAc. The organic phase was dried over Na_2SO_4 followed by evaporation of EtOAc under reduced pressure. After drying overnight at 50 °C, 2-methylbenzimidazole was obtained as pink solid in 93% yield (1.23 g) and >99% purity (HPLC at 215 nm): mp 178−180 °C (lit.[8] 177−178 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.20 (brs,

DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788−11801

1H), 7.44 (brs, 2H), 7.13−7.07 (m, 2H), 2.48 (s, 3H). The spectral data are in agreement with the previously published values.[8]

***trans*-Cinnamic Acid (2).** Into a 10 mL process vial, equipped with a stir bar, were placed benzaldehyde (4 mmol, 410 μL), malonic acid (6 mmol, 624 mg), piperidine (6 mmol, 590 μL), and 1 mL of EtOH. The vial was closed, and the reaction mixture was heated to 140 °C with a 3 min ramp and 1200 rpm stirring speed and was then kept at this temperature for further 10 min. After cooling, the reaction mixture was poured into water and acidified under agitation by the addition of 1 M HCl. The resulting slurry was cooled in an ice-bath for 1 h, after which the precipitate was isolated by filtration and washed with cold water. The product was dried overnight at 50 °C, and **2** was obtained in 78% yield and >99% purity (HPLC at 215 nm): mp 136−137 °C (lit.[8] 136−138 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.42 (brs, 1H), 7.70−7.67 (m, 2H), 7.60 (d, J = 16.1 Hz, 1H), 7.43−7.39 (dd, J = 6.6, 3.7 Hz, 3H), 6.54 (d, J = 16.0 Hz, 1H). The spectral data are in agreement with the previously published values.[8]

Aniline (3). Into a 10 mL process vial, equipped with a stir bar, were placed nitrobenzene (1 mmol, 103 μL), 1.25 mL of MeOH, 125 μL of a 0.02 M stock solution of Fe(acac)$_3$ in MeOH (0.25 mol % catalyst loading), and 1.8 equiv of $N_2H_4{\cdot}H_2O$ (1.8 mmol, 88 μL). The vial was closed, and the reaction mixture was heated at 150 °C for 5 min with 600 rpm stirring speed. After cooling, the solvent was evaporated under reduced pressure, and the crude mixture was dissolved in EtOAc and filtered through a plug of silica gel. After evaporation of EtOAc, pure aniline was obtained in 98% (91 mg) isolated yield and >99% purity (HPLC at 215 nm). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23−7.16 (m, 2H), 6.82−6.77 (m, 1H), 6.72 (dd, J = 8.5, 1.0 Hz, 2H), 3.52 (brs, 2H). The spectral data are in agreement with the previously published values.[8]

(9*R*,10*S*,11*R*,15*S*)-9,10-Dihydro-9,10-[3,4]furanoanthracene-12,14-dione (4). Into a 10 mL process vial, equipped with a stir bar, were placed anthracene (2.45 mmol, 437 mg), maleic anhydride (2.45 mmol 242 mg), and 2 mL of toluene. The vial was closed, and the reaction mixture was heated at 200 °C for 5 min with 600 rpm stirring speed. After cooling, the reaction mixture was further cooled in a refrigerator (∼5 °C) for 3−4 h to enable complete crystallization of the cycloaddition product. The precipitate was filtered, washed with cold toluene, and dried at 50 °C to provide 596 mg (88%) of the colorless product in 97% purity (HPLC at 215 nm): mp 267−268 °C (lit.[8] 265−266 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51−7.45 (m, 2H), 7.37−7.31 (m, 2H), 7.23−7.15 (m, 4H), 4.88 (s, 2H), 3.66−3.65 (m, 2H). The spectral data are in agreement with the previously published values.[8]

2-Chloro-1-(4-methoxyphenoxy)-4-nitrobenzene (5). Into a 10 mL process vial, equipped with a stir bar, 1,2-dichloro-4-nitrobenzene (1 mmol, 191 mg) and 1.1 equiv of 4-methoxyphenol (1.1 mmol, 136 mg) were dissolved in 2 mL of DMA. After the addition of 1.5 equiv of K_2CO_3 (Sigma-Aldrich 347825, ∼325 mesh, 1.5 mmol, 207 mg), the vial was closed and the reaction mixture was heated at 150 °C for 10 min with 600 rpm stirring speed. After cooling, the reaction mixture was transferred to an Erlenmeyer flask and 2 mL of water were added slowly while stirring the reaction mixture vigorously. A precipitate was formed which was intensified by scratching with a glass rod. After further 1 h stirring in the ice-bath, the precipitate was filtered and washed with cold water. Drying overnight at 50 °C gave **5** as yellow solid in 83% yield (232 mg) and 99% purity (HPLC at 215 nm): mp 97−99 °C (lit.[8] 91−93 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (d, J = 2.8 Hz, 1H), 8.15 (dd, J = 9.2, 2.8 Hz, 1H), 7.21−7.15 (m, 2H), 7.09−7.03 (m, 2H), 6.90 (d, J = 9.2 Hz, 1H), 3.79 (s, 3H). The spectral data are in agreement with the previously published values.[8]

4-Nitrophenetol (6). Into a 10 mL process vial, equipped with a stir bar, were placed 4-nitrophenol (5 mmol, 696 mg), K_2CO_3 (5 mmol, 691 mg), bromoethane (6 mmol, 448 μL), and 1.5 mL of EtOH. The vial was closed, and the reaction mixture was heated to 120 °C with a 5 min ramp and 600 rpm stirring speed and was then kept at this temperature for further 10 min. After cooling, the contents of the vial were transferred to a separatory funnel and partitioned between diethyl ether (15 mL) and 2% aqueous NaOH (15 mL). The aqueous layer was again extracted twice with diethyl ether (25 mL). The organic layers were then combined, dried over $MgSO_4$, and concentrated in vacuo. The product was obtained as beige solid in 74% yield (618 mg) and ≥99% purity (HPLC at 215 nm). MW procedure: Heating at 120 °C for 10 min without ramp, 75% yield, mp 62−63 °C (lit.[16b] 60 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 9.3 Hz, 2H), 6.95 (d, J = 9.3 Hz, 2H), 4.15 (q, J = 7.0 Hz, 2H), 1.48 (t, J = 7.0 Hz, 3H). The spectral data are in agreement with the previously published values.[16b]

Propoxybenzene (7). Into a 10 mL process vial, equipped with a stir bar, were placed phenol (5 mmol, 471 mg), K_2CO_3 (5 mmol, 691 mg), 1-bromopropane (6 mmol, 545 μL), and 1.5 mL of EtOH. The vial was closed, and the reaction mixture was heated to 140 °C with a 3 min ramp and 600 rpm stirring speed and was then kept at this temperature for further 5 min. After cooling, the contents of the vial were transferred to a separatory funnel and partitioned twice between diethyl ether (15 mL) and 2% aqueous NaOH (15 mL). The aqueous layer was again extracted twice with diethyl ether (25 mL). The organic layers were then combined, dried over $MgSO_4$, and concentrated in vacuo. The product was obtained as colorless oil in 62% yield (422 mg) and 98% purity (HPLC at 215 nm). MW procedure: Heating at 140 °C for 5 min without ramp, 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.29 (m, 2H), 6.99−6.91 (m, 3H), 3.95 (t, J = 6.6 Hz, 2H), 1.90−1.79 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H). The spectral data are in agreement with the previously published values.[34]

Adipic Acid (8). Into a 10 mL process vial, equipped with a stir bar, were placed cyclohexene (4 mmol, 406 μL), 4.4 equiv H_2O_2 (25% aqueous, 2.2 mL), and 1 mol % of tungstic acid (0.04 mmol, 10 mg). The vial was closed, and the reaction mixture was heated to 130 °C with a 5 min ramp and 800 rpm stirring speed and was then kept at this temperature for further 30 min. After cooling, the contents of the vial were transferred to a round bottomed flask and the residue in the vial was washed into the flask with MeCN. The liquid was removed under reduced pressure at 70 °C, and the solid crude product was dried at 50 °C. The product was washed with ca. 5 mL cold 1 N HCl and dried overnight at 50 °C to obtain adipic acid as colorless solid in 40% yield (234 mg). MW procedure: 40% yield, mp 148−149 °C (lit.[19] 151−152 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.02 (brs, 2H), 2.21 (t, J = 6.4 Hz, 4H), 1.52−1.47 (m, 4H). The spectral data are in agreement with the previously published values.[19]

Propiophenone (9). Into a 10 mL process vial, equipped with a stir bar, were placed 1-phenyl-1-propanol (4 mmol, 548 μL), 4.4 equiv H_2O_2 (25% aqueous, 2.2 mL), 1 mol % of sodium tungstate dihydrate (0.04 mmol, 13 mg), and 1 mol % of methyltrioctylammonium hydrogen sulfate (0.04 mmol, 19 mg). The vial was closed, and the reaction mixture was heated to 135 °C with a 5 min ramp and 800 rpm stirring speed and was then kept at this temperature for further 5 min. After cooling, the reaction mixture was extracted with diethyl ether (3 × 5 mL). To remove any peroxides, the organic phase was washed with a saturated solution of $NaHSO_3$ (2 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give the product as yellow oil in 79% yield (424 mg) and 97% purity (HPLC at 215 nm). MW procedure: 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00−7.97 (m, 2H), 7.60−7.54 (m, 1H), 7.50−7.44 (m, 2H), 3.02 (q, J = 7.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H). The spectral data are in agreement with the previously published values.[35]

α-Cyanocinnamic Acid Ethyl Ester (10). Into a 10 mL process vial, equipped with a stir bar, were placed benzaldehyde (5 mmol, 505 μL), ethyl cyanoacetate (5 mmol, 534 μL), 1 mol % of β-alanine (0.05 mmol, 4.5 mg), and 2.5 mL of toluene. The vial was closed, and the reaction mixture was heated at 150 °C for 8 min with 600 rpm stirring speed. After cooling, the solvent was evaporated and 5 mL of cold EtOH added. Upon stirring, the product precipitated. The precipitate was isolated by filtration and washed with cold water. The product was dried overnight in a desiccator and was obtained as a colorless solid in 73% yield (1.38 g) and 99% purity (HPLC at 215 nm). MW procedure: 80% yield, mp 48−49 °C (lit.[21] 48−49 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.02−8.00 (m, 2H), 7.61−7.49 (m, 3H),

DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788−11801

4.41 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H). The spectral data are in agreement with the previously published values.[21]

Triphenylmethanol (12). Into a 10 mL process vial, equipped with a stir bar, were placed bromobenzene (4 mmol, 420 μL), magnesium turnings (4.1 mmol, 100 mg), and 2 mL of extra dry THF. The vial was ***quickly*** sealed with the cap and heated to 85 °C with a 3 min ramp and 600 rpm stirring speed and was then kept at this temperature for a further 20 min. After cooling, ethyl benzoate (2 mmol, 286 μL) dissolved in 1 mL of extra dry THF was added to the reaction mixture. Again, the vial was ***quickly*** resealed with the cap and heated to 85 °C within a 3 min ramp and 600 rpm stirring speed and was then kept at this temperature for 15 min. After cooling, the reaction mixture was transferred to a round-bottom flask; residues from the vial were washed into the flask with 1 mL of THF. Ten milliliters of 10% HCl was added to dissolve any unreacted magnesium. THF was evaporated, and a yellow slurry remained in the flask, which was extracted with DCM (3 × 25 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from hexane or petroleum ether, to obtain the colorless product in 58% yield (302 mg) and ≥99% purity (HPLC at 215 nm): mp 165−166 °C (lit.[36a] 161−162 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.26 (m, 15H), 2.84 (s, 1H). The spectral data are in agreement with the previously published values.[36b]

3,5-Dimethyl-1-(4-nitrophenyl)-1*H*-pyrazole (14). Into a 10 mL vial, equipped with a stir bar, 4-nitrophenylhydrazine hydrochloride (2 mmol, 379 mg), 1.05 equiv of acetylacetone (2.1 mmol, 215 μL), and 4 mL of EtOH were added. The vial was closed, and the reaction mixture was heated at 160 °C for 2 min with 600 rpm stirring speed. After cooling, the content of the vial was transferred to a separatory funnel, 1 N NaOH (50 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The organic layers were combined and dried over $MgSO_4$. After filtration, the solvent was evaporated and the product was obtained as a yellow/light brown precipitate in 76% yield (330 mg) and ≥99% purity (HPLC at 215 nm). MW procedure: 76% yield, mp 104−105 °C (lit.[37] 101−103 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 9.1 Hz, 2H), 7.69 (d, J = 9.1 Hz, 2H), 6.09 (s, 1H), 2.44 (s, 3H), 2.32 (s, 3H). The spectral data are in agreement with the previously published values.[37]

4-(3,5-Dimethyl-1*H*-pyrazol-1-yl)aniline (15). Into a 10 mL vial, equipped with a stir bar, **14** (1.2 mmol, 261 mg), 2 mol % of Pd/C (10 wt % Pd, 0.024 mmol, 26 mg), 4 mL of EtOH, and 2 equiv of cyclohexene (2.4 mmol, 243 μL) were added. The vial was closed, and the reaction mixture was heated to 170 °C with a 3 min ramp and 800 rpm stirring speed and kept at this temperature for a further 4 min. After cooling, an HPLC for determining the conversion was obtained. If the conversion was <95%, an additional amount of Pd/C was added and the vial was reheated at the same conditions. If the conversion was ≥95%, the content of the vial was filtered through a plug of Celite. The filtrate was evaporated, 1 N NaOH (25 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The organic layers were combined and dried over $MgSO_4$. After filtration, the solvent was evaporated and the product was obtained as a brown, sticky oil in 95% yield (213 mg) and 99% purity (HPLC at 215 nm). MW procedure: Heating at 170 °C for 4 min without ramp, 96% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.06−7.01 (m, 2H), 6.62−6.59 (m, 2H), 5.94 (s, 1H), 5.29 (brs, 2H), 2.15 + 2.13 (ds, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 148.5, 146.8, 139.1, 128.9, 126.1, 113.9, 106.0, 13.8, 12.3. HRMS (APCI): $(M + H)^+$, $([C_{11}H_{13}N_3] + H)^+$: m/z found 188.11810, calcd 188.11822.

4-Chloro-*N*-(4-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)-benzamide (17). Into a 10 mL vial equipped with a stir bar was added 1.1 equiv of 4-chlorobenzoic acid (1.25 mmol, 196 mg). **15** (1.14 mmol, 213 mg) was taken up in 5 mL of MeCN and transferred to the vial. A 1.1 equiv amount of phosphorus trichloride (1.25 mmol, 109 μL) was added dropwise. The vial was closed, and the reaction mixture was heated at 150 °C for 1 min with 600 rpm stirring speed. After cooling, the content of the vial was transferred to a separatory funnel, 1 N NaOH (25 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The organic layers were combined and re-extracted with saturated NaCl (25 mL) and then combined and dried over $MgSO_4$. After filtration, the solvent was evaporated and the product was obtained as a light yellow precipitate which was further washed with a small amount of cold toluene. After filtration, the product was obtained as white precipitate in 55% yield (204 mg) and 97% purity (HPLC at 215 nm). MW procedure: 50% yield, mp 193−194 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (brs, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 6.01 (s, 1H), 2.29 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 149.0, 139.7, 138.2, 137.0, 136.1, 133.1, 129.0, 128.7, 125.4, 121.0, 106.9, 13.5, 12.3. HRMS (APCI): $(M + H)^+$, $([C_{18}H_{16}ClN_3O] + H)^+$: m/z found 326.10570, calcd 326.10547.

5-Methyl-2-(2′-nitrophenylamino)thiophene-3-carbonitrile (23). Into a 10 mL vial equipped with a stir bar were placed 1-iodo-2-nitrobenzene (0.5 mmol, 125 mg), 1 equiv of 2-amino-5-methylthiophene-3-carbonitrile (0.5 mmol, 70 mg), 5 mol % of $Pd(OAc)_2$ (2.5 μmol, 5.5 mg), and 10 mol % of Xanthphos (0.05 mmol, 29 mg). The mixture was suspended in 4 mL of EtOAc/toluene (3:1), and 2 equiv of DBU (1 mmol, 150 μL) was added. The vial was closed, and the reaction mixture was heated at 130 °C for 10 min with 800 rpm stirring speed. After cooling to 55 °C, the crude reaction mixture was washed with ca. 20 mL of water and the aqueous phase extracted with 3 × 15 mL of DCM. The combined organic phases were dried over Na_2SO_4. Filtration over a plug of silica and evaporation of the solvent provided 123 mg (95%) of product as a dark violet-red solid in 97% purity (HPLC at 215 nm). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (brs, 1H), 8.27 (d, J = 8.5, 1.5 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 6.99 (t, J = 7.9 Hz, 1H), 6.80 (s, 1H), 2.49 (s, 3H). The spectral data are in agreement with the previously published values.[27]

2-[(2-Amino]-5-methylthiophene-3-carbonitrile (24). Into a 10 mL vial equipped with a stir bar were placed nitroarene **23** (0.475 mmol, 123 mg), 1.5 mL of absolute EtOH, 2.5 equiv of $N_2H_4{\cdot}H_2O$ (1.8 mmol, 88 μL), and 3 mol % of $Fe(acac)_3$ (756 μL of a 0.02 mM ethanolic solution). The vial was closed, and the reaction mixture was heated at 150 °C for 5 min with 800 rpm stirring speed. After cooling to 55 °C, the solvent was evaporated under reduced pressure, and the crude mixture was dissolved in EtOAc and filtered through a plug of silica gel (10 g). The solvent was evaporated to provide 105 mg (96%) of product in 91% purity (HPLC at 215 nm). The product was pure enough to be used for the next step. **24** in ≥99% purity (HPLC at 215 nm) and 70% yield was obtained by purification by flash chromatography using a 10 g SNAP ULTRA cartridge and petroleum ether/EtOAc (85:15) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (dd, J = 7.8, 1.3 Hz, 1H), 7.11 (td, J = 7.8, 1.4 Hz, 1H), 6.90−6.76 (m, 2H), 6.48 (d, J = 1.3 Hz, 1H), 6.22 (brs, 1H), 3.84 (brs, 2H), 2.28 (d, J = 1.2 Hz, 3H). The spectral data are in agreement with the previously published values.[27]

2-Methyl-10*H*-benzo[*b*]thieno[2,3-*e*][1,4]diazepin-4-amine (25). Into a 10 mL vial equipped with a stir bar were placed aniline **24** (0.45 mmol, 105 mg), 4 mL of EtOAc/EtOH (2:1), and 5 drops of concentrated HCl. The vial was closed, and the reaction mixture was heated at 120 °C for 10 min with 800 rpm stirring speed. After cooling to 55 °C, precipitation by EtOAc, filtration, and additional washing with EtOAc provided 110 mg (91%) of product **25** as a yellow solid in ≥99% purity (HPLC at 215 nm). ^{1}H NMR (300 MHz, MeOD) δ 7.16 (td, J = 7.7, 1.6 Hz, 1H), 7.07 (td, J = 7.6, 1.5 Hz, 1H), 6.96 (dd, J = 7.9, 1.5 Hz, 1H), 6.83 (dd, J = 7.9, 1.4 Hz, 1H), 6.71 (d, J = 1.3 Hz, 1H), 2.33 (d, J = 1.3 Hz, 3H). The spectral data are in agreement with the previously published values.[27]

Olanzapine (18). Into a 10 mL vial equipped with a stir bar were placed benzodiazepine **25** (0.41 mmol, 110 mg) and 3 mL of *N*-methylpiperazine. The vial was closed, and the reaction mixture was heated at 160 °C for 30 min with 800 rpm stirring speed. After cooling to 55 °C, the crude reaction mixture was washed with ca. 30 mL of water and the aqueous phase was extracted with 3 × 20 mL DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using a 25 g SNAP ULTRA cartridge and DCM/MeOH as eluent. Evaporation of the solvent provided 122 mg (96%) of olanzapine in ≥99% purity (HPLC at 215 nm) as off-white crystals.

DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788−11801

MW procedure: 94% yield, mp 192−193 °C (lit.[38] 193−194 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (dd, J = 7.8, 1.4 Hz, 1H), 6.96 (dt, J = 7.5, 1.5 Hz, 1H), 6.88 (dt, J = 7.5, 1.7 Hz, 1H), 6.64 (dd, J = 7.7, 1.1 Hz, 1H), 6.28 (d, J = 1.1 Hz, 1H), 5.30 (s, 1H), 3.68−3.56 (m, 4H), 2.64−2.53 (m, 4H), 2.39 (s, 3H), 2.31 (d, J = 1.1 Hz, 3H). The spectral data are in agreement with the previously published values.[27,38]

***N*-(3-Bromo-4-methylphenyl)-4-(chloromethyl)benzamide (28).** Into a 10 mL vial equipped with a stir bar were placed 3-bromo-4-methylaniline (0.5 mmol, 93 mg), 1.01 equiv of 4-(chloromethyl)-benzoyl chloride (0.505 mmol, 94 mg), and 2 mL of MeCN. The vial was closed, and the reaction mixture was heated at 130 °C for 3 min with 800 rpm stirring speed. After cooling to 55 °C, the crude reaction mixture was washed with approximately 10 mL of 1 N aqueous NaOH, and the aqueous phase was extracted with 3 × 10 mL EtOAc. The combined organic phases were dried over Na_2SO_4. The solvent was evaporated to provide 154 mg (91%) of product **28** in ≥99% purity (HPLC at 215 nm) as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.12 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.67 (dd, J = 8.3, 2.1 Hz, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 1H), 4.85 (s, 2H), 2.32 (s, 3H). The spectral data are in agreement with the previously published values.[29b]

***N*-(3-Bromo-4-methylphenyl)-4-((4-methylpiperazin-1-yl)-methyl)benzamide (29).** Into a 10 mL vial equipped with a stir bar were placed benzamide **28** (0.44 mmol, 149 mg), 3 equiv of *N*-methylpiperazine (1.32 mmol, 146 μL), 3 equiv of triethyl amine (1.32 mmol, 183 μL), and 2 mL of MeCN. The vial was closed, and the reaction mixture was heated at 170 °C for 5 min with 800 rpm stirring speed. After cooling to 55 °C, the crude reaction mixture was poured on ca. 10 mL of water. After crystallization, the product was filtered and washed with additional 10 mL ice-cold water. The white crystals were dried overnight at 50 °C to provide 150 mg (85%) of product **29** in ≥99% purity (HPLC at 215 nm). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.12 (d, J = 2.1 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.67 (dd, J = 8.3, 2.1 Hz, 1H), 7.44 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.6 Hz, 1H), 3.53 (s, 2H), 2.39 (brs, 8H), 2.31 (s, 3H), 2.19 (s, 3H). The spectral data are in agreement with the previously published values.[29b]

4-(Pyridin-3-yl)pyrimidin-2-amine (32). Into a 10 mL vial equipped with a stir bar were placed 3-acetylpyridine (6 mmol, 673 μL) and *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA, 6 mmol, 797 μL). The vial was closed, and the reaction mixture was heated at 170 °C for 3 min with 800 rpm stirring speed. After cooling to 55 °C, the crude reaction mixture was poured on ca. 30 mL of cold diethyl ether. After crystallization, the product was filtered and washed with additional 10 mL of cold diethyl ether. Enone **31** (718 mg, 68% yield) was obtained as red crystals in 93% purity (GC-FID).

Into a 10 mL vial, equipped with a stir bar, were placed enone **31** (1 mmol, 176 mg), 1.1 equiv of guanidine hydrochloride (1.1 mmol, 105 mg), 1.1 equiv of NaOH (1.1 mmol, 44 mg), and 2 mL of *n*-BuOH. The vial was closed, and the reaction mixture was heated at 200 °C for 5 min with 800 rpm stirring speed. After cooling to 55 °C, the crude reaction mixture was poured on ca. 20 mL ice/water. After crystallization, the product was filtered and washed with additional 5 mL cold water and 5 mL of cold EtOAc. The slightly yellow crystals were dried overnight at 50 °C to provide 120 mg (70%) of compound **32** in 97% purity (GC-FID). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.23 (dd, J = 2.3, 0.7 Hz, 1H), 8.68 (dd, J = 4.8, 1.6 Hz, 1H), 8.41−8.35 (m, 2H), 7.53 (ddd, J = 8.0, 4.8, 0.8 Hz, 1H), 7.21 (d, J = 5.2 Hz, 1H), 6.80 (s, 2H). The spectral data are in agreement with the previously published values.[29b]

Imatinib (19). Into a 10 mL vial equipped with a stir bar were placed benzamide **29** (0.41 mmol, 164 mg), 1 equiv of amine **32** (0.41 mmol, 70 mg), 1.4 equiv of KO*t*Bu (0.57 mmol, 65 mg), 8 mol % XPhos (33 μmol, 16 mg), 4 mol % $Pd_2(dba)_3$·$CHCl_3$ (16 μmol, 17 mg), and 2 mL of toluene/*t*-BuOH (1:1). The vial was closed, and the reaction mixture was heated to 160 °C with 3 min ramp and 800 rpm stirring speed and kept for 10 min at this temperature. After cooling to 55 °C, the solvent was evaporated and the residual crude mixture was purified by flash chromatography using a 25 g SNAP ULTRA cartridge and pure methanol as eluent. The desired fractions were combined, and the solvent was evaporated under reduced pressure. The residue was dissolved in ca. 10 mL of DCM and filtered. Evaporation of the solvent provided 143 mg (71%) of imatinib as colorless solid in ≥99% purity (HPLC at 215 nm). MW procedure: Heating at 160 °C for 10 min without ramp, 73% yield, mp 206−209 °C (lit.[29b] 206−207 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 9.28 (s, 1H), 8.99 (s, 1H), 8.68 (d, J = 3.8 Hz, 1H), 8.52−8.46 (m, 2H), 8.08 (s, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.54−7.42 (m, 5H), 7.20 (d, J = 8.3 Hz, 1H), 3.52 (s, 2H), 2.34 (brs, 8H), 2.22 (s, 3H), 2.14 (s, 3H). The spectral data are in agreement with the previously published values.[29b]

5-Chloro-2-methoxy-*N*-(2-phenethyl)benzamide (35). Into a 10 mL vial equipped with a stir bar were placed of 5-chloro-2-methoxy benzoic acid (0.5 mmol, 93 mg), 2 mL of dry THF, 1.1 equiv of 2-phenylethylamine (0.55 mmol, 69 μL), and 1.1 equiv of phosphorus trichloride (0.55 mmol, 49 μL). The vial was closed, and the reaction mixture was heated at 150 °C for 5 min with 800 rpm stirring speed. After cooling to 55 °C, the crude reaction mixture was washed with ca. 20 mL of aqueous NaOH and the aqueous phase was extracted with 3 × 15 EtOAc. The combined organic phases were dried over Na_2SO_4. The solvent was evaporated to provide 138 mg (95%) of product **35** as a light yellow solid in ≥99% purity (HPLC at 215 nm). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 2.8 Hz, 1H), 7.37−7.18 (m, 7H), 6.84 (d, J = 8.8 Hz, 1H), 3.78−3.74 (m, 2H), 3.72 (s, 3H), 2.92 (t, J = 6.7 Hz, 2H). The spectral data are in agreement with the previously published values.[39]

4-[(5-Chloro-2-methoxybenzamido)ethyl]benzenesulfonyl Chloride (36). Into a 10 mL vial equipped with a stir bar were added benzamide **35** (0.48 mmol, 138 mg) and 3 mL of $CHCl_3$. The vial was placed on ice and 0.44 mL sulfonic acid chloride was added dropwise while stirring. The vial was closed. and the reaction mixture was heated at 60 °C for 10 min with 800 rpm stirring speed. After cooling to 55 °C, the crude reaction mixture was washed with ca. 20 mL of a brine/ice mixture and the aqueous phase was extracted with 3 × 15 mL of diethyl ether. The combined organic phases were dried over Na_2SO_4. The solvent was evaporated to provide 171 mg (88%) of product **36** as a light yellow sticky oil in 88% purity (HPLC at 215 nm). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.23 (t, J = 5.5 Hz, 1H), 7.67 (d, J = 2.8 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.49 (dd, J = 8.9, 2.8 Hz, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 8.9 Hz, 1H), 3.80 (s, 3H), 3.53−3.47 (m, 2H), 2.83 (t, J = 7.1 Hz, 2H). The spectral data are in agreement with the previously published values.[39]

4-[(5-Chloro-2-methoxybenzamido)ethyl]-benzenesulfonamide (37). Into a 10 mL vial, equipped with a stir bar, were added sulfonyl chloride **36** (0.44 mmol, 171 mg) and 3 mL of 1,4-dioxane. The vial was placed on ice, and 0.40 mL of concentrated ammonium hydroxide was added dropwise while stirring. The vial was closed, and the reaction mixture was heated at 120 °C for 10 min with 800 rpm stirring speed. After cooling to 55 °C, the crude reaction mixture was washed with ca. 20 mL of a brine/ice mixture and the aqueous phase was extracted with 3 × 15 mL of EtOAc. The combined organic phases were dried over Na_2SO_4. The solvent was evaporated to provide 111 mg (68%) of compound **37** as an off-white solid in 92% purity (HPLC at 215 nm). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (t, J = 5.5 Hz, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 2.8 Hz, 1H), 7.51 (dd, J = 8.9, 2.8 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.32 (brs, 2H), 7.16 (d, J = 8.9 Hz, 1H), 3.82 (s, 3H), 3.55−3.50 (m, 2H), 2.92 (t, J = 7.0 Hz, 2H). The spectral data are in agreement with the previously published values.[40]

Glibenclamide (20). Into a 10 mL vial equipped with a stir bar were added sulfonamide **37** (0.3 mmol, 111 mg), 0.5 equiv of K_2CO_3 (0.15 mmol, 21 mg), and 1.5 mL of DMF. A 2.4 equiv amount of cyclohexyl isocyanate (0.72 mmol, 92 μL) was added dropwise while stirring the reaction mixture. The vial was closed, and the reaction mixture was heated at 80 °C for 10 min with 800 rpm stirring speed. After cooling to 55 °C, the crude reaction mixture was poured on ca. 15 mL of 1 N aqueous HCl solution, and the precipitate was filtered and washed with water. After drying overnight at 50 °C, the crude product was purified by flash chromatography using a 10 g SNAP cartridge and $CHCl_3$/MeOH as eluent. The desired fractions were combined, and the solvent was evaporated under reduced pressure to

DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788−11801

provide 81 mg (54%) of glibenclamide (**20**) as a colorless solid in 98% purity (HPLC at 215 nm). MW procedure: 55% yield, mp 174−175 °C (lit.[41] 168−172 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 2.8 Hz, 1H), 7.85 (d, J = 8.4 Hz, 3H), 7.43−7.36 (m, 3H), 6.88 (d, J = 8.9 Hz, 1H), 6.45 (d, J = 8.0 Hz, 1H), 3.78 (s, 3H), 3.76−3.72 (m, 2H), 3.63−3.54 (m, 1H), 3.03 (t, J = 6.9 Hz, 2H), 1.71−1.55 (m, 5H), 1.30−1.16 (m, 5H). The spectral data are in agreement with the previously published values.[39]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02242.

Additional heating profiles, kinetic experiments, and ^{1}H and ^{13}C NMR spectra of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: do.dallinger@uni-graz.at.
*E-mail: oliver.kappe@uni-graz.at.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279. (b) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945.

(2) (a) *Microwaves in Organic Synthesis*, 3rd ed.; De La Hoz, A.; Loupy, A., Eds.; Wiley-VCH: Weinheim, 2013. (b) Kappe, C. O.; Stadler, A.; Dallinger, D.*Microwaves in Organic and Medicinal Chemistry*, 2nd ed.; Wiley-VCH: Weinheim, 2012. (c) *Microwave Heating as a Tool for Sustainable Chemistry*; Leadbeater, N. E., Ed.; CRC Press: Boca Raton, FL, 2011.

(3) (a) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325. (b) Kappe, C. O.; Dallinger, D. *Mol. Diversity* **2009**, *13*, 71.

(4) For selected reviews covering different fields of microwave chemistry, see: (a) Pedersen, S. L.; Tofteng, A. P.; Malik, L.; Jensen, K. *Chem. Soc. Rev.* **2012**, *41*, 1826. (solid-phase peptide synthesis). (b) Baghbanzadeh, M.; Carbone, L.; Cozzoli, P. D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2011**, *50*, 11312. (nanomaterials). (c) Kempe, K.; Becer, C. R.; Schubert, U. S. *Macromolecules* **2011**, *44*, 5825. (polymer chemistry). (d) Klinowski, J.; Paz, F. A. A.; Silva, P.; Rocha, J. *Dalton Trans.* **2011**, *40*, 321. (materials science). (e) Collins, J. M.; Leadbeater, N. E. *Org. Biomol. Chem.* **2007**, *5*, 1141 (biochemical processes).

(5) For a recent debate on microwave effects in organic synthesis, see: (a) Kappe, C. O.; Pieber, B.; Dallinger, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 1088. (b) Dudley, G. B.; Stiegman, A. E.; Rosana, M. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 7918. (c) Kappe, C. O. *Angew. Chem., Int. Ed.* **2013**, *52*, 7924.

(6) For a review on temperature monitoring in microwave chemistry, see: Kappe, C. O. *Chem. Soc. Rev.* **2013**, *42*, 4977.

(7) The only commercialized example so far employing convective heating of sealed reaction tubes to mimic a microwave experiment is the so-called Q-Tube reactor, a glass pressure reactor with over-pressure release that can be integrated with standard heating devices (for details of the Q-Tube reactor, see: http://www.qlabtech.com). For recently published applications of this technology, see: (a) Blanchard, D.; Cameron, T. S.; Jha, M. *Mol. Diversity* **2013**, *17*, 827. (b) Jha, M.; Edmunds, M.; Lund, K.; Ryan, A. *Tetrahedron Lett.* **2014**, *55*, 5691. (c) Oliverio, M.; Nardi, M.; Costanzo, P.; Cariati, L.; Cravotto, G.; Giofrè, S. V.; Procopio, A. *Molecules* **2014**, *19*, 5599.

(8) Obermayer, D.; Damm, M.; Kappe, C. O. *Chem. - Eur. J.* **2013**, *19*, 15827.

(9) The SiC reactor was inspired by previous research from our group using silicon carbide ceramics in conjunction with microwave reactors: (a) Obermayer, D.; Gutmann, B.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 8321. (b) Gutmann, B.; Obermayer, D.; Reichart, B.; Prekodravac, B.; Irfan, M.; Kremsner, J. M.; Kappe, C. O. *Chem. - Eur. J.* **2010**, *16*, 12182. (c) Review: Kappe, C. O. *Acc. Chem. Res.* **2013**, *46*, 1579.

(10) For the importance of stirring on temperature homogeneity in microwave experiments using cylindrical reaction vessels, see: (a) Hayden, S.; Damm, M.; Kappe, C. O. *Macromol. Chem. Phys.* **2013**, *214*, 423. (b) Obermayer, D.; Damm, M.; Kappe, C. O. *Org. Biomol. Chem.* **2013**, *11*, 4949. (c) Herrero, M. A.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 36.

(11) For details of the Monowave 50 instrument, see: http://www.anton-paar.com/corp-en/products/details/synthesis-reactor-monowave-50.

(12) The ability of a specific solvent to convert microwave energy into heat at a given frequency and temperature is determined by the so-called loss tangent (tan δ), expressed as the quotient, tan $\delta = \varepsilon''/\varepsilon'$, where ε'' is the dielectric loss, indicative of the efficiency with which electromagnetic radiation is converted into heat, and ε' is the dielectric constant, describing the ability of molecules to be polarized by the electric field. In general, solvents used for microwave synthesis can be classified as high (tan δ > 0.5, for example: ethanol, DMSO, methanol, formic acid), medium (tan δ 0.1−0.5, for example: acetic acid, 1,2-dichlorobenzene, NMP, DMF, water), and low microwave absorbing (tan δ < 0.1, for example: chloroform, ethyl acetate, THF, dichloromethane, toluene, hexane). See ref 2 for more details.

(13) Dallinger, D.; Irfan, M.; Suljanovic, A.; Kappe, C. O. *J. Org. Chem.* **2010**, *75*, 5278.

(14) Cantillo, D.; Moghaddam, M. M.; Kappe, C. O. *J. Org. Chem.* **2013**, *78*, 4530.

(15) Dallinger, D.; Lehmann, H.; Moseley, J. D.; Stadler, A.; Kappe, C. O. *Org. Process Res. Dev.* **2011**, *15*, 841.

(16) For laboratory textbooks involving microwave chemistry, see: (a) Leadbeater, N. E.; McGowan, C. B. *Laboratory Experiments Using Microwave Heating*; CRC Press: Boca Raton, 2013. (b) Kappe, C. O.; Dallinger, D.; Murphree, S. S. *Practical Microwave Synthesis for Organic Chemists-Strategies, Instruments, and Protocols*; Wiley-VCH: Weinheim, Germany, 2009. (c) See also: Russell, C. B.; Mason, J. D.; Bean, T. G.; Murphree, S. S. *J. Chem. Educ.* **2014**, *91*, 511.

(17) At the University of Graz, microwave technology has been implemented successfully for many years into several organic chemistry undergraduate and graduate laboratory classes. See for example: Kappe, C. O.; Murphree, S. S. *J. Chem. Educ.* **2009**, *86*, 227 and ref 16b.

(18) Sarju, J.; Danks, T. N.; Wagner, G. *Tetrahedron Lett.* **2004**, *45*, 7675.

(19) Damm, M.; Gutmann, B.; Kappe, C. O. *ChemSusChem* **2013**, *6*, 978 and refs cited therein.

(20) (a) Hulce, M.; Marks, D. W. *J. Chem. Educ.* **2001**, *78*, 66. (b) See also ref 16a.

(21) Eicher, T.; Roth, H. J. *Synthese, Gewinnung und Charakterisierung von Arzneistoffen*; Georg Thieme Verlag: Stuttgart, Germany, 1986; p 52.

(22) (a) Dressen, M. H.; Kruijs, B. H.; Meuldijk, J.; Vekemans, J. A.; Hulshof, L. A. *Org. Process Res. Dev.* **2007**, *11*, 865. (b) Gutmann, B.; Schwan, A. M.; Reichart, B.; Gspan, C.; Hofer, F.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2011**, *50*, 7636.

(23) Glasnov, T. N.; Groschner, K.; Kappe, C. O. *ChemMedChem* **2009**, *4*, 1816.

(24) (a) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Discovery* **2006**, *5*, 51. (b) Alcazar, J.; Oehlrich, D. *Future Med. Chem.* **2010**, *2*, 169. (c) Cao, P.; Leadbeater, N. E. In *Microwave Heating as a Tool for Sustainable Chemistry*; Leadbeater, N. E., Ed.; CRC Press: Boca Raton, FL, 2011; p 73.

(25) (a) Chakrabarti, J. K.; Hotten, T. M.; Tupper, D. E. US5229382(A), Jul 20, 1993. (b) Bhana, N.; Foster, R. H.; Olney, R.; Plosker, G. L. *Drugs* **2001**, *61*, 111.

DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788−11801

(26) Bymaster, F. P.; Calligaro, D. O.; Falcone, J. F.; Marsh, R. D.; Moore, N. A.; Tye, N. C.; Seeman, P.; Wong, D. T. *Neuropsychopharmacology* **1996**, *14*, 87.
(27) Hartwig, J.; Ceylan, S.; Kupracz, L.; Coutable, L.; Kirschning, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9813.
(28) Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. *Nat. Rev. Drug Discovery* **2002**, *1*, 493.
(29) (a) Deadman, B. J.; Hopkin, M. D.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2013**, *11*, 1766. (b) Hopkin, M. D.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2013**, *11*, 1822.
(30) Gorobets, N. Yu.; Yousefi, B. H.; Belaj, F.; Kappe, C. O. *Tetrahedron* **2004**, *60*, 8633.
(31) Lemke, T.; Williams, D. A.; Roche, V. F.; Zito, S. W. *Foye's Principles of Medicinal Chemistry*, 6th ed.; Lippincott Williams & Wilkins: London, 2007.
(32) Velingkar, V. S.; Dandekar, V. D.; Murugananthan, K. *Int. J. Pharm. Pharm. Sci.* **2009**, *1*, 149.
(33) Cervelló, J.; Sastre, T. *Synthesis* **1990**, 221.
(34) Manbeck, G. F.; Lipman, A. J.; Stockland, R. A., Jr.; Freidl, A. L.; Hasler, A. F.; Stone, J. J.; Guzei, I. A. *J. Org. Chem.* **2005**, *70*, 244.
(35) Shen, D.; Miao, C.; Xu, D.; Xia, Ch.; Sun, W. *Org. Lett.* **2015**, *17*, 54.
(36) (a) Lawesson, S.-O.; Yang, N. C. J. *J. Am. Chem. Soc.* **1959**, *81*, 4230. (b) Maekawa, T.; Sekizawa, H.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 7022.
(37) Alberola, A.; Calvo Bleye, L.; González-Ortega, A.; Sádaba, M. L.; Sañudo, M. C. *Heterocycles* **2001**, *55*, 331.
(38) Gao, M.; Shi, Z.; Wang, M.; Zheng, Q.-H. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1953.
(39) Zhao, J.; Li, Z.; Song, S.; Wang, M.-A.; Fu, B.; Zhang, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 5545.
(40) Abbate, A.; Zhang, S.; Van Tassell, B. WO2014/190015, Nov. 27, 2014.
(41) Bergström, C. A. S.; Wassvik, C. M.; Johansson, K.; Hubatsch, I. *J. Med. Chem.* **2007**, *50*, 5858.

DOI: 10.1021/acs.joc.6b02242
J. Org. Chem. 2016, 81, 11788−11801