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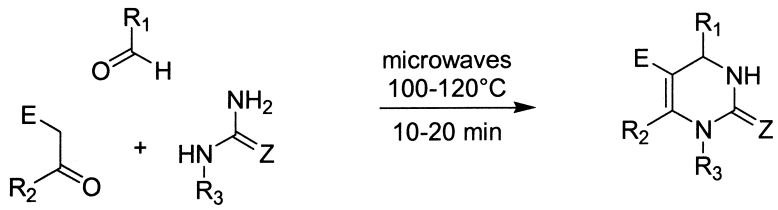

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Automated Library Generation Using Sequential Microwave-Assisted Chemistry. Application toward the Biginelli Multicomponent Condensation

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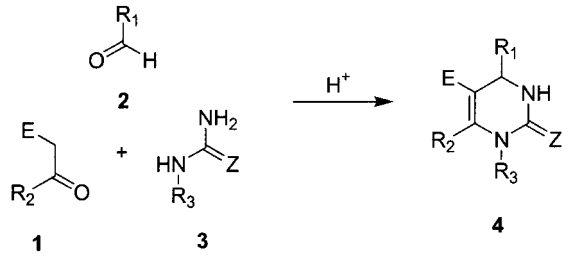
The concept of automated sequential microwave-assisted library synthesis is introduced. For this purpose a dedicated single-mode microwave reactor with a robotics interface including a liquid handler and gripper was employed. The liquid handler allows dispensing of reagents into the Teflon sealed reaction vials, while the gripper moves each sealed vial in and out of the microwave cavity after irradiation. This technology was employed for the Biginelli three-component cyclocondensation reaction. A diverse set of 17 CH−acidic-carbonyl compounds (**1A**−**Q**), 25 aldehydes (**2a**−**y**), and 8 urea/thioureas (**3**α−φ) was used in the preparation of a dihydropyrimidine (DHPM) library. Out of the full set of 3400 possible DHPM derivatives, a representative subset of 48 analogues was prepared using automated addition of building blocks and subsequent sequential microwave irradiation of each process vial. For most building block combinations 10 min of microwave flash heating at 120 °C using AcOH/EtOH (3:1) and 10 mol % $Yb(OTf)_3$ as solvent/catalyst system proved to be successful, leading to an average isolated yield of 52% of DHPMs with >90% purity. For some building block combinations the general conditions were modified, for example, by changing the solvent, catalyst, reaction temperature, or irradiation time. This flexibility is a distinct advantage of sequential over parallel microwave-assisted processes where all reactions are exposed to the same irradiation conditions. When the unattended automation capabilities of the microwave synthesizer are used, a library of this size can be synthesized within 12 h.

Introduction

High-speed microwave-assisted chemistry has attracted a considerable amount of attention in recent years and has been applied successfully in various fields of synthetic organic chemistry,[1−9] including cycloaddition reactions,[2] heterocycle synthesis,[3] the rapid preparation of radiolabeled materials,[4] transition metal catalyzed processes,[5] solvent-free reactions,[6] and phase-transfer catalysis.[7] In fact, it is becoming evident that microwave approaches can be developed for many chemical transformations that require heat. The main benefits of performing reactions under microwave irradiation conditions are the significant rate enhancements and the higher product yields that can frequently be observed.[1−9] Not surprisingly, these features have also attracted interest from the combinatorial/medicinal chemistry community where reaction speed is of great importance.[8,9] One issue, however, that has so far been somewhat neglected in microwave-assisted processes is throughput and automation. In this context we have demonstrated that microwave-assisted processes can be successfully carried out in a parallel fashion using suitable reactor vessels in dedicated multimode microwave cavities.[10] One limitation of this approach is that all reaction vessels during library production are exposed to the same irradiation conditions in terms of reaction time and microwave power. An alternative way to achieve high-throughput in microwave-assisted synthesis would be to perform reactions sequentially in an automated fashion. The benefit of this approach is that apart from the achievable throughput in the library production, fast iterations in protocol development and in optimization of reaction conditions can be realized. Here, we report on the generation of a small library of 48 dihydropyrimidine derivatives via Biginelli three-component condensation, using automated sequential microwave-assisted synthesis.

Scheme 1



Results and Discussion

Biginelli Dihydropyrimidine Synthesis. As a suitable model reaction to explore the concept of automated library production via sequential microwave-assisted synthesis, we have chosen the venerable Biginelli three-component dihydropyrimidine condensation (Scheme 1).[11−13] Multicomponent reactions (MCRs) in general are of increasing importance in organic and medicinal chemistry.[14] In times where

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a premium is put on speed, diversity, and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional linear-type syntheses.[15] The Biginelli protocol is particularly attractive because the resulting dihydropyrimidine (DHPM) scaffold displays a wide range of biological activities, which has led to the development of a number of lead compounds based on that structural core.[16] In recent years a variety of different combinatorial protocols based on the classical Biginelli MCR have been advanced.[13] In general, the standard procedure for the Biginelli condensation involves one-pot condensation of the three building blocks in a solvent such as ethanol, using a strongly acidic catalyst, i.e., hydrochloric acid.[12] One major drawback of this procedure, apart from the long reaction times involving reflux temperatures, is the moderate yields that are frequently obtained when using more complex building blocks. This has led to the development of a number of improved protocols, many of them involving Lewis acids instead of the traditional mineral acid catalysts.[13] Recently, several groups have also reported on microwave-assisted protocols for the Biginelli reaction.[17−21] However, most of these published procedures involve solvent-free protocols using standard domestic microwave ovens,[17−19] which do not allow the generation of high-quality libraries in an automated fashion. Here, we describe the use of a commercially available, single-mode microwave reactor specifically designed for performing rapid chemical synthesis in a high-throughput/combinatorial chemistry environment.

Microwave Chemistry Using the Smith Synthesizer.[22] The microwave instrument comprises a monomode (sometimes also called single-mode) microwave cavity that operates at a frequency of 2.45 GHz with continuous microwave irradiation power from 0 to 300 W. The reaction vials are glass-based ~10 mL closed tubes, sealed with Teflon septa and an aluminum crimp top. Two different designs are available for reactions on either a 0.5−2.0 or a 2.0−5.0 mL scale. For both vial types magnetic stirring bars are available. The process vials are moved into and out of the cavity in an automated fashion by a gripper incorporated into the platform. Inside the microwave cavity these vessels can be exposed to 20 bar of pressure and 250 °C. The temperature is measured with an IR sensor (infrared thermometry) on the outer surface of the process vial. The software algorithm regulates the microwave output power so that the preselected maximum temperature is maintained for the desired reaction/irradiation time. Reagents can either be poured manually into the vials before capping or be dispensed through the Teflon septum via the liquid handler incorporated into the platform. For example, when the liquid handler is used, a sequence of reagent additions from different stock solutions poured into different process vials can be programmed and executed in an automated, unattended fashion. After the irradiation period the reaction vessel is cooled rapidly (20−80 s) to ambient temperature by compressed air (gas jet cooling).

Optimization of Reaction Conditions. To make the Biginelli protocol amenable to an automated library generation format, solvent-free microwave-assisted procedures,[17−19] although being reported to be very effective, were not considered. Instead, attempts were made to dissolve all three

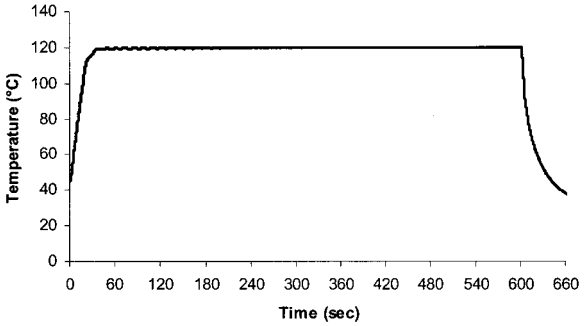

Figure 1. Heating profile for a typical Biginelli condensation in AcOH/EtOH (3:1) under sealed vessel/microwave irradiation conditions: microwave flash heating (300 W, 0−40 s); temperature control using the feedback from IR thermography (constant 120 °C, 40−600 s); active cooling (600−660 s).

types of building blocks (Scheme 1) in solvents that are compatible with the reaction conditions. Since many of the published protocols employ either ethanol or acetic acid as solvents in Biginelli-type condensations,[12] we have decided to use a 3:1 mixture of acetic acid (AcOH) and ethanol (EtOH) for the development of a microwave-assisted solution-phase protocol (see below). Both solvents effectively couple with microwave irradiation, i.e., are able to convert electromagnetic energy of 2.45 GHz into heat energy.[23] This allows the reaction mixture to heat up very rapidly under microwave irradiation conditions, leading to so-called microwave flash heating conditions (Figure 1). Preliminary runs with other solvents, such as dioxane or THF, proved to be far less effective in terms of heating rates and product yields. Furthermore, the AcOH/EtOH solvent combination has the advantage that all building blocks are soluble under the reaction conditions at elevated temperatures. In contrast, the resulting DHPM products would be expected to be comparatively insoluble at room temperature, facilitating product isolation. We next had to consider the use of a suitable catalyst. From our previous experience with microwave-assisted Biginelli condensations at high temperature, it became evident that hydrochloric acid was not the most suitable reaction promoter because of inadvertent decomposition of the urea components **3** to ammonia, leading to unwanted byproducts.[21] We therefore considered the use of more tolerable Lewis acids such as $Yb(OTf)_3$,[24] $InCl_3$,[25] $FeCl_3$,[26] and $LaCl_3$,[27] which recently have all been reported to be very effective catalysts for Biginelli condensations,[24−27] presumably by stabilizing the key *N*-acyliminium ion intermediates.[28] An initial screen of all these catalysts for the model system ethyl acetoacetate (**1A**), benzaldehyde (**2a**), and urea (**3α**) (for building blocks, see Figure 2) revealed that 10 mol % $Yb(OTf)_3$ was the most effective catalyst with the AcOH/EtOH solvent system (Table 1, entries 1−6). Having identified an efficient solvent/catalyst combination, we next dealt with the issue of reaction time and temperature. One of the benefits of using microwave flash heating in sealed vessels is the fact that one is not limited by the boiling point of the solvents or reagents as in conventional synthesis using reflux condensers. After a few optimization cycles, we discovered that 120 °C proved to be a very efficent reaction temperature. Higher temperatures would lead to decreased yields because of the formation of undesired

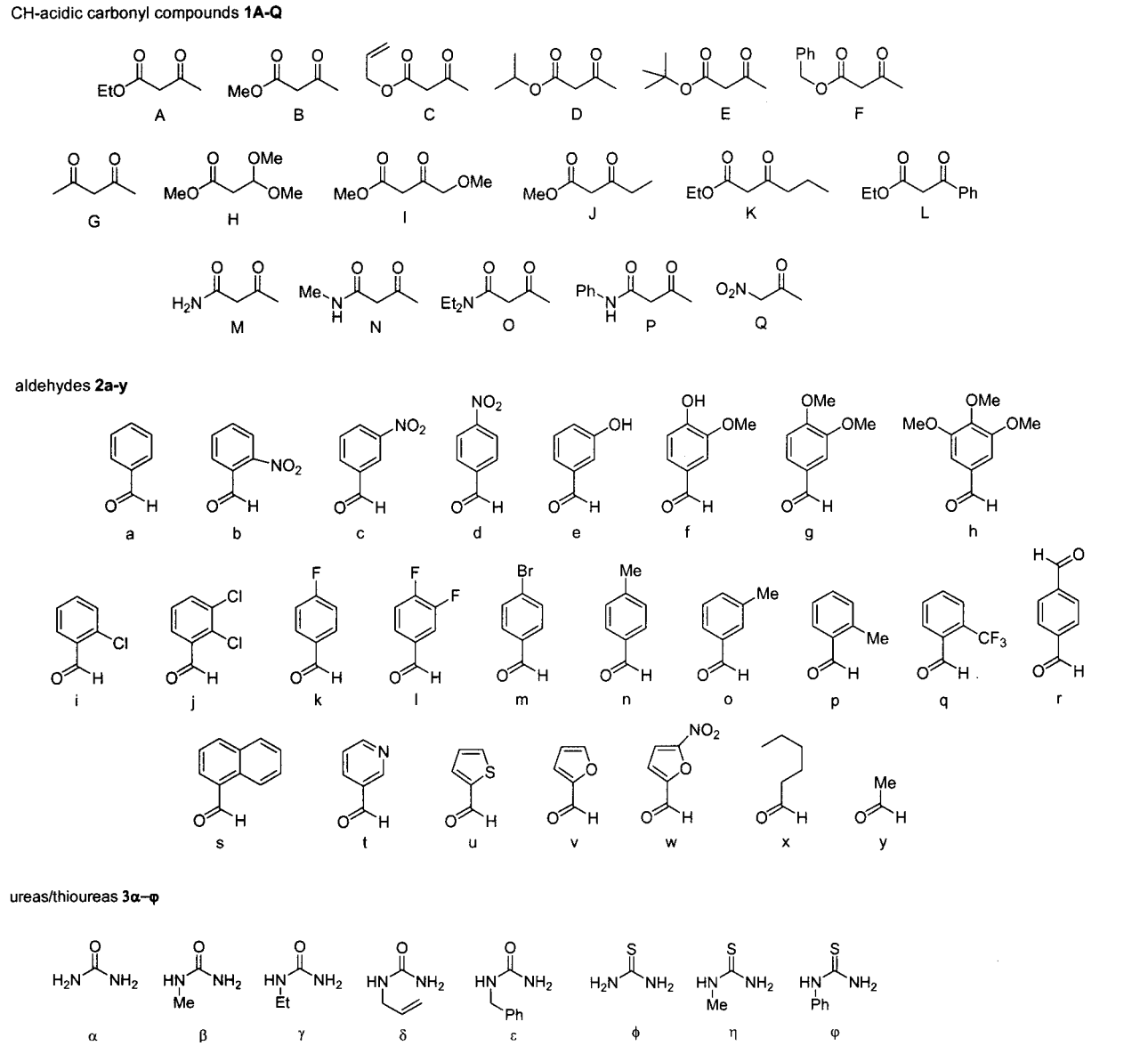

Figure 2. Building blocks for library generation in the Biginelli MCR protocol.

Table 1. Optimization of Microwave-Assisted Biginelli Reactions

entry	DHPM[a]	solvent	catalyst [mol %]	method	temp [°C]	time [min]	yield [%]
1	**4Aaα**	AcOH/EtOH 3:1	$InCl_3$ [10]		120	10	44
2	**4Aaα**	AcOH/EtOH 3:1	$FeCl_3$ [10]		120	10	88
3	**4Aaα**	AcOH/EtOH 3:1	$LaCl_3$ [10]	B	120	10	76
4	**4Aaα**	EtOH	HCl [10]	E	120	10	78
5	**4Aaα**	AcOH/EtOH 3:1	$Yb(OTf)_3$ [10]	A	120	10	92
6	**4Aaα**	AcOH/EtOH 3:1	$Yb(OTf)_3$ [5]		120	10	72
7	**4Aaα**	AcOH/EtOH 3:1	$Yb(OTf)_3$ [10]	A	100	10	56
8	**4Aaα**	AcOH/EtOH 3:1	$Yb(OTf)_3$ [10]	A	120	5	68
9	**4Aaα**	AcOH/EtOH 3:1	$Yb(OTf)_3$ [10]	A	120	15	94
10	**4Aaα**	AcOH/EtOH 3:1	$Yb(OTf)_3$ [10]	A	140	10	67
11	**4Aaϕ**	AcOH/EtOH 3:1	$Yb(OTf)_3$ [10]	A	120	10	43
12	**4Aaϕ**	AcOH/EtOH 3:1	$Yb(OTf)_3$ [10]	A	120	20	55
13	**4Aaϕ**	AcOH/EtOH 3:1	$LaCl_3$ [10]	B	120	10	56
14	**4Aaη**	EtOH	$LaCl_3$ [10]	D	120	10	41
15	**4Avα**	EtOH	$Yb(OTf)_3$ [10]	C	100	20	50
16	**4Mdα**	EtOH	HCl [10]	E	120	15	59

[a] For building blocks **1A**−**Q**, **2a**−**y**, and **3α**−***φ***, see Figure 2.

byproducts (entry 10); lower reaction temperatures on the other hand required longer reaction times for complete conversion (entry 7). For the model system **4Aaα** a total irradiation time of 10 min at 120 °C (entry 5) resulted in 92% isolated yield of pure product. The final DHPM product precipitated directly after the active cooling period (cf. Figure

1) and showed no traces of impurities by ^{1}H NMR analysis. Although an increase in reaction time to 15 min would further increase the yield for this example (entry 9), we have decided generally not to use longer reaction times unless warranted by the specific building block combinations (see below). All reaction were run in the larger 2.0−5.0 mL process vials, using 4.0 mmol of each building block in a total of 1.6 mL of solvent mixture. At a temperature of 120 °C this led to a pressure of ca. 3−4 bar in the vial, well below the accessible limit of 20 bar. Although several authors have shown that higher yields of DHPMs can be obtained by employing either the carbonyl or urea building blocks in excess,[17−19,24−27] we have not optimized for molar ratios of reagents and have used equimolar amounts of building blocks in all experiments.

Having identified an optimized set of reaction conditions for one model substrate of the planned DHPM library, we next looked at potentially troublesome reagents and reagent combinations in our selection of building blocks (Figure 2). Thioureas, for example, are known to give significantly lower yields when employed in the Biginelli condensation.[12,13] We have discovered that for thioureas **3α**−***φ*** $LaCl_3$ is usually the preferred catalyst in a microwave-assisted protocol. Increasing the reaction time to 20 min also significantly increased the yield compared to the 10 min run (entries 11−13). On the other hand furane-2-carbaldehyde is known to be somewhat acid-sensitive. For this particular aldehyde building block, for example, we have devised a modified protocol, using neat ethanol as a solvent at 100 °C (entry 15). Some other examples of reaction conditions fine-tuned to specific building block combinations differing from the standard protocol are also presented in Table 1 (entries 14, 16). The yields for the optimized microwave-assisted Biginelli condensations are in general comparable to or higher than the yields obtained using the standard reflux conditions. More importantly, however, reaction times have been brought down from several hours (4−12 h) under reflux conditions[12] to 10−20 min, using superheated solvents and direct in-core microwave flash heating. The optimization cycles described above can be carried out within a few hours, providing optimized sets of conditions (methods A−E, Table 1) useful for synthesizing a larger library.

Automated Production of a 48-Member DHPM Library. With a set of several optimized reaction conditions for a variety of representative Biginelli condensations in hand, we next turned our attention toward the production of a small library of DHPMs. For structurally diverse representative building blocks, we have chosen a set of 17 individual CH−acidic-carbonyl compounds **1A**−**Q**, 25 aldehydes **2a**−**y,** and 8 urea/thioureas **3α**−***φ*** (Figure 2). Combination of all these building blocks in a Biginelli-type fashion would lead to a library of 3400 individual DHPMs. To demonstrate the practicability of the concept, we decided to generate a representative subset of 48 DHPM analogues, involving all building blocks shown in Figure 2. While the optimization experiments described above (Table 1) were carried out manually, i.e., adding individual reagents, catalysts, and solvents into the process vials before capping of the vial, we now attempted to automate this process as far as possible making use of the liquid handler/gripper capabilities of the microwave synthesizer.[22] For that purpose, stock solutions of defined concentrations of all CH−acidic-carbonyl components **1A**−**Q** in acetic acid were prepared and stored in designated rack positions of the robot (for experiments employing methods C−E, EtOH was used as solvent). Similarly, all of the aldehydes **2** were dissolved in absolute ethanol, the only exception being aldehydes **2h** and **2r**, which would not be soluble in the required concentration in ethanol. All urea/thiourea derivatives **3α**−***φ*** and the catalysts $Yb(OTf)_3$ and $LaCl_3$ were weighed directly into the process vials before capping. After all building blocks and reaction conditions were entered into the software,[22] the sequential irradiation of all 48 process vials was programmed, identifying the rack position of the corresponding stock solutions of **1A**−**Q** and **2a**−**y.** Each vial would then be moved sequentially in and out of the microwave cavity by the gripper after the appropriate building blocks were dispensed into the corresponding vials via the Teflon septa. Irradiation using the conditions specified in Table 2 produced the desired DHPMs in 18−92% isolated yield (average yield 52%). As can be seen from the data presented in Table 2 and Figure 2, considerable variations in all three building blocks **1**−**3** are tolerated. Thus, all five variable substituents (R_1−R_3, E, Z; see Scheme 1) around the DHPM scaffold **4** can be modified, increasing the structural diversity of DHPM analogues that can be synthesized. (For a structural representation of all 48 DHPMs, see Figure S1 in the Supporting Information.) In the majority of cases, the solid DHPM derivatives would precipitate directly from the reaction mixture after active cooling. The remaining examples crystallized after the crude reaction mixture was poured onto ice−water. ^{1}H NMR spectra were obtained from all samples to check their chemical identity and purity. All products had at least >90% purity; in most cases no signals other than product peaks could be identified from the ^{1}H NMR spectrum. While the 48 examples of DHPM analogues presented in Table 2 are a representative subset of the full 3400 member library, it should be stressed that not all combinations of building blocks may lead to DHPMs in such a high state of purity. For some of the examples given in Table 2 the yields were not as high as previously reported using different (e.g., solvent-free) Biginelli protocols. Undoubtedly, these yields could be further optimized by fine-tuning the microwave-assisted reaction conditions, i.e., by varying the molar ratios of reagents or using different solvent/catalyst combinations. No attempts were made along these lines because the protocols described above deliver quantities of several 100 mg of pure DHPM products. The speed, ease of generation/isolation, etc. far outweigh the higher yields that may be obtainable by other protocols, i.e., solvent-free procedures that cannot be easily automated. With an average irradiation time of ca. 15 min (including the time needed for dispensing reagents and moving vials in and out of the cavity) the generation of the 48-member library could be achieved within 12 h. Since the instrument is designed for fully automated unattended operation, a library of this size can conveniently be prepared overnight. In summary, we have developed an automated protocol for the preparation of DHPM libraries

Table 2. Conditions and Yields for DHPM Library Generation (48 Members)

DHPM[a]	method[b]	temp [°C]	time [min]	workup[c]	yield [%]
4Aaα	A	120	10	a	92
4Aaγ	A	120	10	b	18
4Aaϵ	A	120	10	b	43
4Aaϕ	B	120	10	a	56
4Aaη	D	120	10	a	41
4Abα	A	120	10	a	54
4Aeϕ	C	120	20	b	45
4Agα	C	120	10	a	52
4Aiα	A	120	10	a	68
4Alα	C	120	10	a	61
4Aqα	A	120	20	a	49
4Arα[d]	C	120	10	a	78
4Asδ	C	120	10	b	41
4Atα	A	120	10	b	30
4Auα	A	120	10	a	89
4Avα	C	100	20	a	50
4Axα	A	120	10	b	35
4Ayα	C	120	20	a	67
4Bfα	C	100	15	a	46
4Bhα	A	120	10	a	62
4Bkα	A	120	10	a	81
4Bnϕ	D	120	20	a	58
4Bpα	C	120	10	a	73
4Bwα	C	100	10	a	34
4Ccβ	A	120	10	b	51
4Daα	C	120	10	a	50
4Dcα	C	120	15	b	73
4Dcδ	A	120	10	b	34
4Eaα	C	120	10	a	49
4Fjβ	A	120	10	b	25
4Gaα	C	120	10	a	53
4Goα	C	120	10	a	68
4Haα	C	120	20	a	31
4Hhα	E	120	20	a	31
4Hlα	C	120	20	a	35
4Icα	A	120	10	b	35
4Jjβ	C	120	10	b	26
4Jlα	A	120	10	b	64
4Kdα	C	120	10	a	41
4Lcα	A	120	20	b	40
4Maφ	E	120	15	a	21
4Mdα	E	120	15	a	59
4Nbα	A	120	10	a	66
4Omα	A	120	10	b	61
4Paα	A	120	10	b	55
4Pfα	E	100	15	b	28
4Piϕ	B	120	10	b	89
4Qaα	B	100	15	a	83

[a] For building blocks **1A**−**Q**, **2a**−**y**, and **3α**−**φ**, see Figure 2. For a graphical representation of all DHPM products, see Figure S1 in the Supporting Information. [b] For description of methods A−E, see Table 1 and Experimental Section. [c] See Experimental Section. [d] 2.0 mmol of bis-aldehyde **2r** were employed.

using Biginelli MCR strategies, a structural scaffold that continues to be of interest for the combinatorial chemistry community.[13,29−31]

Concluding Remarks

In related work[10] we have described high-speed parallel reactions carried out in specifically designed multimode microwave reactors. While this method allows for a considerable throughput that can be achieved in the relatively short time frame of a microwave-enhanced chemical reaction, the individual control over each reaction vessel in terms of reaction temperature/pressure is limited. As an alternative to parallel synthesis, we have reported herein the automated sequential synthesis of libraries. Irradiating each individual reaction vessel separately not only gives better control over the reaction parameters but also allows for the rapid optimization of reaction conditions. In contrast to the parallel mode, not all reaction vessels are exposed to the same irradiation conditions. To ensure similar temperatures in a parallel setup, the same amount of the identical solvent has to be used in each reaction vessel because of the dielectric properties involved. For the preparation of relatively small libraries where delicate chemistries are to be performed, the sequential format is therefore preferred.

Apart from the automated generation of libraries, microwave-assisted synthesis in general is likely to have a tremendous impact on the medicinal/combinatorial chemistry communities. Compared to traditional processing of organic synthesis, microwave-enhanced chemistry saves significant time and very often improves yields. It has also been demonstrated in a number of examples that previously practically impossible transformations are successfully completed using microwave irradiation.[1−9] It should be stressed that in general the rate enhancements seen in microwave-assisted synthesis can be attributed to the very rapid heating of the reaction mixture (flash heating) and the high temperatures that can be obtained rather than to any specific or nonthermal microwave effect.[8] However, the short reaction times open up new approaches for rapid testing of ideas and fast iterations in protocol development, as demonstrated here successfully for the Biginelli reaction. While microwave heating is today still considered by some as a laboratory curiosity, we believe that this technology will be used extensively in the future for many chemical processes requiring heat.

Experimental Section

General Methods. All building blocks **1**−**3** were purchased from commercial sources and used without further purification. Lewis acid catalysts $Yb(OTf)_3 \cdot H_2O$ (Aldrich 40532-9), $LaCl_3 \cdot 7H_2O$ (Aldrich 26207-2), $InCl_3$ (Aldrich 42941-4), and $FeCl_3 \cdot 6H_2O$ (Aldrich 20792-6) were purchased from Aldrich Chemical Co. with the specifications given. ^{1}H NMR spectra were recorded on a Bruker AMX360 or AMX500 instrument in $CDCl_3$ or DMSO-d_6, operating at 360 or 500 MHz, respectively.

Microwave Irradiation Experiments. The Smith synthesizer (PersonalChemistry AB)[32] was used in the standard configuration as delivered, including proprietary Workflow Manager software (version 1.1). Optimization experiments (Table 1) were performed in the "single-run" mode, i.e., by manual filling of reaction vials and by specifying the irradiation time and maximum temperature. Library generation (Table 2) was done in an automated fashion, using the liquid handler capabilities of the instrument/software. For that purpose, each of the required 48 2.0−5.0 mL process vials was filled with 4.0 mmol of the corresponding urea/thiourea building blocks **3α**−**φ** and 10 mol % (0.4 mmol) of Lewis acid catalyst (for method E, 100 μL of 4 M HCl in

dioxane, Aldrich 34554−7, was employed). The vials were sealed with the Teflon septum and aluminum crimp, using an appropriate crimping tool. Every vial was then placed in its correct position in the rack of the Smith synthesizer as specified by the software. The 3.3 M stock solutions of CH−acidic-carbonyl compounds **1A**−**Q** in AcOH and 10.0 M stock solutions of aldehydes **2a**−**y** were prepared and similarly stored in designated rack positions. If solutions could not be prepared because of insufficient solubility (**2h, 2r**), the particular building block was added manually to the urea/thiourea and catalyst components were added directly into the vial. For conditions C−E, stock solutions of the corresponding CH−acidic-carbonyl compounds in EtOH were additionally prepared. By use of the liquid handler, 4.0 mmol aliquots of aldehydes **2a**−**y** (400 μL) and carbonyl compounds **1A**−**Q** (1200 μL) were each dispensed into the process vials containing the appropriate urea/thiourea and catalyst (Table 2). After an individual vessel had been filled, the vial was moved in and out of the microwave cavity, where irradiation for 10−20 min at 100−120 °C (see Table 2) was performed. After the full irradiation sequence was completed, racks containing the processed vials were stored at 4 °C for 8 h. In the case of precipitation, the solid products **4** were filtered, washed with cold (4 °C) EtOH, and dried (workup a, Table 2). Where no precipitation was experienced (workup b, Table 2), the crude reaction mixture was treated with 10 mL of ice−water and allowed to stand for 12 h at 4 °C. The solid products **4** were filtered and treated as above. The purity of all DHPM products was >90% according to ^{1}H NMR measurements (360 MHz). ^{1}H NMR spectral data for all 48 DHPMs, including melting points, literature melting points, and reference information (where available), are presented in the Supporting Information.

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Supporting Information Available. ^{1}H NMR spectral data, structural formulas, melting points, literature melting points (where available), and systematic names of all 48 DHPM products **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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