High-Throughput Microwave-Assisted Organic Synthesis: Moving from Automated Sequential to Parallel Library-Generation Formats in Silicon Carbide Microtiter Plates

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A 48 deep-well microtiter plate system for sealed vessel parallel microwave synthesis is described. The plate consists of a standard 6 × 8 matrix of 48 wells with a maximum working volume of 300 μL and is made out of strongly microwave-absorbing sintered silicon carbide. In combination with an alumina sealing plate equipped with adequate conical bore holes for sample withdrawal, the setup can be used for microwave processing at temperatures up to ∼200 °C and 20 bar of pressure. The microtiter plate setup displays excellent temperature and reaction homogeneity and was used for the generation of a 30-member library of 2-aminopyrimidines.

Introduction

Since the first reports on the use of microwave heating to carry out organic chemical transformations in 1986,[1] more than 3500 articles have been published in the area of microwave-assisted organic synthesis (MAOS).[2−4] In particular, after 2000, the number of publications related to MAOS has increased dramatically to a point where it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale. In many instances, microwave heating under sealed vessel conditions has been shown to dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions compared to conventional synthetic methods.[2−4]

The many advantages of this enabling technology have not only been exploited for organic synthesis[2−4] but have proven particularly valuable in the context of medicinal chemistry/drug discovery projects where speed is often a critical factor.[5] With high-speed microwave processing, many reaction parameters such as reaction temperature and time, variations in solvents, additives and catalysts, or the molar ratios of the substrates can be evaluated in a few hours to optimize the desired chemistry. Compound libraries can subsequently be rapidly synthesized, often using automated robotic formats. In addition, MAOS technology can facilitate the discovery of novel reaction pathways since the extreme reaction conditions attainable by microwave heating sometimes lead to unusual reactivity which cannot always be duplicated by conventional heating.[2−4] This serves to expand "chemical space", in general, and "biologically relevant, medicinal chemistry space", in particular.[5]

In 2001, we introduced the concept of automated sequential microwave-assisted library synthesis employing dedicated single-mode microwave reactors with incorporated robotic vial-handling and liquid-dispensing modules.[6] The typically short reaction times experienced in MAOS (minutes compared to hours) make this approach very attractive if comparatively small compound libraries need to be synthesized (20−100 compounds). In this case, automated sequential processing under high-speed microwave conditions becomes almost as efficient as applying a parallel format using conventional heating. However, if larger compound libraries (>200 compounds) need to be generated, the sequential approach can become impractical since the timesaving aspect of microwave synthesis is diminished by having to irradiate each reaction mixture individually.

Several attempts have therefore been made to perform library syntheses in deep-well microtiter plates using multimode microwave-heating technology, combining the benefits of parallel and microwave processing.[7−13] Early pioneering work[7,8] employed conventional polypropylene microtiter plates using domestic microwave ovens as heating sources. These studies clearly highlighted the problems associated with the use of this technology, namely, the (i) thermal instability of the polypropylene plate under comparatively high-temperature microwave conditions[8,9] and (ii) the formation of significant temperature gradients between individual wells, leading to a nonuniform temperature distribution across the microwave-transparent plates.[8,9] While the issue of temperature stability can be resolved in part by utilizing PTFE (Teflon) or HTPE (high-temperature polyethylene) as plate materials,[9] dealing with transient and static temperature gradients in a setup of this type is a nontrivial affair. Typically, a microwave-absorbing solvent/reaction mixture in a well located on the outside region of the plate will show a significantly lower temperature than the same

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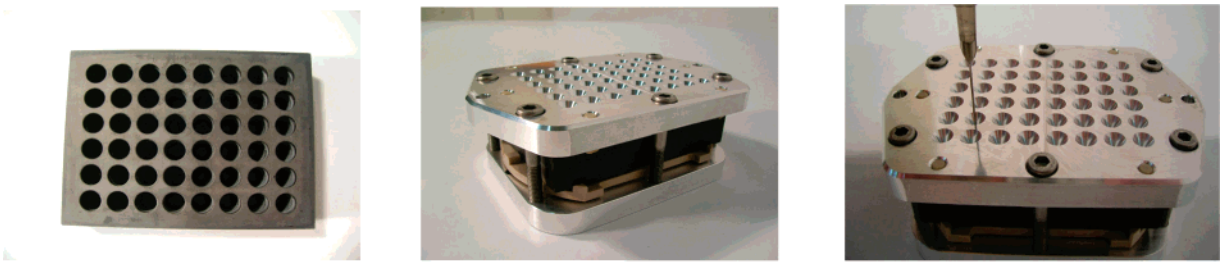


Figure 1. (a) Prototype 48 deep-well microtiter plate (82 × 62.5 × 18 mm) made of sintered silicon carbide. **(b)** Sealed microtiter plate setup (118 × 80 × 46 mm) consisting of the SiC deep-well plate on an alumina base with a PEEK spacer, covered with an alumina top plate with corresponding bore holes for sample withdrawal, and fixed with six stainless steel hex bolts for use in a multimode microwave reactor. For a detailed drawing, see Figure S3 in the Supporting Information. **(c)** Detailed view of the sealing mechanism. A needle is shown penetrating the Ø 1.2 mm hole in the top aluminum sealing plate, the Viton sealing mat, and the PFA foil to reach inside one well.

material located in a well in the middle of the plate when irradiated in a microwave field.[9,10] The lower temperatures seen in the exterior wells are the result of both radiative heat loss from the plate to the ambient air and a lower microwave coupling (wells on the exterior of the microtiter plate do not have neighboring wells containing solvent and thus lack the ability to efficiently couple to the microwave field).[9] These temperature differences may lead to significantly reduced conversions or product purities in some of the wells of the plate.[8−10]

To address these problems, custom-built variations of PTFE microtiter plates were developed[9,11] that contain strongly microwave-absorbing materials such as graphite pellets[9] or high-absorbing liquids[11] located on the outside perimeter of the plate. In a related strategy, deep-well plates that are made of a strongly microwave-absorbing material (carbon-doped Teflon) were recently commercialized.[12] Here, the polymeric material used for the construction of the plates, not the specific solvent/reaction mixture contained in a well, absorbs the microwave energy. This means that the individual wells will be heated by microwave irradiation regardless of the dielectric properties of the reaction mixture. This system has been used successfully for several microwave-assisted parallel processes.[13]

However, a significant limitation of the currently available microtiter plate systems is the fact that none of these parallel set-ups allows MAOS to be performed under sealed vessel conditions in a pressure range similar to what can be attained with single mode reactors (∼20 bar).[3] Therefore, microwave chemistry in microtiter plates has so far been limited to the use of high-boiling solvents under open-vessel conditions[7,8,10,11] or to sealed-vessel reaction conditions that will cause only a small overpressurization (2−4 bar).[13,14] This means that one of the key advantages of controlled microwave heating,[2−4] namely, the ability to superheat low-boiling solvents far above their boiling point, is lost. Furthermore, in the context of library synthesis, optimized protocols that are often obtained with a single-mode microwave reactor in a sequential iterative format cannot be directly adapted to a multimode parallel plate format.

Herein, we describe the development and use of a prototype 48 deep-well microtiter plate for the construction of a 30-member library of 2-aminopyrimidines using sealed-vessel parallel microwave processing. The 6 × 8 deep-well microtiter plate is made of highly temperature resistant silicon carbide and, because of its unique sealing mechanism, can be used at reaction conditions involving pressures of up to 20 bar.

Results and Discussion

Microtiter Plate Development. On the basis of our recent experience using silicon carbide as passive heating element for MAOS,[15] this material was also considered for the construction of a deep-well microtiter plate. Sintered silicon carbide is chemically completely inert, strongly microwave absorbing, and because if its high melting point (∼2700 °C) and very low thermal-expansion coefficient, can be employed at extremely high temperatures.[16] Problems experienced with the thermal stability of conventional polypropylene or other Teflon-based microtiter plates[8−11] can therefore be excluded. For the current prototype, a 82 × 62.5 × 18 mm plate, made by sintering a corresponding green compact of silicon carbide, was employed. The upper surface of the plate contained a standard 6 × 8 matrix of 48 wells with a total filling volume of 410 μL (Figure 1a). The wells are shaped in classical round-bottom design and are dedicated for a maximum working volume of 300 μL.

To allow runs under closed-vessel conditions, an appropriate sealing mechanism was used, consisting of a 10 mm alumina top plate equipped with adequate conical bore holes (Ø 1.2 mm) for sample withdrawal and an attached sealing mat made of Viton Fluoroelastomer (1.0 mm), a disposable 0.3 mm PFA foil to cover the SiC plate, and an alumina base with a PEEK spacer.[17] The assembly is fixed with six stainless steel hex bolts. Finger-tight closure ensures tightness up to 25 bar (Figure 1b). With this setup, it was possible to superheat a range of common solvents (ethanol, water, acetonitrile, THF, and toluene) far above their boiling points without any loss of material. In a representative test run, 300 μL of ethanol, in each of the 48 wells, was heated to a temperature of 180 °C which corresponds to a pressure of ∼25 bar inside the well. Control experiments confirmed that cross-contamination between wells does not occur (see Figure S1 in the Supporting Information).

The plate system shown in Figure 1b is designed in such a way that the resulting crude reaction mixtures are removed by syringe from the individual wells by introducing a needle (Ø < 1.2 mm) through the sealing mechanism shown in Figure 1c, *before* the setup is disassembled. With this method, a typically >80% recovery of the reaction mixture

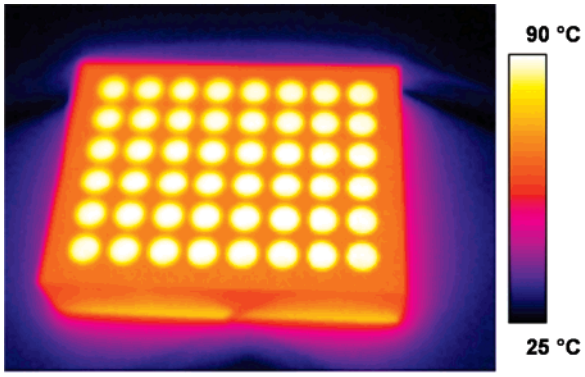


Figure 2. IR thermal image of a silicon carbide microtiter plate containing 300 μL of water in each of the 48 wells exposed to 2.45 GHz microwave irradiation inside a multimode microwave cavity. The recorded average temperature inside the 48 wells after 1 min of irradiation at 300 W was 89.0 °C with a maximum measured deviation between individual wells of 0.3 °C. The average temperature on the surface of the plate outside the wells was measured at 72 °C.

can be achieved using appropriate needles. If required, an even higher recovery (>95%) can be obtained by applying repetitive wash cycles. For operation in a standard multimode microwave reactor, up to four microtiter plate systems ($4 \times 48 = 196$ wells) can be mounted on a dedicated turntable (see Figure S2 in Supporting Information).

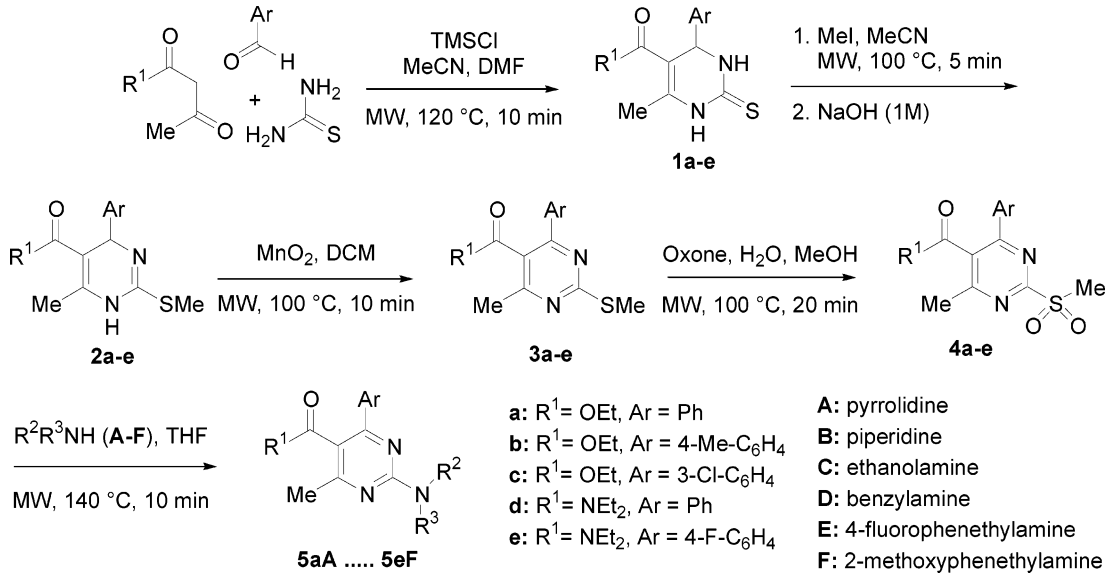
Temperature and Reaction Homogeneity. The temperature homogeneity across microtiter plates exposed to microwave irradiation can be difficult to control (see above).[8−11] Nonetheless, achieving homogeneity with respect to the temperature distribution in individual wells is of critical importance for the success, general applicability, and reproducibility of any parallel library synthesis. With the use of strongly microwave-absorbing silicon carbide as plate material, the microwave absorption characteristics of the individual reaction mixtures contained in the 48 wells are practically irrelevant, since the semiconducting plate itself will absorb microwave energy much stronger than any organic material contained inside the wells. As shown in Figure 2, exposing the silicon carbide plate filled with 300 μL of water in each of the 48 wells to 300 W of microwave irradiation for 60 s leads to a very homogeneous heating of the entire plate, with minimal deviations (<0.3 °C) in the temperatures recorded in the individual water-filled wells. Even when vastly different filling volumes (60−300 μL of water) were employed, the monitored temperature differences between the wells were minimal (<2 °C) (see Figure S4 in the Supporting Information).

In a subsequent series of experiments, we were interested in determining if the excellent *temperature homogeneity* observed for heating the "naked" silicon carbide plate would also translate to *reaction homogeneity* for a chemical transformation using the fully sealed plate setup shown in Figure 1b. For this purpose, we have chosen the acid-catalyzed esterification of benzoic acid with ethanol as a model reaction (EtOH/1 M aq H_2SO_4 = 2:1 v/v). Initial optimization experiments in a single-mode microwave instrument demonstrated that a 47% HPLC conversion (215 nm) can be achieved after 20 min at 140 °C (7 bar). This esterification proved to be somewhat sensitive to the reaction temperature because microwave heating at the reduced temperature of 130 °C for 20 min produced only 37% conversion, whereas processing at 150 °C for the same time period resulted in 58% conversion (See Figure S5 in the Supporting Information). Any significant temperature differences between individual wells of the microtiter plate would therefore translate to differences in conversion. Gratifyingly, by performing the esterification reaction in the sealed microtiter plate (Figure 1b, 300 μL reaction volume) at an internal temperature of 145 °C (surface temperature 130 °C, see discussion below) for 20 min, we found that the conversions in all 48 wells were virtually identical (57−59%, average conversion 57.7%, SD = 0.6; see Figure S6 in the Supporting Information). Similarly, an experiment was devised to investigate the effect of different filling volumes ranging from 0 to 300 μL per well. Again, the data obtained indicate that there is only a small effect of the filling volume on the resulting temperature (and therefore on conversions) in the well (see Figure S7 in the Supporting Information).

For the performance of a reaction under sealed vessel conditions in the setup shown in Figure 1b, the plate system is mounted on a turntable inside a multimode microwave cavity (Figure S2 in the Supporting Information). The reaction temperature is monitored and controlled using the feedback from an IR temperature sensor integrated into the bottom of the cavity that records the bottom surface temperature of the silicon carbide plate. As can be seen in Figure 2, the measured temperatures inside the wells are significantly higher than the temperatures recorded on the surface of the plate by the IR camera. This general phenomenon was seen for all the cases studied, regardless of the solvent employed, with temperature differences ranging from 15 to 20 °C depending on the final temperature range reached. This was additionally confirmed by simultaneously measuring the temperature inside individual wells in the sealed plate setup (Figure 1b) with internal fiber optic probes. In the current prototype design, a calibration factor of 1.11 was derived from comparing internal well temperatures (fiber-optic probes) with the measured plate-surface temperature (IR sensor), and this is used to correlate the measured surface temperature to the actual internal reaction temperature (see Figure S8 in the Supporting Information). By applying this calibration factor, we obtained results for the described benzoic acid esterification reactions performed at 145 °C reaction temperature (monitored plate surface temperature 130 °C) furnishing 58% conversion, which are in acceptable agreement with the data obtained from the single-mode run (58% conversion at 150 °C).

Application Toward Library Synthesis. Having successfully demonstrated the heating homogeneity across the multiwell plate, we were interested in using our prototype plate setup (Figure 1b) for the construction of a 30-member library of 2-aminopyrimidines using solution-phase chemistry. In a recent publication,[18] we have elaborated an efficient and rapid microwave-assisted solution-phase method for the synthesis of 2-amino-4-arylpyrimidine-5-carboxylic acid derivatives of type **5** (Scheme 1). The five-step linear protocol involves an initial Biginelli multicomponent reaction leading to dihydropyrimidine-2-thiones **1**, which are subse-

Scheme 1



quently S-alkylated with methyl iodide (**1** → **2**). The resulting 2-methylthiodihydropyrimidines **2** are sequentially oxidized first with manganese dioxide (**2** → **3**) and then with oxone to provide 2-methylsulfonyl-pyrimidines **4** which serve as excellent precursors for the generation of a variety of 2-aminosubstituted pyrimidines via displacement of the reactive sulfonyl group with amines (**4** → **5**).[18]

All steps in the sequence were conducted using automated sequential microwave-assisted processing in a single-mode reactor.[18] Using this technology, we generated a set of 5 sulfones (**4a**−**e**) from the appropriate building blocks (Scheme 1), and subsequently, they were reacted with six primary and secondary aliphatic amines **A**−**F** to furnish the desired 2-aminopyrimidine library **5**. Out of the full possible matrix of 30 aminopyrimidine products **5aA**−**5eF**, two subsets were previously generated including six products derived from treatment of sulfone **4a** with amines **A**−**F** and an additional four library members obtained by reaction of sulfones **4b**−**e** with amine **A**.[18] The goal of the present work was to generate the full 30-member 2-aminopyrimidine library **5aA**−**5eF** in a single microwave irradiation experiment using microtiter plate technology (THF, 145 °C, ∼7 bar) and to compare the results with the previously obtained data employing sequential library synthesis.[18]

Before embarking on the use of the silicon carbide microtiter plates for library synthesis, we felt that an important aspect needed to be clarified first. From the heating experiments described above and from our previous studies involving silicon carbide passive heating elements,[15] it is very evident that the silicon carbide plate itself will strongly absorb microwave energy and will subsequently transfer the generated heat via conduction phenomena to the reaction mixture. This means, that all of the "microwave heating" of the reaction mixture using this technology essentially occurs by conventional conduction and convection principles, similar to an oil-bath experiment generating a hot-vessel surface and temperature gradients. In addition, it has to be assumed that there is no possibility for any direct interaction of the microwave field[4] with specific molecules in the reaction mixture contained in the wells since all of the energy will either be absorbed by the silicon carbide plate or reflected by the aluminum sealing plate on top (Figure 1b). Therefore, it appears that many of the presumed benefits of microwave synthesis[2−4] may be lost using this technique.[19]

To obtain a more detailed view, we have reinvestigated all five reaction steps leading to aminopyrimidine **5aF** (Scheme 1)[18] both in the presence and in the absence of a 10 × 18 mm silicon carbide passive heating element cylinder using standard 10 mL microwave process vials in a single mode reactor.[15] Since under these conditions a significant amount of microwave energy will be absorbed by the heating element immersed in the reaction vial and not by the reaction mixture itself, this experimental setup to some extent will mimic the situation within the microtiter plate. The results of these control experiments are summarized in Table 1.

Gratifyingly, we find that, regardless of the microwave-assisted reactions being carried out in the presence or absence of a passive heating element, the isolated product yields in all five cases were virtually identical (Table 1). It is also evident that the effect of using a passive heating element will be most pronounced for those cases where the reaction mixture itself is not strongly microwave absorbing, that is, where an unpolar solvent with a low loss tangent (tan δ)[20] was employed. Notably,, for the oxidation of dihydropyrimidine **2a** to pyrimidine **3a** with MnO_2 performed in DCM (tan $\delta = 0.042$), a 64 W average magnetron output power is required to heat the reaction mixture at 100 °C. In the presence of the strongly absorbing silicon carbide heating element, this value is reduced to 13 W under otherwise identical reaction conditions. Similarly, for the transformation of sulfone **4a** to **5aF** carried out at 140 °C in THF (tan $\delta =$ 0.047) the required power is reduced by almost 90% from 136 to 18 W. Importantly, the significantly reduced input of microwave irradiation/energy to the reaction mixture and the indirect heating by conduction and convection via the heating element had no influence on the reaction outcome, as the isolated product yields and purity profiles remained virtually identical. The above experiments therefore indicate that the use of "self-absorbing" microtiter plates for MAOS is indeed

Table 1. Evaluation of the Use of Silicon Carbide (SiC) Heating Elements for the Five-Step Microwave Synthesis of 2-Aminopyrimidine **5aF** (Scheme 1)[a]

		without SiC heating element		with SiC heating element	
reaction[a]	solvent (tan δ)[b]	yield (%)[c]	MW power (W)[d]	yield (%)[c]	MW power (W)[d]
→ **1a**	MeCN/DMF (0.062/0.161)	62	16	65	7
1a → **2a**	MeCN (0.062)	94	10	94	8
2a → **3a**	DCM (0.042)	90	64	91	13
3a → **4a**	MeOH (0.659)	92	10	94	6
4a → **5aF**	THF (0.047)	82	136	84	18

[a] Single-mode sealed-vessel microwave irradiation at set maximum temperatures in the presence and absence of silicon carbide passive heating elements. For further details, see Scheme 1 and the Experimental Section. [b] Data for tan δ values were obtained from ref 3a. [c] Yields refer to isolated yields of pure products. [d] Average microwave magnetron output power used after the set maximum reaction temperature was reached.

Table 2. LC-ELSD/MS Conversion and Masses Found for 2-Aminopyrimidines **5** Obtained from Sulfones **4a**−**e** and Amines **A**−**F** (Scheme 1)

product	plate position	conversion[a]	MW (calcd)	MW $(M + H)^+$
5aA	1A	>99	311.4	312.1
5aB	1B	81	325.4	326.2
5aC	1C	>99	301.3	302.1
5aD	1D	27	347.4	348.1
5aE	1E	88	379.4	380.1
5aF	1F	>99	391.5	392.0
5bA	2A	>99	325.4	326.1
5bB	2B	>99	339.4	340.2
5bC	2C	>99	315.4	316.2
5bD	2D	19	361.4	362.0
5bE	2E	>99	393.5	394.2
5bF	2F	>99	405.5	406.2
5cA	3A	>99	345.1	346.0
5cB	3B	>99	359.9	360.1
5cC	3C	<1	355.8	-
5cD	3D	43	381.9	382.0
5cE	3E	>99	413.9	414.1
5cF	3F	>99	425.9	426.1
5dA	4A	>99	338.5	339.1
5dB	4B	50	352.5	353.2
5dC	4C	71	328.4	329.0
5dD	4D	5	374.5	375.1
5dE	4E	56	406.5	407.0
5dF	4F	71	418.5	419.2
5eA	5A	91	356.4	357.1
5eB	5B	53	370.5	371.1
5eC	5C	>99	346.4	347.0
5eD	5D	17	392.5	393.1
5eE	5E	68	424.5	425.1
5eF	5F	81	436.5	437.0

[a] Conversions were determined from the relative peak areas (%) of the ELSD chromatograms, see Experimental Section for details.

feasible and should have no detrimental effect on the chemical transformations performed in these devices.

With all the above information in hand, we set out to generate the full 30-member library of 2-aminopyrimidines **5** described in Scheme 1 using sulfones **4a**−**e** and amines **A**−**F** as precursors on a 0.01 mmol scale (150 μL reaction volume). For synthesizing the 5 × 6 combinatorial matrix, columns 1−5 of the plate were loaded with the five sulfones **4a**−**e**, and rows A-F were loaded with the six amines **A**−**F**. The chosen reaction conditions for the nucleophilic displacements were essentially the same as for the single-mode runs[18] (1.2 equiv of the amine, THF, 145 °C internal temperature, 10 min). The results of the library synthesis are shown in Table 2. To our delight, with one exception (**5cC**), all 30 reactions were successful and cleanly generated the expected 2-aminopyrimidine products as confirmed by LC-MS analysis. While in the majority of cases very high conversion to the desired products was observed, in some instances conversions were moderate (Table 2). We believe these lower yields to be the consequence of the particularly difficult building block combinations involved and not to be the result of inherent inhomogeneities in the microtiter plate (see above). This is also evident from the fact that the HPLC traces of the single-mode runs (10 library members fully characterized)[18] were virtually identical with the data obtained in the parallel processing experiment for those samples. It should be noted that no cross-contamination between the contents of the wells was observed during the synthesis of the 2-aminopyrimidine library.

To also compare isolated yields, we have performed an additional microtiter plate experiment where the amination reaction **4a** + **F** → **5aF** was run in a more concentrated fashion on a 0.1 mmol scale in one single well of the plate (300 μL). From this experiment, 32 mg of product **5aF** (85%) was isolated via column chromatography which corresponded nicely to the 83% yield obtained from a microwave experiment performed using the same concentration, volume, and time/temperature regime in a single-mode reactor using an ultralow-volume processing vial (200−500 μL filling volume).[21]

Conclusions

In conclusion, we have demonstrated that parallel microwave synthesis can be carried out efficiently in sealed deep-well microtiter plates made from highly temperature resistant silicon carbide material. Since the plate material itself is strongly microwave absorbing, the absorbance characteristics of the reaction mixtures contained in individual wells are irrelevant. As confirmed by temperature and reactivity measurements, all 48 wells in the setup used are heated uniformly when exposing the silicon carbide plate to microwave irradiation, regardless of the filling volumes employed. The unique sealing mechanism of the plate allows processing of reaction volumes up to 300 μL at reaction temperatures of 200 °C and pressures of up to 20 bar.

Experimental Section

General and Materials. For general experimental techniques and materials, see ref 18.

LC-ELSD/MS Analysis. Electrospray (ES) mass spectra and LC-MS analyses with evaporative light-scattering detec-

tion (ELSD, Sedex 75 detector) were recorded on a PE Sciex API 3000 instrument with an HP1100 HPLC equipped with binary pump, column compartment, diode-array detector, single quadrupole mass spectrometer detector, and a C18 column (Waters Xterra MS C-18X, 3 mm) at 40 °C with a flow of 1.0 mL/min. Two mobile phases (mobile phase A, 100% water, 0.01% TFA; mobile phase B, 100% acetonitrile, 0.01% TFA) were employed to run a gradient condition from 10−100% B in 7.5 min with UV detection at 210 nm and MS scanning range from 100−1000 amu. Injections of 1 μL were used.

Microwave Irradiation Experiments. Microwave-assisted synthesis using silicon carbide microtiter plates was carried out in a Synthos 3000 multimode microwave reactor (Anton Paar GmbH).[22] The individual wells of the plate (100−300 μL recommended filling volume) are filled with a micropipette. After filling, the PFA foil is used to cover the well plate, and the alumina top plate is fixed finger tight with the six hex bolts (see Figure 1b). The whole assembly is placed on a dedicated plate rotor inside the Synthos 3000 instrument (see Figure S2 in the Supporting Information). During irradiation, the surface temperature of the plate is monitored by IR thermography, and suitable maximum microwave power levels are employed to avoid overheating (Figure S9 in the Supporting Information). To obtain the proper internal reaction temperature, a calibration factor of 1.11 is applied (see main text for discussion). After it has been cooled down to about 50 °C with forced air cooling, the plate can be removed from the cavity. To prevent cross contamination, the assembly must not be dismantled before the individual reaction products are recovered via syringe. The contents of each well can be removed with a syringe; then, the wells can be further rinsed with solvent to obtain the product quantitatively. After every well has been rinsed, the assembly can be dismantled and washed with any solvent for purification.

Reaction Homogeneity. Esterification of Benzoic Acid. In a 10 mL microwave Pyrex reaction vessel, benzoic acid (1.0 mmol, 123 mg) was dissolved in a mixture of 2 mL of ethanol and 1 mL of aqueous 1 M sulfuric acid. The vessel was sealed and exposed to microwave irradiation (Initiator 8, Biotage AB) for 20 min at different temperatures (see Figure S5 in the Supporting Information). The conversions for the individual runs were measured by HPLC. For the microtiter plate experiments (Figure S6), a stock solution was prepared (10 mL of ethanol, 5 mL of sulfuric acid (1 M), 5 mmol (620 mg) of benzoic acid), and each of the 48 wells was filled with 300 μL of this mixture. Microwave processing and handling of the plate under microwave conditions was performed as described above.

Microwave Syntheses Using Silicon Carbide Passive Heating Elements (Table 1). The experiments were performed in 10 or 20 mL Pyrex microwave vessels using an Initiator Eight instrument (Biotage AB) according to the procedures previously reported.[18] For runs involving heating elements, a 10 × 18 mm silicon carbide heating element was additionally placed in the Pyrex reaction vessel. Since the SiC cylinder itself has a volume of 1.2 mL,[15] the reaction volume in some cases had to be adjusted to keep the same amount of head space in the closed vial, by either lowering the amount of reaction volume or by increasing the vessel size.

Generation of a 30-Member Library of 2-Aminopyrimidines 5 Using a Silicon Carbide Microtiter Plate (Table 2). Stock solutions of the five sulfones (**4a**−**e**, 0.13 mmol in 1 mL THF) and the six amines **A**−**F** (0.16 mmol in 1 mL THF) were prepared. Subsequently, 75 μL (0.01 mmol) of the sulfone stock solutions was combined with 75 μL (0.012 mmol) of the appropriate amine stock solution in 30 of the wells in the plate, resulting in a total filling volume of 150 μL per well. To generate the 5 × 6 combinatorial matrix, columns 1−5 of the plate were loaded with the five sulfones **4a**−**e**, and rows A−F were loaded with the six amines **A**−**F**. Subsequently, the microtiter plate was sealed as described above and exposed to microwave irradiation for 10 min at 145 °C (surface temperature 130 °C). After the plate was cooled, the contents of each well were removed with a syringe and collected in suitable vessels for automated analysis by LC-MS (Table 2).

Synthesis and Isolation of 2-Aminopyrimidine 5aF from a Microtiter Plate and Single-Mode Microwave Experiment. A 0.5 mL Pyrex Biotage microwave reaction vessel (filling volume 200−500 μL), equipped with a stirring bar and a small piece of SiC, was filled with a solution of the sulfone **4a** (32 mg, 0.1 mmol) in 300 μL of THF and methoxyphenylethylamine (20 μL, 21 mg, 0.12 mmol). After the vessel was sealed, the mixture was irradiated in an Initiator 8 microwave reactor (Biotage, AB) at 140 °C for 10 min. For the corresponding experiment with the silicon carbide plate, one well of the plate was filled with the identical reaction mixture and was irradiated in the Synthos 3000 (Anton Paar GmbH). After the mixtures were cooled, 32 (83%) and 33 mg (85%), respectively, quantities of product **5aF** were isolated by column chromatography using a mixture of petroleum ether and ethyl acetate (2:1) as an eluent. The spectral and physical data of both compounds were identical in all respects with identical material obtained previously.[18]

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Supporting Information Available. Additional pictures of microtiter plate set-ups and reaction homogeneity studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) 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 $\delta = \epsilon''/\epsilon'$. A reaction medium with a high tan δ at the standard operating frequency of a microwave synthesis reactor (2.45 GHz) is required for good absorption and, consequently, for efficient heating. Solvents used for microwave synthesis can be classified as high (tan $\delta > 0.5$), medium (tan δ 0.1−0.5), and low microwave absorbing (tan $\delta < 0.1$). Microwave synthesis in low-absorbing solvents is often not feasible, unless either the substrates or some of the reagents/catalysts are strongly polar and therefore microwave absorbing.

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