JOURNAL OF combinatorial CHEMISTRY

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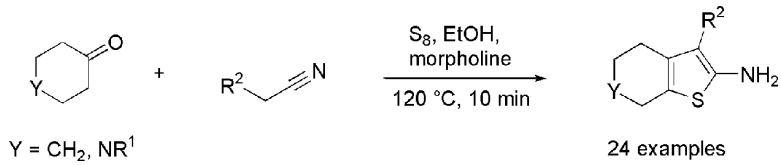
J. Comb. Chem., **2008**, 10 (6), 863-868• DOI: 10.1021/cc800081b • Publication Date (Web): 23 September 2008



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Microwave-Assisted Parallel Synthesis of Fused Heterocycles in a Novel Parallel Multimode Reactor

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Received May 15, 2008

New rotor types using disposable glass vials for small-scale parallel synthesis in multimode microwave reactors are introduced. One rotor comprises 16 groups of four vials, whereas the second uses four silicon carbide plates with a 6 × 4 matrix to process the vials. Both rotors achieve utmost temperature homogeneity upon microwave irradiation and can be used for microwave-mediated reactions at temperatures of up to 200 °C and pressures of 20 bar. The generation of three different heterocycle libraries furnishing thiophenes, oxindoles, and benzimidazoles using the new rotor types is described.

Introduction

Combinatorial chemistry and parallel synthesis are important tools in drug discovery,[1] which are used to find (high-throughput screening),[2] evaluate, and optimize hit compounds into leads (hit-to-lead)[3] and, ultimately, to optimize leads into development candidates (lead optimization).[4] Any technology that can reduce the time required for parallel synthesis of compounds in these drug discovery phases is an asset to the medicinal chemist. Through the application of microwave irradiation to parallel synthesis, the time frame for hit-to-lead optimization, as well as the overall drug development process time, can be significantly reduced.[5]

Whereas high-throughput screening requires only small quantities of compound for testing, the hit-to-lead and lead-optimization phases require significantly greater quantities (>20 mg) for comprehensive analytical and biological characterization. Commercially available microwave reactors[6] offer two different principles to achieve milligram to gram quantities of compounds. Focused libraries (20−100 members) can be synthesized either sequentially using monomode reactors with automated vial handling systems[7] or in parallel employing suitable rotors and reaction vessels in multimode cavities.[8] Performing syntheses in parallel in multimode microwave systems provides an additional time advantage over sequential synthesis in monomode cavities because all reactions in a given parallel synthesis can be performed at one time. However, widespread use of parallel synthesis in multimode microwave systems has thus far been limited because of the inability to achieve homogeneous heating of each reaction vessel. This is largely because sample heating via microwave irradiation is highly influenced by the coupling efficiency of each individual mixture. Even closely related substrates display a significant deviation in microwave coupling efficiency.[9] As a result some reaction vessels do not reach the target temperature and the optimal yield is not achieved. With this work, we demonstrate the reliability of new rotor types for a multimode microwave reactor (Synthos 3000, Anton Paar GmbH)[6a] in achieving homogeneous heating of all samples in the parallel syntheses of libraries of heterocyclic compounds in 20−140 mg quantities.

Two rotor types for microwave-assisted parallel synthesis have been developed for use in combination with the Synthos 3000,[6a] a 64-position rotor and a 96-position rotor (Figure 1). Both rotor types feature disposable 5 mL glass vials equipped with a PTFE seal and a screw cap, which are suitable for temperatures of up to 200 °C and pressures of 20 bar. The 64-position rotor consists of 16 PTFE vial holders for four vials each, while the 96-position rotor consists of four silicon carbide (SiC) blocks with a standard 6 × 4 matrix into which the reaction vials are placed. The transfer of each set of four reaction vials is easily achieved using a vial handling tool (Figure 2), which can also vent all four vials simultaneously (see Supporting Information for more details). Temperature control can be accomplished by IR sensing of

Figure 1. Parallel Synthesis Rotors 64MG5 and 4 × 24MG5 (Anton Paar GmbH).

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10.1021/cc800081b CCC: $40.75
Published on Web 09/23/2008

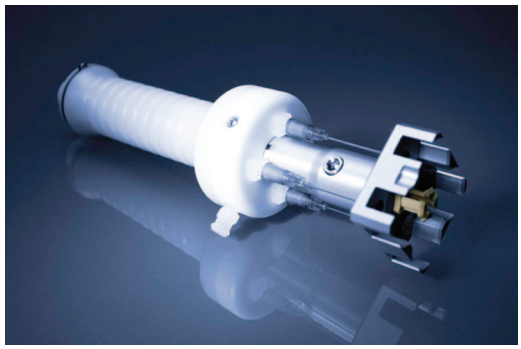


Figure 2. Vial handling tool for simultaneous handling and venting of four vials (Anton Paar GmbH).

either the bottom of the glass reaction vessel or, in the case of the 96-position rotor, the silicon carbide block surface.

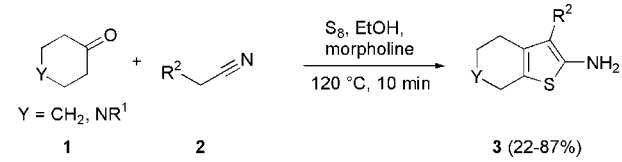
The setup using SiC in the 96-position rotor is especially convenient for parallel synthesis. As demonstrated in recent publications, SiC is an excellent microwave absorber and can be used in microwave processes, where additional microwave coupling is required.[10,11] In addition, SiC has a very high heat capacity and conductivity ensuring perfect temperature homogeneity of not only the SiC block but also the reaction vessels. Thus, the contents of the individual reaction vessels have no influence on the final temperature achieved and even weakly absorbing reaction mixtures are easily heated to the desired temperatures.[10] This 96-position rotor allows, for the first time, the application of microwave assisted parallel synthesis to all types of reaction mixtures independent of the coupling efficiencies while ensuring homogeneous temperature conditions.

To demonstrate the applicability of the new rotors, libraries of thiophenes, oxindoles, and benzimidazoles have been synthesized. Fused thiophenes have gained considerable interest over the decades, being important structural motifs not only in natural compounds[12] but also in dyes,[13] agrochemicals, and pharmaceutically active compounds,[14] such as the analgesic tinoridine[15] or the tranquilizer brotizolam (Lendormin).[16] The 2-amino derivatives, especially, show a broad scope of applications.[17] Similarly, oxindoles are part of many natural compounds, such as alkaloids,[18] and as such have attracted the interest of the pharmaceutical industry.[19] For example, 3-substituted oxindoles show antiproliferative potential in oncology.[20−23] Finally, benzimidazoles are frequently under investigation because of their broad spectrum of pharmacological activities, such as antiviral, antihistamine, antifungal, antiparasitic, and cytotoxicity.[21,24] All three heterocyclic scaffolds are clearly of importance in drug discovery, and as such, the rapid generation of libraries via microwave-assisted parallel synthesis is of significant interest.

Results and Discussion

It has been previously shown that upon microwave irradiation, a 48-well SiC block is heated homogeneously.[11] In this work it was also demonstrated that, when the same reaction is performed in each of the 48 wells, almost identical results are observed. To demonstrate homogeneous heating of our 24-well SiC block, NMP was heated to 100 °C in each of the 24 reaction vessels, and the block was then monitored using IR thermography. The average temperature of the 24 wells was 97.8 °C with a standard deviation of 1.4%. (see Supporting Information) In addition, benzoic acid was esterified in ethanol and sulfuric acid for 25 min at 140 °C in each of the 24 wells. The average conversion to ethyl benzoate was 61.3% with a standard deviation of 2.5% (see Supporting Information for details) further illustrating the homogeneity of heating of the 24-well SiC block.

Scheme 1. Generation of 2-Aminothiophenes by Gewald Synthesis



2-Amino Benzo[*b*]thiophenes by Gewald Synthesis. The rise of microwave-mediated chemistry recently renewed interest in the development of rapid and efficient variations of the classical Gewald synthesis.[25] Herein, we discuss a one-pot procedure for the rapid generation of a 24-member benzo[*b*]thiophene library from activated nitriles employing elemental sulfur.

Following a simplified Gewald protocol, a mixture of an appropriate ketone **1**, an activated nitrile **2**, and elemental sulfur, was heated to 120 °C for 10 min in ethanol as the solvent in the presence of morpholine, acting as organic base (Scheme 1). The use of six cyclic ketones and four nitriles resulted in a 24-member library of the corresponding benzo[*b*]thiophenes. The use of the nitriles gives immediate access to the desired 2-amino derivatives without any further transformation steps thus avoiding the need to introduce an amino group into an existing thiophene scaffold.

The applied protocol was initially optimized in a monomode microwave reactor (Biotage Optimizer EXP)[6b] and then transferred to the multimode instrument (Synthos 3000)[6a] using the 64-position rotor. No significant difference regarding yield and purity was observed when identical reaction conditions were used with the two different microwave systems.[5e,26] The members of the 2-amino thiophene library have been synthesized in 22−87% yields and excellent purities as measured by HPLC at a wavelength of 254 nM (Table 1). The majority of compounds were purified using reverse-phase LC/MS, and the major impurities that remained after synthesis were unreacted starting material and sulfur. Compound **3fd** could only be isolated in 22% because of the poor solubility of the compound, leading to difficulties during chromatographic purification (see Supporting Information for ^{1}H NMR and HPLC chromatograms).

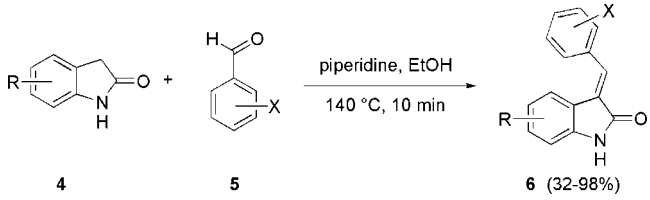
Decoration of the Oxindole Scaffold. Microwave-assisted synthesis of oxindoles has been previously reported.[23] In the presented procedure a classic Knoevenagel condensation step starting from commercially available oxindoles under microwave irradiation allows the generation of various 3-benzylidene oxindole derivatives. By combination of six oxindoles **4** with four benzaldehydes **5** in ethanol with substoichiometric amounts of piperidine and heating to 140 °C for 10 min the 24 desired benzylidine oxindoles were successfully synthesized in good to high yields (50−98%) and excellent

Table 1. 24-Member Thiophene Library by One-Step Gewald Synthesis

thiophene	Y	R^1	R^2	amount	yield[a]
3aA	CH_2		COO*t*Bu	62 mg	48%
3aB	CH_2		COOBn	54 mg	37%
3aC	CH_2		CN	48 mg	53%
3aD	CH_2		$CONH_2$	40 mg	40%
3bA	NR^1	Ac	COO*t*Bu	56 mg	53%
3bB	NR^1	Ac	COOBn	38 mg	32%
3bC	NR^1	Ac	CN	32 mg	41%
3bD	NR^1	Ac	$CONH_2$	39 mg	46%
3cA	NR^1	COOEt	COO*t*Bu	50 mg	52%
3cB	NR^1	COOEt	COOBn	58 mg	55%
3cC	NR^1	COOEt	CN	51 mg	70%
3cD	NR^1	COOEt	$CONH_2$	54 mg	69%[b]
3dA	NR^1	COO*t*Bu	COO*t*Bu	41 mg	46%
3dB	NR^1	COO*t*Bu	COOBn	45 mg	46%
3dC	NR^1	COO*t*Bu	CN	40 mg	57%[c]
3dD	NR^1	COO*t*Bu	$CONH_2$	38 mg	51%
3eA	NR^1	COOBn	COO*t*Bu	62 mg	75%
3eB	NR^1	COOBn	COOBn	51 mg	56%[c]
3eC	NR^1	COOBn	CN	48 mg	72%
3eD	NR^1	COOBn	$CONH_2$	42 mg	59%
3fA	NR^1	Bn	COO*t*Bu	79 mg	87%
3fB	NR^1	Bn	COOBn	59 mg	59%
3fC	NR^1	Bn	CN	40 mg	56%[b]
3fD	NR^1	Bn	$CONH_2$	17 mg	22%[d]

[a] Isolated yield after preparative HPLC/MS, using TFA as eluent. [b] Formic acid was used as eluent. [c] Product could be isolated by filtration. [d] NH_3/NH_4HCO_3 was used as eluent.

Scheme 2. Decoration of Oxindole Scaffolds by Knoevenagel Condensation



purities as measured by HPLC at a wavelength of 254 nM. (Scheme 2). Analysis of the crude reaction mixtures via LC/MS showed that clean conversion to the desired benzylidene oxindoles was obtained for all reactions. The products were isolated in a parallel fashion via filtration and subsequent washing of the precipitate with ethanol. Those oxindoles which displayed a degree of solubility in ethanol resulted in a reduced isolated yield using this isolation procedure (e.g., **6aB**, **6aC**, **6aD**).

To demonstrate that the optimized synthesis procedure is independent of rotor type the reactions were carried out in both the 64-position rotor, as well as in the 96-position rotor with the 6 × 4 silicon carbide blocks. Because of the excellent heat capacity of the silicon carbide, its surface temperature correlates perfectly with the vial temperature. A sensed IR temperature of 140 °C, regardless of whether it is measured at the bottom of the glass vials (64-position rotor) or on the SiC surface (96-position rotor) provides comparable yields and purities and hence reaction conditions in each vial.

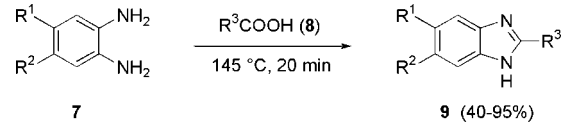
One-Step Synthesis of Multiple-Substituted Benzimidazoles. Several microwave-assisted syntheses to obtain substituted benzimidazoles have been presented,[27] but one-pot, one-step procedures in the microwave are rare.[28] Herein we describe a simple and efficient parallel method for the generation of such multiple substituted benzimidazole cores using readily available phenylene diamines. In the 96-position rotor, eight phenylene diamines **7** and three carboxylic acids **8** were reacted at 145 °C for 20 min. The carboxylic acids **8** were used in considerable excess, acting simultaneously as substrate and solvent. Even in this extreme case, where large variations in temperature between reaction vessels is expected,[9] the SiC block ensured homogeneous temperatures across all reaction vessels (see Supporting Information for a corresponding FTIR thermographic image) leading to high yields (40−95%) and excellent purities, as measured by HPLC at a wavelength of 254 nM, for 22 of the desired 24 benzimidazoles. In addition, the results obtained were the same as those obtained in monomode experiments.

Table 2. Optimized Yields of 24-Member Oxindole Library

oxindole	R	X	amount	yield[a]
6aA	H	3,4-MeO	83 mg	78%
6aB	H	3-Br	76 mg	67%
6aC	H	3-MeO	47 mg	50%
6aD	H	4-Cl	55 mg	57%
6bA	6-Br	3,4-MeO	71 mg	84%
6bB	6-Br	3-Br	80 mg	89%
6bC	6-Br	3-MeO	58 mg	75%
6bD	6-Br	4-Cl	71 mg	90%
6cA	6-Cl	3,4-MeO	73 mg	78%
6cB	6-Cl	3-Br	87 mg	87%
6cC	6-Cl	3-MeO	82 mg	96%
6cD	6-Cl	4-Cl	77 mg	89%
6dA	5-COOMe	3,4-MeO	86 mg	96%
6dB	5-COOMe	3-Br	91 mg	97%
6dC	5-COOMe	3-MeO	79 mg	98%
6dD	5-COOMe	4-Cl	58 mg	71%
6eA	5-NO_2	3,4-MeO	83 mg	91%
6eB	5-NO_2	3-Br	87 mg	90%
6eC	5-NO_2	3-MeO	79 mg	95%
6eD	5-NO_2	4-Cl	70 mg	83%
6fA	6-Me	3,4-MeO	73 mg	73%
6fB	6-Me	3-Br	79 mg	74%
6fC	6-Me	3-MeO	58 mg	64%
6fD	6-Me	4-Cl	74 mg	81%

[a] Isolated yield after trituration with EtOH.

Scheme 3. Preparation of substituted benzimidazoles from phenylene diamines



Library Generation Concepts. A 24-member library can be generated with both rotor types following different logical loading of six vial holders. In case of the Gewald synthesis, the 64-position rotor was used, and all vials of one holder are charged with sulfur and one of the ketones, while the four nitriles are varied (see Supporting Information for appropriate loading patterns). Accordingly, each vial holder represents its own subset of the library. This makes it easy to transfer the vials afterward to corresponding 6 × 4 racks for workup and analytics.

The logical arrangement of rows and columns in the 6 × 4 SiC blocks of the 96-position rotor simplify the set up and preparation of experiments and allow the use of multichannel pipettes to apply reagents and add solvent. The provided 6 × 4 matrix of the silicon carbide blocks not only allows a combination of six by four building blocks to be applied but also eight by three combinations can be carried out with

Table 3. 24-Member Benzimidazole Library from Substituted Phenylene Diamines

benzimidazole	R^1	R^2	R^3	amount	yield[a]
9aA	Me	Me	H	122 mg	95%
9aB	Me	Me	Me	110 mg	78%
9aC	Me	Me	Et	99 mg	64%
9bA	Cl	Cl	H	104 mg	82%
9bB	Cl	Cl	Me	115 mg	84%
9bC	Cl	Cl	Et	120 mg	82%
9cA	Me	H	H	106 mg	82%
9cB	Me	H	Me	105 mg	73%
9cC	Me	H	Et	136 mg	86%
9dA	Br	H	H	93 mg	71%
9dB	Br	H	Me	119 mg	88%
9dC	Br	H	Et	137 mg	95%
9eA	Cl	H	H	106 mg	83%
9eB	Cl	H	Me	123 mg	88%
9eC	Cl	H	Et	132 mg	87%
9fA	H	H	H	52 mg	40%
9fB	H	H	Me	106 mg	72%
9fC	H	H	Et	108 mg	67%
9gA	CF_3	H	H	51 mg	55%
9gB[b]	CF_3	H	Me	n.d.[c]	n.d.[c]
9gC[b]	CF_3	H	Et	n.d.[c]	n.d.[c]
9hA	F	F	H	105 mg	82%
9hB	F	F	Me	98 mg	72%
9hC	F	F	Et	127 mg	84%

[a] Isolated yield after trituration with water. [b] Product not isolated because of large amount of byproduct. [c] n.d. = not determined.

ease (see Supporting Information for the appropriate loading pattern of the oxidole and benzimidazole synthesis, respectively).

Another interesting benefit when applying the SiC blocks is the lower microwave power needed. Because of the heat capacity of the SiC, just 700 W are required to heat up the 96-position rotor to 140 °C rapidly, while the maximum of 1400 W is applied to accomplish short heating ramps with the 64-position rotor. In addition, only low power (on average 300 W) is needed to maintain the target temperature within the 96-position rotor, whereas about 700 W are required to keep the 24 vials in the 64-position rotor at the reaction temperature. Despite the difference in power required, identical results were obtained when the oxindole synthesis was performed with both rotors.

Conclusions

In conclusion, we have developed simple and practicable methods for parallel library generation of three individual pharmaceutically interesting heterocyclic scaffolds. Each library could be performed at once from commercially available building blocks and with application of the optimized reaction procedures from monomode reactors and without further optimization. Even for libraries with 24 members, the time saving benefit compared to sequential processing is significant (20 min versus 8 h for the benzimidazole synthesis). This time saving can be even larger if the full capacity of the new rotors (e.g., 64- of 96-member libraries) is utilized. In addition, it has been demonstrated that both rotors, but especially the 96-position rotor with it is 6 × 4 SiC reaction blocks, are easy to use and give rise to homogeneous temperatures during parallel synthesis.

Experimental Section

General. All building blocks and solvents were purchased from commercial suppliers and were used without any further purification. ^{1}H NMR spectra were recorded in DMSO-d_6, on Bruker Avance 400 (400 MHz) and 500 (500 MHz) NMR spectrometers. Mass spectra (positive and negative) were taken on a Agilent LC/MSD SL instrument (LCMS1: 1100 series LC/MSD) in the ESI− mode. HPLC analysis was performed on an Agilent 1100 Series with autosampler and UV detector (254 nm). The separation was carried out using a Phenomenex analytical column (Mercury Gemini C18, 3 μm, 2.0 × 20 mm), employing a mobile phase from (A) 5 mM NH_4HCO_3/20 mM NH_3 in water and (B) acetonitrile HPLC grade. The following gradients were applied at a flow rate of 1.0 mL/min: 0.0 min 5% B, 0.0−2.5 min 5% → 95% B, 2.5−2.8 min 95% B, 2.8−3.1 min 95% → 5% B. Preparative HPLC purification was conducted on a Agilent 1100 system (HPLC/MS, MSD SL) using Waters analytical columns (SunFire, C 18, 5 μm, 50 × 19 mm or SunFire, C 18, 10 μm, 150 × 50 mm, respectively).

Microwave Experiments. Microwave-assisted synthesis was carried out in a Synthos 3000 multimode microwave reactor (Anton Paar GmbH) employing either Rotor 64MG5 or Rotor 4 × 24MG5. Both rotor types use disposable standard glass vials (Wheaton, 13−425, 15 × 45 mm, 0.3−3 mL recommended operation volume). The vials are sealed applying a lip-type PTFE seal and tightened with a PEEK screw cap. Whereas Rotor 64MG5 requires symmetric loading patterns in the provided vial holders to achieve utmost temperature homogeneity, the vials can be placed individually in any position of the four 6 × 4 silicon carbide plates. During irradiation the surface temperature of either the vials (Rotor 64MG5) or the silicon carbide plates (Rotor 4 × 24MG5) is measured by IR thermography. Although the sensed surface temperature is somewhat lower than the current inside reaction temperature, there is a nice agreement with reported (IR) reaction temperature from other microwave instrumentation.[5e,11,26] After the reaction the vials are cooled down to 50 °C by forced air cooling, to release any remaining overpressure, the vials can be pierced through a corresponding bore hole in the screw cap before opening.

Generation of a 24-Member Library of 2-Amino Benzo[*b*]thiophenes. Each vial was equipped with an appropriate stir bar and charged accordingly with 50 mg corresponding keto-compound (**1a**−**f**, 0.21−0.51 mmol), 1.1 equiv of nitrile (**2A**−**D**), and 1.5 equiv of elemental sulfur. Finally 1.5 equiv of morpholine and 0.9 mL of dry ethanol were added. For reliable temperature homogeneity, Rotor 64MG5 was charged with six groups of four vials. The vials were sealed and closed appropriately, heated up to 120 °C (1000 W maximum output power) and kept at this temperature for additional 10 min. After they were cooled, the vials were vented (four at a time) with the corresponding venting tool, and the mixtures were subjected to HPLC analysis. To isolate the products, the mixtures were concentrated in vacuum; the residue was dissolved in DMSO (0.75 mL each) and purified by preparative HPLC. Freeze-drying furnished the individual thiophenes (**3aA**−**fD**) in yields of 22−87% and excellent purity. For comprehensive analytical data see the Supporting Information.

Generation of a 24-Member Library of Oxindole Derivatives. Each vial was equipped with an appropriate stir bar and charged accordingly with 50 mg corresponding oxindole (**4a**−**f**, 0.24−0.38 mmol). Equimolar amounts of benzaldehyde derivatives (**5A**−**D**) have been added, as well as 0.2 equiv of piperidine, together with 1 mL of dry ethanol. The vials were sealed and closed appropriately, heated up to 140 °C and kept at this temperature for additional 10 min. For temperature homogeneity, Rotor 64MG5 was charged with six groups of four vials. When employing Rotor 4 × 24MG5, one SiC plate was equipped with 24 vials placing the oxindoles **4** in the corresponding columns and the benzaldehydes **5** in the corresponding rows to follow the 6 × 4 matrix. After they were cooled, the vials were vented (four at a time) with the corresponding venting tool (Figure 2). The precipitates formed were filtered off, triturated with ethanol, and dried to obtain the functionalized oxindoles **6aA**−**fD** in yields of 50−98% and excellent purity. For comprehensive analytical data see the Supporting Information. Practically no difference in yield or purity could be observed when utilizing the different rotor types for the reaction.

Generation of a 24-Member Library of Substituted Benzimidazoles. Each vial was equipped with an appropriate stir bar and charged accordingly with 125 mg of phenylene diamine (**7a**−**h**, 0.67−0.86 mmol) and 1 mL of carboxylic acid (**8A**−**C**). The experiment was conducted without any additional solvent because the carboxylic acids applied in substantial excess act as reagent and solvent in this reaction. To logically fill the 6 × 4 matrix when eight different phenylene diamines, combined with three carboxylic acids, were used, each carboxylic acid was filled into two neighboring columns (1−2, 3−4, and 5−6, respectively) of the 6 × 4 SiC plate, and the corresponding diamines were placed in every second position (1, 3, 5 or 2, 4, 6, respectively) of one row. Thus, any row of the plate contains two different diamines in alternating manner and all three acids (see Supporting Information for the appropriate loading pattern of the 6 × 4 SiC plate). The vials were sealed and closed appropriately, heated up to 145 °C within 2 min and kept at this temperature for additional 20 min. After they were cooled, the vials were vented (four at a time) with the corresponding venting tool (Figure 2). After it was cooled, each mixture was poured into saturated aqueous potassium carbonate solution. The formed precipitate was filtered off, triturated with water, and dried in vacuum to obtain the desired benzimidazoles **9aA**−**hC** in high purity and yields of 40−95%. For comprehensive analytical data, see the Supporting Information.

Acknowledgment. We thank J. Zach and F. Paus (Anton Paar GmbH) for technical assistance.

Supporting Information Available. Additional pictures of the silicon carbide plate setup, charts with all product structures, and NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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